

Role of RDW and MPV in Diagnosis of Colorectal Polyps and Carcinoma: A Case-Control Study

Kolorektal Polip ve Karsinom Tanısında RDW ve MPV'nin Rolü: Vaka-Kontrol Çalışması

Mustafa Cengiz¹, Abdurrahman Şahin², Kamil Özdil³, Hacı Mehmet Sökmen³

¹Dr. A. Y. Ankara Onkoloji Eğitim Ve Araştırma Hastanesi, Gastroenteroloji Bölümü, Ankara, Türkiye.

²Fırat Üniversitesi Tıp Fakültesi, Gastroenteroloji Bölümü, Elâzığ, Türkiye.

³Ümraniye Eğitim Ve Araştırma Hastanesi, Gastroenteroloji Bölümü, İstanbul, Türkiye.

Dergiye Ulaşma Tarihi:28/04/2015 Dergiye Kabul Tarihi:28/05/2015 Doi: [10.5505/aot.2015.96268](https://doi.org/10.5505/aot.2015.96268)

ÖZET

Giriş ve Amaç: Ortalama trombosit hacmi (MPV) kırmızı kan hücresi dağılım genişliği (RDW) testleri rutin tam kan sayımında bulunan basit testlerdir. İnflamasyon, MPV ve RDW değerlerinde değişiklikler yapabilir. Bu çalışmada KRK, adenom ve sağlıklı kontrollerin MPV ve RDW değerlerini karşılaştırmayı amaçladık.

Yöntem ve Gereçler: KRK veya irritabl barsak hastalığı şikâyetleri nedeniyle kolonoskopik tarama yapılan vakaların MPV ve RDW değerleri geriye dönük olarak değerlendirilmiştir. Kolonoskopi ve histopatolojik bulgularına göre hastalar KRK, adenom ve normal kontrol grubu olmak üzere 3 ayrı gruba ayrıldı. Sonrasında adenom grubu displazi ve villöz komponent varlığına göre yüksek olasılıklı prekanseröz ve düşük olasılıklı prekanseröz olarak 2 alt gruba ayrıldı.

Bulgular: Çalışmaya ardışık toplam 602 hasta alındı. Bunlardan KRK grubunda (n=130)'si, adenom grubunda (n=241)'si ve normal kolonoskopik bulguları olan (n=233)'si hasta kontrol grubundaydı. KRK grubunda diğer gruplara nazaran hemoglobin, MCV değerleri daha düşükken trombosit sayıları daha yüksek bulundu (P<0.001). MPV ortanca değerleri KRK, adenom ve kontrol grupları arasında karşılaştırıldığında sırasıyla (7,51-7,91-7,90 ve P<0,001). Ayrıca RDW median değerleri grupları arasında (15,7-14,6-14,4 ve P<0,001) istatistiksel olarak anlamlı bulundu. Adenom alt grupları karşılaştırıldığında düşük-yüksek olasılıklı gruplar arasında sadece RDW açısından istatistiksel anlamlı fark tespit edildi (14,4-14,8,ve P=0.02). MPV değerleri açısından gruplar arasında fark bulunamadı (7,89-8,04 ve P>0.05).

Tartışma ve Sonuç: Kolonoskopik taramaya alınacak vakalarda RDW ve MPV değerleri dikkate alınmalıdır.

Anahtar Kelimeler: Adenom, Karsinom, MPV, RDW

ABSTRACT

Introduction: Mean platelet volume (MPV) and red cell distribution width (RDW) are simple tests in routine complete blood count. We aimed to evaluate RDW and MPV values of patients with colorectal carcinoma (CRC), adenoma and healthy controls.

Methods: The MPV and RDW values of participants who underwent colonoscopic examination for CRC screening or irritable bowel syndrome related symptoms were evaluated retrospectively. Patients were divided into three groups as CRC group, adenoma group and control group according to colonoscopic and histopathological findings. Patients with adenomas were separated into two subgroups according to dysplasia and villous component as high probable precancerous (HPP) and low probable precancerous (LPP) groups.

Results: A total of consecutive 602 participants were enrolled into the study. There were n=130 patients in CRC, n=241 patients adenoma group and n=233 in control group. The CRC group had lower hemoglobin levels, MCV values and higher platelet count compared to adenoma group and control group. The median MPV values of CRC group (7.51) were lower than adenoma group (7.91) and control group (7.90) (P<0.001, for both). The median RDW value of CRC group (15.7) was significantly higher than adenoma group (14.6) and controls (14.4) (P=0.01, for both). Adenoma subgroups comparison reveals that the only different parameter was RDW between LPP and HPP (14.4 vs. 14.8, P=0.02). The MPV values are similar in both groups (7.89 vs. 8.04, P>0.05).

Discussion and Conclusion: The RDW and MPV values should be taken into consideration in patients who underwent colonoscopic screening.

Key words: Adenoma, carcinoma, MPV, RDW

Giriş

Kolorektal kanser (KRK) dünyada kanser ilişkili morbidite ve mortalitenin en sık nedenlerinden biridir (1). Kanserlerin %95'inden fazlası adenomatöz polipten orijin alır. KRK'lerin büyük bir çoğunluğu normal görünümlü mukozadan adenoma, displazi ve nihai olarak karsinoma geçiş gösteren sıralı yolakla meydana gelir. Genelde 50 yaşından sonra adenomatöz polipler sıklıkla görülmekle beraber poliplerin büyük bir çoğunluğu adenokarsinoma ilerlemez (2). Yüksek evre displazi ve önemli villöz komponent gibi bazı histolojik özelliklerin nihai kanser oluşmasını tahmin etmede değerleri vardır. KRK tanısının erken konması kanser ilişkili mortaliteyi azaltmakta ve sağkalımı arttırmaktadır. Ayrıca KRK taraması bazılarının prekanseröz özellikleri olabilecek poliplerin tespit edilmesinde ve çıkarılmasında önem arz etmektedir. Bu bulguların doğrultusunda kolonoskopik takip önerilmektedir. KRK taraması için gaitada gizli kan, kolonoskopik veya radyolojik prosedürler uygulanmaktadır. Ancak KRK taraması için yaygın bir şekilde kabul gören herhangi bir kan testi bulunmamaktadır.

Kırmızı kan hücreleri (RBC), beyaz kan hücreleri ve trombositleri içeren dolaşımdaki kan hücrelerinin sayılıp şekillendirilmesi için elektronik analiz cihazları kullanılmaktadır. Toplam hücre sayımı yapılmasının yanı sıra bu cihazlar ayrıca ortalama hücre hacmini ve hücre boyutunun dağılımını tahmin etmede kullanılmaktadırlar. Kırmızı hücre dağılım genişliği (RDW) eritrosit popülasyonunun değişkenliğinin ölçüsüdür (3). Artmış RDW retikülositlerin dolaşıma olgunlaşmadan salınmasına neden olan bir sürü hastalıkta görülebilir. Aneminin ayırıcı tanısının yanı sıra yükselmiş RDW değerleri kalp yetmezliği, kardiyovasküler olaylar, çölyak hastalığı ve inflamatuvar barsak hastalığı aktivitesi ile ilişkili bulunmuştur (4). Ayrıca RDW'deki artışların artmış inflamatuvar markırlarla ilişkili olduğu bulunmuştur (5,6).

Trombositler; koagulyasyonda, inflamasyonda, trombozda ve aterosklerozda önemli rol oynayan çok

sayıda cisimleri üretir ve salgılarlar. Ortalama trombosit hacmi (MPV) inflamasyonu gösteren ve en geniş olarak çalışılan moleküllerden biridir. Trombosit sayısı ve MPV birbiriyle ters ilişkilidir böylelikle toplam trombosit kütlesi yaklaşık olarak sabit kalmaktadır (7). Yüksek MPV belirlenmiş değişik önemli risk faktörleri ile ilişkili bulunmuştur ve kardiyovasküler, serebrovasküler hastalıklar ve arteriyel ve venöz tromboza neden olan düşük evre inflamasyonla ilişkilidir. Yüksek evre inflamasyonla ilişkili olan romatoid artrit veya Ailevi Akdeniz Ateş (FMF) ataklarında düşük MPV değerleri tespit edilmiştir (8). Literatürde kanser hastalarının RDW değerlerini araştıran az sayıda çalışma bulunmaktadır (9, 10). Ayrıca kanser hastalarının MPV değerlerini araştıran çalışmaların sayısı daha da azdır (11). Öyle ki bu çalışmalarda hem Kürk'le hasta sayısı az hem de sağlıklı kontrollerle karşılaştırma yapılmamıştır. Ayrıca literatürde kolon adenomlarının RDW ve MPV değerleri hakkında veri bildiğimiz kadarıyla bulunmamaktadır.

Bu çalışmada amacımız; KRK tanısı alan hastalar veya kolon polipi olan hastaların RDW ve MPV değerlerinin normal sağlıklı kontrollerin değerleriyle karşılaştırılmasıdır. Ayrıca alt grup analizde düşük ve yüksek derece displazili adenomları olan hastaların değerlerini karşılaştırmayı amaçladık.

Gereç ve Yöntem

Hastalar:

Bu retrospektif çalışmaya KRK taraması veya irritabl barsak hastalığı şikayetleri nedeniyle total kolonoskopi yapılan hastalar alındı. Vakalar kolonoskopik ve histopatolojik bulgularına göre KRK grubu, adenom grubu ve normal kontrol olmak üzere 3 ayrı gruba ayrıldı. Hastaların demografik özellikleri, kolonoskopi yapılma nedenleri, yaş, cinsiyet, eski tıbbi hikaye ve kolonoskopi işlemi esnasında laboratuvar testleri binası önlemek için hastaların bulgularından haberdar olmayan klinisyen tarafından veri tabanına kaydedildi. Kolonoskopi

işleminde önce hastaların onayı alındı. Vakaların demografik ve klinik bilgileri analiz edildi. Kanseri olan hastalar anemi durumuna bakılmaksızın çalışmaya alındı. Öncesinde KRK nedeniyle opere olan ve kolonoskopik takip için işlem yaptıran hastalar çalışmadan dışlandı. Tam kan sayım (CBC) değerleri tanı anında ve herhangi bir kan ürünü replasmanı yapılmadan elde edilen kanlardan çalışıldı.

Kolon polipi olan hastalar histopatolojik olarak displazi derecesine ve villöz komponent varlığına göre 2 ayrı alt gruba ayrıldı; yüksek olasılıklı prekanseröz (yüksek dereceli displazi veya villöz adenom) ve düşük olasılıklı prekanseröz (tübüler/tübülovillöz adenom ve düşük derece displazi). Kolonoskopi esnasında birden fazla polip tespit edildiğinde derecesi en yüksek olan displazi ile villöz komponenti olan polip çalışmaya alındı. Kolonoskopide polip tespit edilen veya kolonoskopik bulguları normal olan vakaların son 3 ayda var olan CBC değerleri çalışmaya dahil edilmiştir. Kronik diyare veya demir eksikliği anemisi etiyojisini aydınlatmak için kolonoskopi yapıp işlemde normal veya polip tespit edilen hastalar yanlış sonuçları engellemek için dışlanmıştır.

Bütün gruplar için, RDW veya MPV değerlerini etkileyecek diyabet, tiroit disfonksiyonu, inme, tromboembolik olaylar, kalp yetmezliği, kardiyovasküler olaylar ve inflamatuvar bozuklukları gibi kronik rahatsızlığı olan hastalar çalışmadan dışlanmıştır. Ayrıca hem RDW hem de MPV değerlerine ulaşamayan hastalar çalışmadan dışlanmıştır.

Laboratuvar testleri:

Hemoglobin (HB), mean corpuscular volume (MCV), RDW, trombosit sayısı, beyaz küre (WBC) ve MPV değerleri Advia 2120 (Siemens Healthcare Diagnostics Inc., Tarrytown, New York, USA) cihazı kullanılarak tespit edilmiştir. Ayrıca RDW hesaplaması (standart sapma (SD)/MCV X 100%) denklemi kullanılarak yapılmıştır.

İstatistiksel analizler:

İstatistiksel analizler SPSS 21. Versiyonu kullanılarak yapıldı. Değişkenler normal

dağılıp dağılmadığını araştırmak için görsel (histogram, olasılık plotları) ve analitik metotlar (Kolomogorov-Smirnov/Shapiro-Wilk's testleri) kullanıldı. Normal dağılım gösteren değişkenler için ortalama ve standart sapma kullanılırken normal dağılmayan değişkenler için ortanca ve aralık değerleri verildi. Normal dağılım gösteren değişkenler 3 grup arasında karşılaştırılınca varyans analiz ile değerlendirme yapıldı ve bonferroni düzeltmesi Student T testi ile yapıldı. Normal dağılmayan değişkenler için Kruskal Wallis testleri ve Bonferroni düzeltmesi Mann-Whitney U testi kullanılarak yapıldı. Ayrıca düşük derece ve yüksek derece displazi grupları arasında parametreler Man Whitney U testi kullanılarak değerlendirildi. P değeri için 0,05'ten küçük olan değerler istatistiksel olarak anlamlı kabul edildi.

Sonuçlar

Bu çalışmaya toplamda 602 ardışık vaka alındı. Vakalar KRK grubu, adenom grubu ve normal kontrol olmak üzere 3 ayrı gruba ayrıldı. Karsinom grubunda 130 hasta varken bunların %57,7'si erkekti. Toplamda 241 adenom hastasının %64,5'i erkek hastalardan oluşuyordu. Ayrıca kolonoskopisi normal olan 233 sağlıklı vaka çalışmada yer aldı. KRK grubunda bulunan vakaların yaşları diğer her iki gruptan daha büyüktü ve fark istatistiksel olarak anlamlıydı (P<0.001). Cinsiyet açısından gruplar arasında istatistiksel olarak anlamlı farklılık yoktu.

Karsinom grubunda diğer her iki gruba nazaran daha düşük HB ve MCV değerleri bulunurken trombosit değerleri daha yüksek bulundu ve farklılık istatistiksel olarak anlamlıydı (Bütün değişkenler için P<0,001). Trombosit sayısı adenom grubunda sağlıklı gruba göre daha düşüktü (P=0.03) ayrıca MCV değerleri daha yüksekti (P=0,03). MPV değerleri karşılaştırıldığında karsinom, adenom ve sağlıklı grupların değerleri sırasıyla 7,51 (5,6-11,1)-7,91 (5,89-13,70)-7,90 (5,89-18,60) olarak tespit edildi. Karsinom ve adenom grupları ve karsinom

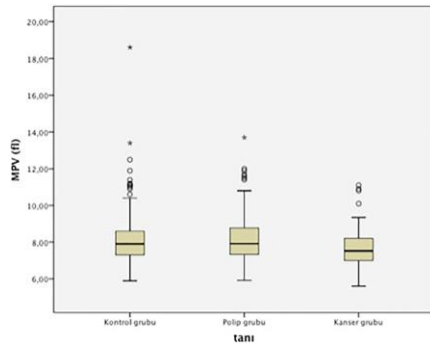
ile kontrol grupları arasında MPV açısından anlamlı istatistiksel fark bulunurken ($P<0,001$). Polip grubu ile kontrol grubu arasında istatistiksel anlamlı fark bulunamadı ($P>0,05$). Ayrıca ortanca RDW değerleri açısından gruplar karşılaştırıldığında KRK grubunda adenom grubuna göre daha yüksek değerler tespit edildi. (15,7 ile 14,6 ve $P<0,001$). Ayrıca KRK grubu ile kontroller arasında da RDW açısından

istatistiksel anlamlı fark bulundu (15,7 ile 14,4 ve $P<0,001$). Ancak adenom grubu ile kontrol grubu arasında anlamlı fark bulunamadı (14,6 ile 14,4 ve $P>0,05$). Çalışmaya alınan vakaların klinik özellikleri ve laboratuvar değerlerinin karşılaştırılması Tablo 1’de özetlenmiştir. Ayrıca MPV ve RDW değerlerinin gruplar arasında karşılaştırılması sırasıyla Şekil 1 ve Şekil 2’de gösterilmiştir.

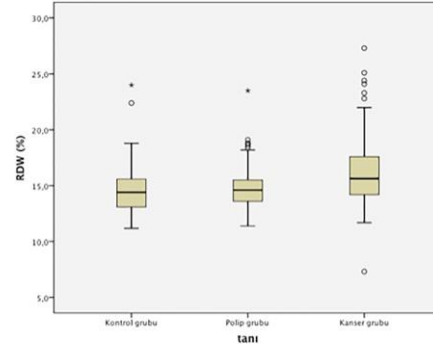
Tablo 1: Vakaların klinik özellikleri ve laboratuvar değerlerinin karşılaştırılması

	Kontrol grubu	Adenom grubu	Karsinom grubu	P değeri
Yaş (yıl)	53,3 ±13,1	57 ±11,8	62,8 ± 12,8	<0.001
Cinsiyet Erkek (%)	136 (%58,6)	156 (%64,5)	75 (%57,7)	0.26
Hemoglobin ^a (g/dL)	13,8 (12,1-17,3)	14 (11,9-17,7)	11,8 (5,7-19,6)	< 0.001
Trombosit ^a (/mm ³ ×10 ³)	259 (125-509)	252 (122-526)	335 (98-822)	< 0.001
MPV ^a (fL)	7,9 (5,89-18,6)	7,91 (5,92-13,7)	7,51 (5,6-11,1)	< 0.001
RDW ^a (%)	14,4 (11,2-24)	14,6 (11,4-23,5)	15,7 (7,3-27,3)	< 0.001
MCV ^a (fL)	86,5 (62,9-97,5)	87,3 (66,9-99,3)	83,3 (63,4-98)	< 0.001

MCV: ortalama corpuscular hacim RDW: Kırmızı kan hücresi dağılım genişliği; MPV: Ortalama trombosit hacmi. (^a) Data median olarak temsil edilmiştir (range).



Şekil 1: Grupların MPV değerlerinin karşılaşı.



Şekil 2: Grupların RDW değerlerinin karşılaşı.

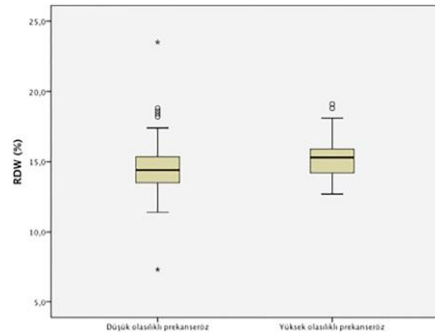
Polip grubu düşük olasılıklı prekanseröz ve yüksek olasılıklı prekanseröz olmak üzere 2 gruba ayrılmıştı. Düşük olasılık grubunda 148 hasta bulunurken yüksek olasılık grubunda 93 hasta bulunuyordu. Yaş açısından yüksek olasılık grubu daha yaşlı hastalardan oluşmaktaydı. Bu alt grupların demografik ve karakteristik özellikleri ve CBC sonuçlarının karşılaştırılması Tablo

2’ gösterilmiştir. RDW değerleri yüksek olasılık grubunda daha yüksek olmak üzere her iki grup arasında karşılaştırıldığında farklılık istatistiksel olarak anlamlı bulundu (14,4 ile 14,8 ve $P=0,02$). Bu karşılaştırma Şekilde 3’te gösterilmiştir. Ancak MPV değerleri gruplar arasında istatistiksel olarak anlamlı farklı değildi (7,89 ile 8,04 ve $P>0,05$).

Tablo 2: Polip alt grupların demografik ve laboratuvar özelliklerinin karşılaştırılması.

	Düşük derece grup	Yüksek derece grup	P değeri
Yaş (yıl)	55,2 ± 12,4	59,7 ± 10,3	< 0,001
Cinsiyet Erkek (%)	91 (86,1,5)	64 (68,8)	0,25
Hemoglobin ^a (g/dL)	14,2 (11,9-17,7)	13,9 (11,9-17,5)	0,47
Trombosit (/mm ³ x 10 ³)	251 (122-518)	252 (139-526)	0,81
MPV ^a (fL)	7,89 (6,5-11,9)	8,04 (5,92-13,7)	0,48
RDW ^a (%)	14,4 (11,4-23,5)	14,8 (12,7-19,1)	0,02
MCV ^a (fL)	87,1 (66,9-99,3)	87,3 (69,2-97,2)	0,81

MCV: ortalama corpuscular hacim RDW: Kırmızı kan hücresi dağılım genişliği; MPV: Ortalama trombosit hacmi. (^a) Data median olarak temsil edilmiştir (range).

**Şekil 3:** Polip alt gruplarının RDW değerlerinin karşılaştırılması

Tartışma

Bu çalışmada KRK grubu, adenom grubu ve kontrol gruplarının CBC parametrelerini karşılaştırdık ve sonuçta KRK hasta grubunda RDW değerlerinde artış izlenirken MPV değerlerinde düşüş olduğu tespit edildi. Kolonik poliplerin ise CBC parametreleri üzerine ciddi bir etkileri olmadığı görüldü. Polip özelliğine göre tek anlamlı farklılık RDW değerlerinde tespit edildi.

Aşkar veya gizli gastrointestinal sistem kanamaları KRK en önemli bulgularından biridir. Gastrointestinal kanama ve demir eksikliği anemisi erkeklerde ve menopoz sonrası kadınlarda kolorektal değerlendirme için 2 önemli endikasyondur. Gastrointestinal sistemden kronik kan kaybı demir eksikliği anemisi yapar öyle ki demir eksikliği anemisine bağlı olarak KRK hastalarında HB ve MCV değerleri düşük bulunurken RDW ve trombosit değerleri yüksek bulunur. Bizim sonuçlarımız bu gerçeğe uyuşmaktadır. Ayrıca Spell ve ark'ının yaptığı bir çalışmada RDW değerlerinin sağ kolon kanserlerinde yüksek derecede

sensitif ve spesifik olduğu tespit edilmiş. Bu çalışmada kontrol grubunda %12'lik bir RDW yüksekliği tespit edilmişken KRK grubunda bu oran %69 olarak bulunmuş. Sağ taraf KRK, sol taraf KRK ve kontrol gruplarının ortalama RDW değerleri sırasıyla 16,8- 15- 13,3 olarak bulunmuş. İlginç olarak CBC'nin diğer parametreleri (HB, MCV) ile RDW'nin kombinasyonunda tek başına RDW'nin sensitivite ve spesifitesini artırılmamıştır. Eritrosit hacmindeki değişkenlik aşkar anemiden önce ortaya çıkmaktadır ve normal CBC ile birlikte artmış RDW erken demir eksikliği anemisinin iyi sensitif ve spesifik bir belirteçidir (9). Ayrıca demir eksikliğini tespit etmekte artmış RDW diğer laboratuvar testlerinden daha duyarlıdır (12).

Yapılan bazı çalışmalarda tıbbi checkup için başvuran hastalarda anemi durumundan bağımsız olarak RDW değerlerinin inflamatuvar markırlarla (yüksek sensitif C reaktif protein (CRP) ve eritrosit sedimentasyon hızı (ESR)) ilişkili olduğu bulunmuştur (5, 13). İnflamasyonun eritropoez ve dolaşımdaki eritrosit yarı ömrü üzerindeki etkisi anizositoza neden olup RDW değerlerinde artışa neden olabilmektedir (14). Yapılan bir çalışmada RDW değerlerindeki 1 SD artışın kanser mortalitesinde %28'lik bir artışla ilişkisi olduğu tespit edilmiştir. İlginç olarak RDW'nin mortalite ile olan ilişkisi inflamasyonun varlığına bağımlı değildir (6). Bizim çalışmamızda kanser bağımlı inflamasyon ve kronik hastalık anemisi anemi durumu ve artmış RDW durumu ile ilişkili olabilir.

Dolaşımdaki küçük ve büyük yapıdaki trombositlerin sınıflandırılmasında sistemik

inflamasyonun şiddeti değerlendirilmelidir (8). Artmış MPV düzeyleri genelde vasküler risk faktörleri, immün trombositopenik durumlar, düşük derece inflamatuvar durum ve edinsel dev trombosit bozukluklarla ilişkilidir. Düşük MPV değerleri ise sitotoksik tedavi sonrası kemik iliği aplazisi, hipersplenizm, reaktif trombositosis yüksek dereceli inflamasyon ve Wiskott-Aldrich sendromu ile ilişkilidir (15). Kanser bir sürü proinflamatuvar sitokin salgılandığı sistemik inflamatuvar bir bozukluktur. Birkaç proinflamatuvar sitokin kemik iliğindeki hematopoetik hücrelerin maturasyonuna etki ederek hematopoetik hücrelerin dolaşıma salgılanmasına neden olur. Yüksek derece inflamasyonla ilişkili durumlar (aktif inflamatuvar barsak hastalığı, Romatoid Artrit, FMF atağında) genel olarak dolaşımdaki küçük trombositlerle ve düşük MPV değerleri ile ilişkili iken aynı durumlar remisyonda iken veya anti-inflamatuvar ilaç kullanımı dolaşımdaki daha büyük trombositlerle ve daha yüksek MPV değerleri ile ilişkilidir (8). Yüksek derece inflamasyon MPV ile negatif ilişkilidir. Adenomdan karsinom gelişimi malign hücrelerin mukozal tabakayı geçmesi ve sonuç olarak sistemik yüksek inflamatuvar durum oluşması ile sonuçlanır. Öyle ki KRK hastalarında düşük MPV değerleri beklenen bir durumdur.

Bu çalışmada MPV'nin KRK ve adenom ile olan ilişkisini araştırdık ve kolon poliplerinin MPV üzerine önemli bir etkinliği olmadığı sonucuna vardık ancak düşük MPV değerleri KRK ile ilişkiliydi. Yapılan bir çalışmada Bevacizumab tedavisi alan metastatik KRK hastalarında MPV değerlendirilmiş (11). Bu çalışmada bulunan ortalama MPV değerleri bizim sonuçlardan daha yüksek olarak bulunmuş. Öyle ki bu çalışmadaki hastaların çoğu opere olmuş ve metastatik KRK olarak sınıflandırılmış. Bizim daha düşük MPV değerlerini bulmamızın bir nedeni de hastaların opere olmadan ve tanı konar konmaz değerlerine bakılması nedeniyledir. Öyle ki metastatik KRK hastalarının bir kısmında kitle rezeke edilmediği için değerlendirme aşamasında lezyondan salınan bazı sitokinler megakaryosit ve MPV değerlerini

etkilemiştir. Ayrıca biz çalışmamızda opere olmuş ve takip kolonoskopi olan hastaları dışladığımız için bizim değerler daha düşük olarak bulundu. Böylelikle bizim sonuçlarımızla KRK'nin net olarak MPV üzerine olan etkisi net ve açık olarak tespit edilmiş olmaktadır. Adenom ve kontrol grupları karşılaştırıldığında anlamlı fark bulamadık ayrıca düşük-yüksek olasılık prekanseröz adenomlar arasında da istatistiksel anlamlı fark bulunmadı. Bu sonuç gösteriyor ki; polipi olan hastalarda polipin özelliğinden bağımsız olarak mukoza tabakasına sınırlanmış düşük derece inflamasyon MPV değerlerine etki etmemektedir. Öte yandan prekanseröz derecesi ile RDW arasında ilişki tespit edildi. Düşük derece inflamasyon RDW değerlerini etkilerken MPV değerleri etkilenmemektedir. İnflamasyonun mukozanın ötesine geçmesiyle trombositosis ve MPV düşüşü meydana gelmektedir.

Çalışmamızın bazı kısıtlamaları mevcuttu şöyle ki; retrospektif dizayn olması, nispeten özellikle adenom grubunda düşük hasta sayısı varlığı olarak sayılabilir. Ayrıca retrospektif dizayndan dolayı polip çapı değerlendirilemedi. Ancak polip çapı hem yapan kişiye bağlıdır hem de genelde yaklaşık olarak değerlendirildiği için sağlıklı sonuç vermeyecektir. Kişiler arasındaki bu değişkenliğin etkisinden kurtulmak için polip boyutu ile değerlendirme subjektif olabileceği için çalışmada değerlendirilmemiştir. Ayrıca biz bu çalışmada KRK hastaların tanı anındaki CBC değerlerini değerlendirdik ilerde prospektif olarak tanı anında, operasyon sonrası ve kemoradyoterapi sonrası değerlendirme yapılması hastalık trendinde bu markerlerin rolünü daha iyi bildirecektir.

Sonuç olarak, KRK hastalarında MPV değerleri düşük olarak bulunurken displazi ve adenomun villöz komponenti varlığı RDW değerlerini arttırmaktadır. Bu çalışmanın sonuçlarına göre, kolonoskopik tarama yapılacak hastalarda RDW ve MPV değerleri dikkate alınmalıdır. Kanser ve inflamasyonun kemik iliği dolaşımdaki hematopoetik hücreler üzerine etkilerini

araştırmak için randomize kontrollü ve prospektif çalışmalara ihtiyaç vardır.

Çıkar Çatışması: Yok

Kaynaklar:

1. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer* 2010; 127: 2893-2917
2. Levin B, Lieberman DA, McFarland B, Andrews KS, Brooks D, Bond J et al. Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps, 2008: a joint guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology. *Gastroenterology* 2008; 134: 1570-1595
3. Dixon LR. 1997. The complete blood count: physiologic basis and clinical usage. *J Perinat Neonatal Nurs* 1997; 11: 1-18
4. Song CS, Park DI, Yoon MY, Seok HS, Park JH, Kim HJ et al. Association between red cell distribution width and disease activity in patients with inflammatory bowel disease. *Dig Dis Sci* 2012; 57: 1033-1038
5. Lippi G, Targher G, Montagnana M, Salvagno GL, Zoppini G, Guidi GC. Relation between red blood cell distribution width and inflammatory biomarkers in a large cohort of unselected outpatients. *Arch Pathol Lab Med* 2009; 133: 628-632
6. Perlstein TS, Weuve J, Pfeffer MA, Beckman JA. Red blood cell distribution width and mortality risk in a community-based prospective cohort. *Arch Intern Med* 2009; 169: 588-594
7. Bath PM, Butterworth RJ. Platelet size: measurement, physiology and vascular disease. *Blood Coagul Fibrinolysis* 1996; 7: 157-161
8. Gasparian AY, Ayvazyan L, Mikhailidis DP, Kitas GD. Mean platelet volume: a link between thrombosis and inflammation? *Curr Pharm Des* 2011; 17: 47-58
9. Spell DW, Jones DV, Jr., Harper WF, David Bessman J. The value of a complete blood count in predicting cancer of the colon. *Cancer Detect Prev* 2004; 28: 37-42
10. Baicus C, Caraiola S, Rimbaz M, Patrascu R, Baicus A. Utility of routine hematological and inflammation parameters for the diagnosis of cancer in involuntary weight loss. *J Investig Med* 2011; 59: 951-955
11. Mutlu H, Berk V, Karaca H, Erden A, Aslan T, Akca Z. Treatment regimen with bevacizumab decreases mean platelet volume in patients with metastatic colon cancer. *Clin Appl Thromb Hemost* 2012; 18: 546-548
12. Van Zeben D, Bieger R, van Wermeskerken RK, Castel A, Hermans J. Evaluation of microcytosis using serum ferritin and red blood cell distribution width. *Eur J Haematol* 1990; 44: 106-109
13. Lappe JM, Horne BD, Shah SH, May HT, Muhlestein JB, Lappe DL et al. Red cell distribution width, C-reactive protein, the complete blood count, and mortality in patients with coronary disease and a normal comparison population. *Clin Chim Acta* 2011; 412: 2094-2099
14. Weiss G, Goodnough LT. Anemia of chronic disease. *N Engl J Med* 2005; 352: 1011-1023
15. Aksoy S, Kilickap S, Hayran M, Harputluoglu H, Koca E, Dede DS ve ark. Platelet size has diagnostic predictive value for bone marrow metastasis in patients with solid tumors. *Int J Lab Hematol* 2008; 30: 214-219.

The utility of diffusion-weighted imaging in differentiation of papillary and clear cell subtypes of renal cell carcinoma

Renal Hücreli Kanserde Difüzyon Ağırlıklı MR Görüntüleme Kullanılarak Papiller ve Şeffaf Hücreli Subtiplerin Ayırt Edilmesi

Hale Çolakoglu Er¹, Elif Peker², Ayşe Erden², Erdem Öztürk³

¹Şehitkamil Devlet Hastanesi, Radyoloji Bölümü, Gaziantep, Turkey

²Ankara Üniversitesi Tıp Fakültesi, Radyoloji Ana Bilim Dalı, Ankara, Turkey

³Ankara Üniversitesi Tıp Fakültesi, Üroloji Ana Bilim Dalı, Ankara, Turkey

Received: 22/12/2014 Accepted: 18/02/2015 Doi: [10.5505/aot.2015.25238](https://doi.org/10.5505/aot.2015.25238)

ÖZET

Amaç: Bu çalışmadaki amacımız, papiller tip ile şeffaf hücreli renal hücreli kanser alt tiplerini ayırt etmede difüzyon ağırlıklı görüntülemenin yararlılığını belirlemektir.

Yöntem: Papiller tip ve şeffaf hücreli tip renal kanseri olan toplam 16 olgu retrospektif olarak değerlendirilmiştir. İnceleme 3 Tesla alan gücüne sahip manyetik rezonans cihazında gerçekleştirilmiştir. Renal kitle konturları T2 ağırlıklı görüntülerden de faydalanılarak sınırlanmış ve kistik-nekrotik dejenerasyon alanları dışarıda kalacak şekilde elle çizilen ilgi alanı (freehand ROI) kullanılarak kitlelerin solid komponentlerinin $b=50 \text{ sn/mm}^2$ ve $b=1000 \text{ sn/mm}^2$ DAG'lerde görünür difüzyon katsayı (apparent diffusion coefficient =ADC) değerleri ve ortalama sinyal intensite (SI) değerleri ile böbreğin normal parankiminin ortalama sinyal intensite (SI) değerleri ölçülmüştür. Normal parankimin sinyal intensite değerlerinin ölçümü için ROI kortikomedüller bileşmeye yerleştirilmiştir.

Bulgular: Ortalama ADC değeri papiller RHK' larda $(0.991 \pm 0.143 \times 10^{-3} \text{ mm}^2/\text{sn})$ şeffaf hücreli RHK'lardan istatistiksel olarak anlamlı derecede düşüktü $(1.296 \pm 0.277 \times 10^{-3} \text{ mm}^2/\text{sn})$ ($p<0.05$). Ayrıca papiller RHK grubunda, $b=1000 \text{ sn/mm}^2$ DAG'lerde ölçülen ortalama SI değerleri (22.8 ± 6.3) , normal parankimden (43.4 ± 14.8) ; şeffaf hücreli RHK grubunda $b=50 \text{ sn/mm}^2$ DAG'lerde ölçülen ortalama SI değerleri (102 ± 27.5) , normal parankimden (138.8 ± 33) istatistiksel olarak farklıydı ($p<0.05$).

Sonuç: Papiller ve şeffaf hücreli kanser subtiplerinin ayırt edilebilmesinde difüzyon ağırlıklı görüntüleme faydalı bir yöntem olabilir. Papiller hücreli kanserlerin sınırları, $b=1000 \text{ sn/mm}^2$; şeffaf hücreli kanserlerin sınırları ise $b=50 \text{ sn/mm}^2$ DAG'lerde daha net olarak seçilebilmektedir. Bulgularımızın desteklenmesi için daha geniş hasta serisini kapsayan çalışmalara gereksinim vardır.

Anahtar Kelimeler: Renal hücreli kanser; magnetik rezonans görüntüleme; difüzyon ağırlıklı görüntüleme; görünür difüzyon katsayısı.

ABSTRACT

Objective: To determine the utility of diffusion-weighted imaging (DWI) in differentiation of papillary and clear cell subtypes of renal cell carcinoma (RCC).

Methods: A total of 16 patients with papillary RCC and clear cell RCC were enrolled in this retrospective study. Patients underwent MRI with a 3.0-Tesla wholebody system (MAGNETOM Verio, Siemens, Erlangen, Germany) using a standard body matrix coil. Apparent diffusion coefficient (ADC) values and signal intensity (SI) values at $b=50 \text{ s/mm}^2$ $b=1000 \text{ s/mm}^2$ DWI of solid components of the renal masses and SI values of normal renal parenchyma were measured. A freehand ROI was drawn around the peripheral margin of the tumor on the diffusion images excluding the cystic or necrotic portions, while referring to the T2-weighted conventional images for verification of lesion boundaries. To measure SI values of normal renal parenchyma, ROIs were placed on the normal corticomedullary junction.

Results: Mean ADC value was statistically significantly lower in papillary RCC $(0.991 \pm 0.143 \times 10^{-3} \text{ mm}^2/\text{s})$ than in that of clear cell RCC $(1.296 \pm 0.277 \times 10^{-3} \text{ mm}^2/\text{s})$. For the papillary RCC group, there was statistically significant difference ($p<0.05$) between mean SI values of normal parenchyma (22.8 ± 6.3) and lesion (43.4 ± 14.8) at $b=1000 \text{ s/mm}^2$ DWI; for the clear cell RCC group there was statistically significant difference ($p<0.05$) between mean SI value of normal parenchyma (138.8 ± 33) and lesion (102 ± 27.5) at $b=50 \text{ s/mm}^2$ DWI.

Conclusion: For discrimination of papillary and clear cell subtypes of RCC, DWI seems to be a useful method. The boundaries of papillary RCC can be more clearly perceived on $b=1000 \text{ s/mm}^2$ and that of clear cell RCC on $b=50 \text{ s/mm}^2$ DWI. However, more extensive research on a larger series of patients are needed to support our findings.

Key words: renal cell carcinoma, magnetic resonance imaging, diffusion weighted imaging, apparent diffusion coef

Introduction

The most common renal malignancy is renal cell carcinoma (RCC) originates from the renal

parenchyma. The global incidence of RCC has increased over the past twenty years by 2% per year (1). The most common subtypes include



clear cell RCC (70% of RCC cases), papillary RCC (10–15%), and chromophobe RCC (5%) (2,3).

Diffusion-weighted imaging (DWI) is a magnetic resonance imaging (MRI) technique based on the molecular mobility of water (4). On DWI, lesions with dense cellularity and poor interstitium that restrict the mobility of water molecules exhibit high signal intensity (5). The apparent diffusion coefficient (ADC) allows for quantification of diffusivity, which is shown to be restricted in the majority of malignancies due to higher cellularity compared to surrounding tissue. The measurable data obtained by DWI can give opinion about the nature of the lesions in various parts of the body and help to characterize them without using intravenous contrast medium (6).

Characterization of the renal tumors before operation is necessary for clinical decision and evaluation of prognosis (3). Recent studies on MRI of the renal tumors showed that ADC values obtained by DWI may provide a new quantitative data for differentiating benign tumors from the malignant ones and may help identifying pathologic subtypes of the neoplasms (7,8). The aim of this study was to determine the utility of DWI in discrimination of papillary and clear cell subtypes of RCC.

Materials and Methods

Patients

A total of 29 patients with renal mass underwent dynamic renal MRI using 3.0 Tesla system in our radiology department between October 2012 and November 2014 were retrospectively analyzed. Thirteen patients were excluded for absence of histopathologic results. Sixteen patients (14 male, 2 female; age range, 37-75 years, mean 58 years) whose histopathological data were available were included to the study. Nine patients had clear cell RCC, 7 patients had papillary type RCC.

MR techniques

The patients underwent MRI at 3.0 Tesla whole-body system (Magnetom Verio, Siemens) using standard body matrix coil. The imager operates with a maximum gradient strength of 45 mT/m and a slew rate of 200 mT/m/s in all three directions. Conventional

MR images and DW images were acquired during the same procedure. The MR imaging examination consisted of coronal T2-weighted half-Fourier single-shot turbo spin-echo (HASTE) multi breathhold images, axial T2-weighted turbo spin-echo (TSE) BLADE images, axial T2-weighted images with fat saturation, axial dual echo T1-weighted gradient-echo images, axial DW images, and axial 3D fat suppressed T1-weighted gradient echo (VIBE: Volume Interpolated Breathhold Examination) images. All pulse sequence parameters used in this study are listed in detail in Table 1.

After the acquisition of precontrast routine sequences for renal MR imaging, DW images with three different b values (50,400, and 1000 s/mm²) were obtained in the axial plane using a single-shot multi-slice echoplanar imaging (EPI) sequence with spectral adiabatic inversion recovery fat suppression and the following parameters: repetition time/echo time, 5500/75 ms; EPI factor,122; field of view, 380×296 mm; matrix size,128×102; slice thickness, 5.0 mm; distance factor, 20%; averages, 4; reduction factor, 2; and receiver bandwidth, 2442 Hz/Px. The acquisition time for the DWI was 4min and 24 seconds.

Image interpretation

The ADC maps were automatically generated by using a monoexponential decay model including all three b-values at Siemens Software Version syngo MR B17. ADC values and signal intensity of normal renal parenchyma and solid components of the renal masses were determined as follows: Freehand (ROI)s covering the tumor was defined for the lesions detected on the diffusion images, while referring to the T2-weighted conventional sequence for verification of lesion boundaries. Diffusion-weighted images with $b = 50 \text{ s/mm}^2$ was used for the mixed cystic and solid lesions and $b=1000 \text{ s/mm}^2$ DWI was selected for the evaluation of solid lesions. On each slice, the high signal intensity of tumor boundaries was traced manually and ROIs were copied to the corresponding ADC map to measure ADC values. To measure SI values of normal renal parenchyma, ROIs were placed in the normal corticomedullary junction of the kidney. Signal intensities of normal kidney and papillary RCC were measured on $b=1000 \text{ s/mm}^2$ diffusion



images. Signal intensities of normal kidney and clear cell RCC was measured on b=50

s/mm² diffusion images.

Table 1. Pulse sequence parameters

	T2-weighted HASTE	T2- weighted TSE BLADE	T1- weighted GE (In-opp phase)	DWI EPI b=50, 400,1000 s/mm ²	T1-weighted 3D GE VIBE (dynamic)
Parameter					
Matrix (fr x p)	320x224	320x256	320x224	128x102	320x224
Slice thickness (mm)	5.0	7.0	5.0	5.0	3.0
Distance factor	20%	20%	20%	20%	20%
TR (ms)	1400	2500	206	5500	3.92
TE (ms)	93	89	TE (i) 2.46 TE (o) 6.15	75	1.39
Flip angle (degree)	180	140	70	-	9
Fat suppression		SPAIR	-	SPAIR	Q-fat sat
Reduction factor	2	2	2	2	2
NEX	1	1	1	4	1
Number of slices	30	30	35	25	64 (per phase)
FoV (mm)	380x380	380x380	380x224	380x296	380x308
Plane	Coronal	Transvers	Transvers	Transvers	Transvers
Band width (Hz/Px)	446	300	280	2442	400
Breathing control	Breath hold	Navigator	Breath hold	Free//Navigatr	Multibreath hold
Acquisition time (min:s)	0:42	4:32	0:40	4:24	1:08

Statistical analysis

Statistical analysis was performed using a commercially available software (Statistical Package for Social Sciences, version 15.0, SPSS Inc., Chicago, Illinois, USA). The results were reported as means±SD. The t test was used to compare the differences between mean ADC values obtained in papillary RCC and clear cell RCC groups. Also, significances of the differences between mean SI values at diffusion-weighted images with b = 50 s/ mm² of clear cell RCC and normal parenchyma were analyzed with t test. Significances of the differences between mean SI values at diffusion-weighted images with b = 1000 s/ mm² of papillary RCC and normal parenchyma were analyzed with paired t-test (paired samples t test). Significances of the differences between mean SI values at diffusion-weighted images with b = 400 s/ mm² of papillary RCC and normal parenchyma; clear cell RCC and normal parenchyma were analyzed with paired

t-test (paired samples t test). P values less than 0.05 were deemed to indicate a statistically significant difference.

Results

The mean ADC value was significantly lower in papillary RCC ($0.991 \pm 0.143 \times 10^{-3}$ mm²/s) than in that of clear cell RCC ($1.296 \pm 0.277 \times 10^{-3}$ mm²/s) (p<0.05) (Fig 1). For the papillary RCC group, there was statistically significant difference (p<0.05) between mean SI values of normal parenchyma (22.8 ± 6.3) and lesion (43.4 ± 14.8) at b=1000 s/mm² DWI; for the clear cell RCC group, there was statistically significant difference (p<0.05) between mean SI values of normal parenchyma (138.8 ± 33) and lesion (102 ± 27.5) at b=50 s/mm² DWI. For the papillary RCC group, there was not statistically significant difference (p>0.05) between mean SI values of normal parenchyma (62.5 ± 21.8) and lesion (75 ± 28.8) at b=400 s/mm² DWI. For the clear cell group, there was not statistically significant difference (p>0.05) between mean SI values of normal parenchyma



(58.8 ± 9.4) and lesion (54.1 ± 15.4) at $b=400$ s/mm² DWI.

The MRI findings of lesions are presented in Table 2. Examples of our cases is presented in Figs. 2 and 3.

Table 2. MRI findings of lesions

	T1- weighted GE	T2-weighted HASTE	T2- weighted TSE BLADE	DWI b=50 s/mm ²	DWI b=400 s/mm ²	DWI b=1000s/mm ²	ADC	T1-weighted 3D GE VIBE(dynamic)
1	Isointense	Hyperintense	Hyperintense	Isointense	Hyperintense	Hyperintense	Hypointense	Not performed
2	Isointense	Hypointense	Hypointense	Isointense	Hyperintense	Hyperintense	Hypointense	Not performed
3	Isointense	Hypointense	Hypointense	Isointense	Hyperintense	Hyperintense	Hypointense	Not performed
4	Iso-hypointense	Hypo-hyperintense	Hypo-hyperintense	Isointense	Hyperintense	Hyperintense	Hypointense	Not performed
5	Isointense	Hypointense	Hypointense	Isointense	Hyperintense	Hyperintense	Hypointense	Moderate enhancement
6	Isointense	Hypointense	Hypointense	Isointense	Hyperintense	Hyperintense	Hypointense	Moderate enhancement
7	Iso- hyperintense	Hypo- Hyperintense	Hypo- Hyperintense	Isointense	Hyperintense	Hyperintense	Hypointense	Not performed
8	Hypointense	Hypointense	Hypointense	Isointense	Hyperintense	Hyperintense	Hypointense	Not performed
9	Iso- hyperintense	Hypointense	Hypointense	Isointense	Hyperintense	Hyperintense	Hypointense	Moderate enhancement
10	Iso- hyperintense	Hypo- Hyperintense	Hypo- Hyperintense	Hypo- Hyperintense	Iso- hyperintense	Iso- hyperintense	Hypo- Hyperintense	Not performed
11	Iso-hypointense	Iso- hyperintense	Iso- hyperintense	Hypo- Hyperintense	Iso- hyperintense	Iso- hyperintense	Hypo- Hyperintense	Not performed
12	Hypointense	Hypo- Hyperintense	Hypo- Hyperintense	Hypo- Hyperintense	Iso- hyperintense	Iso- hyperintense	Hypo- Hyperintense	Not performed
13	Hypo- Hyperintense	Iso- hyperintense	Hypo- Hyperintense	Hypo- Hyperintense	Iso- hyperintense	Iso- hyperintense	Hypo- Hyperintense	Not performed
14	Hypo- Hyperintense	Iso- hypointense	Hipo- Hiperintens	Hypo- Hyperintense	Iso- hyperintense	Iso- hyperintense	Hypo- Hyperintense	Not performed
15	Iso-hypointense	Iso- hyperintense	Iso- hyperintense	Hypo- Hyperintense	Iso- hyperintense	Iso- hyperintense	Hypo- Hyperintense	Heterogen enhancement
16	Iso-hypointense	Iso- hyperintense	Iso- hyperintense	Hypo- Hyperintense	Iso- hyperintense	Iso- hyperintense	Hypo- Hyperintense	Heterogen enhancement



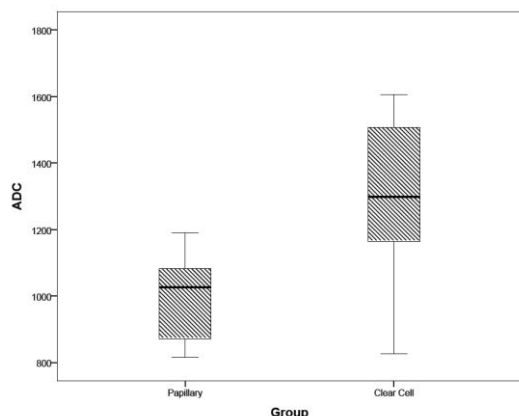


Figure 1. Graphic representation of the ADC values ($\times 10^{-3} \text{ mm}^2/\text{s}$) of papillary and clear cell RCC groups.

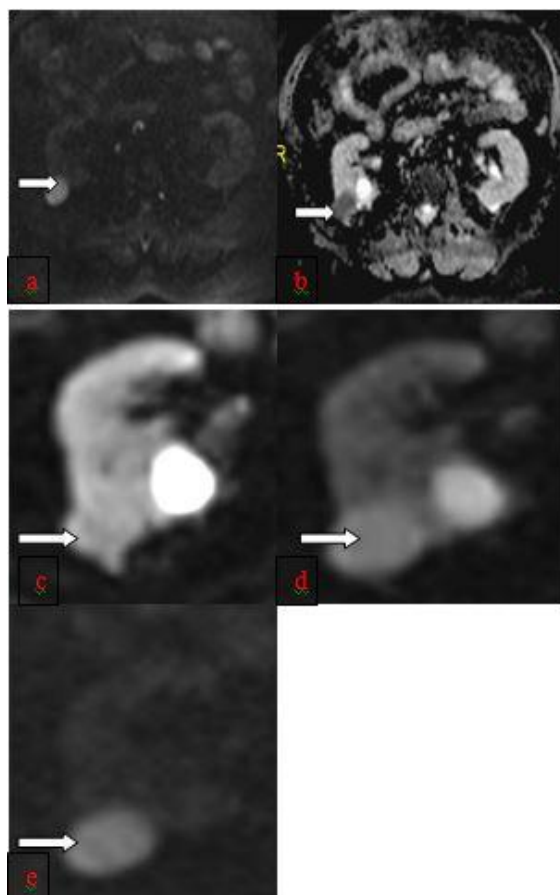


Figure 2. a–e. A 68 year-old-male with papillary RCC. Arrows show the tumor. (a) Axial DW imaging obtained with b value of 1000 s/mm^2 . Mean signal intensity value is measured 40. (b) ADC map shows that the ADC of the tumor is $0.90 \times 10^{-3} \text{ mm}^2/\text{s}$. (c) In DW images obtained with b value of 50 s/mm^2 the papillary RCC (showed with arrow) was hardly distinguishable from adjacent parenchyma (d) DW images obtained with b value of 400 s/mm^2 , (e) in DW images obtained with b value of 1000 s/mm^2 , the papillary RCC has

become more clearly visible by the suppression of the surrounding tissue.

Discussion

Recent studies suggested that DWI could provide comparable accuracy to contrast-enhanced MRI in identifying renal lesions (7,9). In our study, we found that the mean ADC value was statistically significantly lower in papillary RCC than in that of clear cell RCC. In a study conducted by Wang et al, clear cell RCCs demonstrated higher ADCs than papillary RCCs and chromophobic RCCs ; with b values of 0 and 800 s/mm^2 , papillary RCCs showed lower ADCs than chromophobic RCCs, while with b values of 0 and 500 s/mm^2 , no significant difference in ADC was seen between papillary RCCs and chromophobic RCCs (8). In the study of Paudyal et al, a significant difference in ADC values between clear cell carcinoma and non-clear cell carcinoma was found (10). Yu et al. presented that the ADC value was also statistically different between clear cell RCC and non-clear cell RCC, and between different grades of clear cell RCC except grade I vs II and grade III vs IV (11). Inci et al. found statistically significant difference with ADC values and b factors of 500 and 1000 in types of renal carcinoma, the mean ADC value of chromophobe cell carcinoma was significantly higher than that of papillary cell carcinoma and clear cell carcinoma (12). We did not evaluate chromophobe cell carcinoma, because we had only one patient with this subtype. Taouli et al. have reported that DW imaging can be used to characterize renal lesions; however, compared with contrast enhanced MR imaging, it is less accurate . Our study focused on the efficacy of DWI, the relationship between DWI and contrast enhanced MR imaging in differentiation of subtypes of renal cell carcinoma was not evaluated. In the study of Sandrasegaran et al, there was no significant difference between the ADCs of clear cell cancers and non-clear cell cancers (13). However, they used minimum ADC per lesion whereas we used mean ADC value.

A wide range in ADCs in subtypes of renal cell carcinoma has been reported in the literature: We found mean ADC value $0.991 \pm 0.143 \times 10^{-3} \text{ mm}^2/\text{s}$ in papillary RCC and $1.296 \pm 0.277 \times 10^{-3} \text{ mm}^2/\text{s}$ in clear cell RCC, which were different in the study of Yu et al ($1.053 \pm$



0.380 in papillary RCC and 1.469 ± 0.417 in clear cell RCC). This probably is caused by using different b values. The mean ADC values in our study were similar to the mean ADC values in the study of Inci et al. ($0.90 \pm 0.16 \times 10^{-3} \text{ mm}^2/\text{s}$ in papillary RCC and $1.23 \pm 0.13 \times 10^{-3} \text{ mm}^2/\text{s}$ in clear cell RCC). Zhang

et al. indicated that the ADC values measured with low b values showed high standard deviations (14).

In the study of Wang et al, higher b values than 800 s/mm^2 , such as 1000 s/mm^2 , were not selected because according to their experience, when a b value of 1000 sec/mm^2

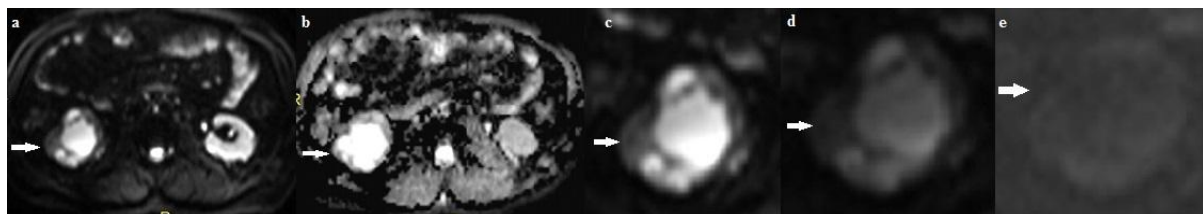


Figure 3. a–e. A 60 year-old-female with clear cell RCC. Arrows show the tumor with cystic and necrotic areas. (a) Axial DW imaging obtained with b value of 50 s/mm^2 . Mean signal intensity value is measured 98. (b) ADC map shows that the ADC of the tumor is $1.42 \times 10^{-3} \text{ mm}^2/\text{s}$. (c) In DW images obtained with b value of 50 s/mm^2 the clear cell RCC (showed with arrow) was clearly visible because of shining of cystic areas (d) DW images obtained with b value of 400 s/mm^2 (e) in DW images obtained with b value of 1000 s/mm^2 , the clear cell RCC was hardly distinguishable from adjacent parenchyma.

is used, the signal-to-noise ratio (SNR) of DW images decreases so significantly that part of the images cannot be evaluated. In our study, we used $b = 1000 \text{ s/mm}^2$ value because it seemed more appropriate for distinguishing RCC subtypes by using ADCs and we did not experience difficulties in analyzing images due to low SNR.

Different from the other studies, we also measured mean SIs on diffusion weighted images. For the papillary RCC group, there was statistically significant difference ($p < 0.05$) between mean SI value in $b = 1000 \text{ s/mm}^2$ values between normal parenchyma (22.8 ± 6.3 and lesion (43.4 ± 14.8). For the clear cell RCC group, there was statistically significant difference between mean SI value in $b = 50 \text{ s/mm}^2$ values between normal parenchyma (138.8 ± 33 and lesion (102 ± 27.5). This allows us to discriminate the lesion borders easily on $b = 1000 \text{ s/mm}^2$ diffusion images and on $b = 50 \text{ s/mm}^2$ diffusion images, respectively for papillary RCC and clear cell RCC.

In previous studies, investigators have evaluated the value of DWI in assessing the cellularity of renal masses. In the study of Squillaci et al, the mean ADC value of renal tumors did not significantly correlate with tumor cellularity (15). Rosenkrantz et al, have reported that ADC values, obtained with b

values 0 and 400 and 0 and 800 s/mm^2 , were lower among high-grade than among low-grade ccRCC (16).

Diffusion-weighted imaging has been limited due to its artifacts associated with respiratory motion, peristalsis and cardiac pulsations. Breath-hold EPI technique (17) which we also used in our study helps DWI to become feasible to cope such artifacts seen in abdomen imaging (18,19). Most of the recent studies on DWI usually performed with 1.5 T MRI system. In the present investigation, we used a 3-T MRI which had advantage of improved SNR compared to 1.5 T. However, comparative studies showed high correlation of the ADC values between both field strengths (20, 21).

Our study had some limitations. We assessed small number of patients in our study. Further studies with a large number of populations are necessary to confirm our findings. Several factors such as ROI shape, partial-volume effects, MRI equipment, intraobserver variability affect the ADC measurements (22,23). Possible measurement errors due to above-mentioned factors may lead to misdiagnoses and should be taken into consideration when DWI is used to discriminate the RCC subtypes.

Conflict of Interest: None



References

1. National Cancer Institute. Surveillance, Epidemiology, and End Results Program. SEER stat fact sheets: kidney and renal pelvis cancer, 2013.
2. Nickerson ML, Jaeger E, Shi Y, Durocher JA, Mahurkar S, Zaridze D, et al. Improved identification of von Hippel-Lindau gene alterations in clear cell renal tumors. *Clin Cancer Res* 2008; 14:4726–34.
3. Crepel M, Jeldres C, Perrotte P, Capitanio U, Isbarn H, Shariat SF, et al. Nephron-sparing surgery is equally effective to radical nephrectomy for T1BN0M0 renal cell carcinoma: a population-based assessment. *Urology* 2010; 75:271–5.
4. Holdsworth SJ, Bammer R. Magnetic resonance imaging techniques: fMRI, DWI, and PWI. *Semin Neurol* 2008; 28:395–406.
5. Koh DM, Collins DJ. Diffusion-weighted MRI in the body: applications and challenges in oncology. *AJR Am. J. Roentgenol* 2007; 188:1622–35.
6. Elmi A, Hedgire SS, Covarrubias D, Abtahi SM, Hahn PF, Harisinghani M. Apparent diffusion coefficient as a non-invasive predictor of treatment response and recurrence in locally advanced rectal cancer. *Clin Radiol* 2013; 68:524–531.
7. Taouli B, Thakur RK, Mannelli L, Babb JS, Kim S, Hecht EM, et al. Renal lesions: characterization with diffusion-weighted imaging versus contrast-enhanced MR imaging. *Radiology* 2009; 251:398–407.
8. Wang H, Cheng L, Zhang X, Wang D, Guo A, Gao Y, et al. Renal cell carcinoma: diffusion-weighted MR imaging for subtype differentiation at 3.0 T. *Radiology* 2010; 257:135–43.
9. Kim S, Jain M, Harris AB, Lee VS, Babb JS, Sigmund EE, et al. T1 hyperintense renal lesions: characterization with diffusion-weighted MR imaging versus contrast-enhanced MR imaging. *Radiology* 2009; 251: 796–807.
10. Paudyal B, Paudyal P, Tsushima Y, Oriuchi N, Amanuma M, Miyazaki M, et al. The role of the ADC value in the characterisation of renal carcinoma by diffusion-weighted MRI. *British Journal of Radiology* 2010; 83:336–43.
11. Yu X, Lin M, Ouyanga H, Zhou C, Zhang H, et al. Application of ADC measurement in characterization of renal cell carcinomas with different pathological types and grades by 3.0 T diffusion-weighted MRI. *European Journal of Radiology* 2012; 81:3061–3066.
12. İnci E, Hocaoglu E, Aydin S, Cimilli T. Diffusion weighted magnetic resonance imaging in evaluation of primary solid and cystic renal masses using the Bosniak classification. *Eur J Radiol* 2012; 81:815–20.
13. Sandrasegaran K., Sundaram P., Ramaswamy R. Akisik FM, Rydberg MP, Lin C, et al. Usefulness of Diffusion-Weighted Imaging in the Evaluation of Renal Masses *AJR* 2010; 194:438–445 .
14. Zhang JL , Sigmund EE , Chandarana H , Rusinek H, Chen Q, Vivier PH, et al . Variability of renal apparent diffusion coefficients: limitations of the monoexponential model for diffusion quantification. *Radiology* 2010 ; 254: 783 – 792.
15. Squillaci E, Manenti G, Di Stefano F, Miano R, Strigari L, Simonetti G. Diffusion-weighted MR imaging in the evaluation of renal tumours. *J Exp Clin Cancer Res* 2004; 23:39–45.
16. Rosenkrantz AB, Niver BE, Fitzgerald EF, Babb JS, Chandarana H, Melamed J. Utility of the apparent diffusion coefficient for distinguishing clear cell renal cell carcinoma of low and high nuclear grade. *American Journal of Roentgenology* 2010; 195:344–51.
17. Müller MF , Edelman RR . Echo planar imaging of the abdomen . *Top Magn Reson Imaging* 1995 ; 7 : 112 – 119 .
18. Matoba M , Tonami H , Kondou T , Yokota H, Higashi K, Toga H, et al . Lung carcinoma: diffusion-weighted MR imaging—preliminary evaluation with apparent diffusion coefficient . *Radiology* 2007 ; 243: 570 – 577 .
19. Inan N , Arslan A , Akansel G , Anik Y, Sarisoy HT, Ciftci E, et al . Diffusionweighted imaging in the differential diagnosis of simple and hydatid cysts of the liver . *AJR Am J Roentgenol* 2007; 189: 1031–1036 .
20. Cornfeld DM, Weinreb JC. MR imaging of the prostate: 1.5T versus 3T. *Magn Reson Imaging Clin N Am* 2007; 15:433–48. 40.
21. Habermann CR, Gossrau P, Kooijman H, Graessner J, Cramer MC, Kaul MG, et al. Monitoring of gustatory stimulation of salivary glands by diffusion-weighted MR imaging: comparison of 1.5T and 3T. *AJNR Am J Neuroradiol* 2007; 28:1547–51.
22. Feuerlein S, Pauls S, Juchems MS, Stuber T, Hoffmann MH, Brambs HJ, et al. Pitfalls in abdominal diffusion-weighted imaging: how predictive is restricted water diffusion for malignancy. *AJR Am Roentgenol* 2009; 193:1070–1076.
23. Le Bihan D, Poupon C, Amadon A, Lethimonnier F. Artifacts and pitfalls in diffusion MRI. *J Magn Reson Imaging*. 2006; 24:478–88.



Intraoral Reconstruction with Microsurgical Free Flaps

Serbest Fleplerle Ağız İçi Defektlerinin Rekonstrüksiyonu

Hakan Uzun¹, Ozan Bitik², Ela Cömert³, Caner Kılıç³, Samet Özlügedik³, Ümit Tunçel³

¹Dr. A. Y. Ankara Oncology Training And Research Hospital, Plastic Reconstructive and Aesthetic Surgery, Ankara, Turkey

²Hacettepe University Faculty of Medicine, Department of Plastic Reconstructive and Aesthetic Surgery, Ankara, Turkey

³Dr. A. Y. Ankara Oncology Training And Research Hospital, Department of Otorhinolaryngology, Ankara, Turkey

Received: 29/04/2015 Accepted: 05/05/2015 Doi: [10.5505/aot.2015.02986](https://doi.org/10.5505/aot.2015.02986)

ÖZET

Amaç: Yazarlar, tek bir merkezde intraoral bölge için gerçekleştirilen serbest flep rekonstrüksiyonlarını değerlendirmeyi amaçlamışlardır.

Yöntemler: Baş boyun bölgesindeki defektlerin rekonstrüksiyonu için 4 yıllık süre içinde onbir tane serbest doku nakli gerçekleştirildi. Hastalar, defekt lokalizasyonu, uygulanan flepler, komplikasyonlar ve hastanede yatış süreleri açısından değerlendirildi.

Bulgular: Yedi hasta serbest radial önkol flebi ile, iki hasta serbest vertikal rektus abdominis muskulokütan flebi ile, bir hasta serbest transvers rektus abdominis muskulokütan flebi ile bir hasta da serbest fibula osteomuskulokütan flebi ile rekonstrükte edildi. Fleplerin hiçbirinde anastomozda tromboz veya hematoma nedeniyle reeksplorasyon yapılmadı. Flep kaybı görülmedi. Mortalite veya major morbidite ile karşılaşılmadı. Ortalama hastanede yatış süresi 21.1 gündü (11-25 gün).

Sonuç: Ağız içi defektlerinin rekonstrüksiyonu için multidisipliner yaklaşım desteklenmelidir. Uzun ameliyat süresi, donör alan morbiditesi ve mikrocerrahi başarısızlığı gibi riskleri olmasına rağmen serbest doku nakilleri birçok kompleks defektin onarımına olanak sağlamaktadır.

Anahtar Kelimeler: serbest flep; intraoral rekonstrüksiyon; mikrocerrahi.

ABSTRACT

Objective: The authors aimed to evaluate the outcomes of free flap reconstructions performed for intraoral region in a single center.

Methods: Eleven free flaps have been performed for defects of the head and neck over a 4-year period. The patients were evaluated in terms of defects, flaps performed, complications and hospital stays.

Results: Seven patients were reconstructed with radial forearm free flap, one patient was reconstructed with free transverse rectus abdominis musculocutaneous flap, two patients were reconstructed with free vertical rectus abdominis musculocutaneous flap and the remaining one was reconstructed with free fibula osteomuskulocutaneous flap. None of the flaps required reexploration for anastomotic thrombosis or hematoma. No flap failure occurred. We did not encounter any mortality or major morbidity. The average hospital stay was 21.1 days with a range from 11 to 25 days.

Conclusions: Multidisciplinary approach should be encouraged for the reconstruction of intraoral defects. The versatility of free tissue transfers allows reconstruction of most complex defects; although it carries significant risks, including longer operative times, donor site morbidity, recipient site complications and microsurgical failure, and longer hospital stays.

Keywords: free flap, head and neck oncology, intraoral reconstruction, microsurgery.

Introduction

Since the development of free tissue transfer and microsurgical techniques in the 1980s, microvascular free flap tissue transfers have largely become the gold standard for reconstruction of complex head and neck

defects¹⁻³. One distinct advantage of free tissue transfer is its utility (surface area, volume, vascularity, diversity of tissue type) when compared to local or regional tissue transfer. As a result, a large variety of defect dimensions and locations can be reconstructed, allowing for larger oncologic resections,

improved tissue coverage and lower patient morbidity.

Over time, there have been significant changes in reconstructive techniques, with gravitation towards a narrower set of donor sites and a reduction in complication rates^{4,5}. The selection and outcomes of free tissue transfers in head and neck reconstructions were evaluated in this study. Outcomes were based on donor and recipient site and indication for reconstruction. Despite the widespread use of this technique in the head and neck, not all free flap donor sites or recipient sites are equivalent. Furthermore, a single percentile to describe failure rates is misleading. We evaluated patients who presented for a microvascular free flap reconstruction of a complex head and neck defect in order to better understand the potential risks and benefits of each type of free tissue transfer.

Methods

Patient Selection

The patients who presented between March 2011 and April 2015 for a microvascular free flap reconstruction of a head and neck defect were included (n=11). The selection of the donor site depended on the defect (cutaneous, soft tissue, or bone), and surgeon preference. Demographic characteristics examined included: surgical indication, duration of hospital stay, and complications.

Results

Patient and Flap Characteristics

All of the patients were males with a mean age of 54. Indications for reconstruction

included defect following resection of a primary or recurrent malignancy (75%, n=6), a secondary reconstruction (25%, n=5). The distribution of microvascular free flaps used for reconstruction of the defects was as follows: radial forearm fasciocutaneous flap (RFFF) (63,6%, n=7), vertical rectus abdominis musculocutaneous (VRAM) flap (18,2%, n=2), transverse rectus abdominis musculocutaneous (TRAM) flap (9,1%, n=1), and free fibula osteomusculocutaneous flap (9,1%, n=1). Ipsilateral facial artery and its venae comitantes were used for microsurgical anastomosis. In one patient contralateral facial vessels were dissected. One patient who previously underwent bilateral neck dissection and radiotherapy required saphenous vein grafts due to the unavailability of facial vessels. Superior thyroid vessels were chosen for anastomosis in that case. One artery and one vein anastomosis were performed for each flap. Aside from rectus flaps, two-team approach was used. The average hospital stay was 21.1 days with a range from 11 to 25 days.

Defect Characteristics

All of the patients had squamous cell carcinoma. Two patients had cancers located on floor of the mouth (Figure 1). One patient had cancer located over the palatopharyngeal fold which extended to lateral and posterior parts of the tongue. They were reconstructed with free RFFF (Figure 2). Two patients underwent partial glossectomy and functional surgery with RFFF was contemplated. One patient underwent hemimandibulectomy and was reconstructed with free fibula osteomusculocutaneous flap (Figure 3). Four patients required release of adhesions between base of tongue and lower lip. Three rectus abdominis flaps and one RFFF were utilized to create new sulcus and lower lips.

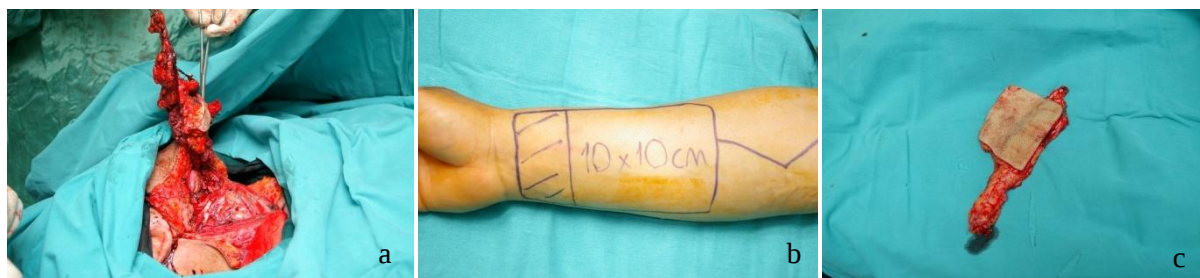


Figure 1a: The defect of the floor of the mouth just before the the specimen was resected en bloc **b:** Planning of the RFFF **c:** Harvested RFFF



Figure 2a: The 3D defect of the palatopharyngeal region, retromolar region and lateral part of the floor of the mouth exposing carotid vessels. **b:** Planning of the RFFF **c:** Insetting of the RFFF **d:** Postoperative 14th day appearance

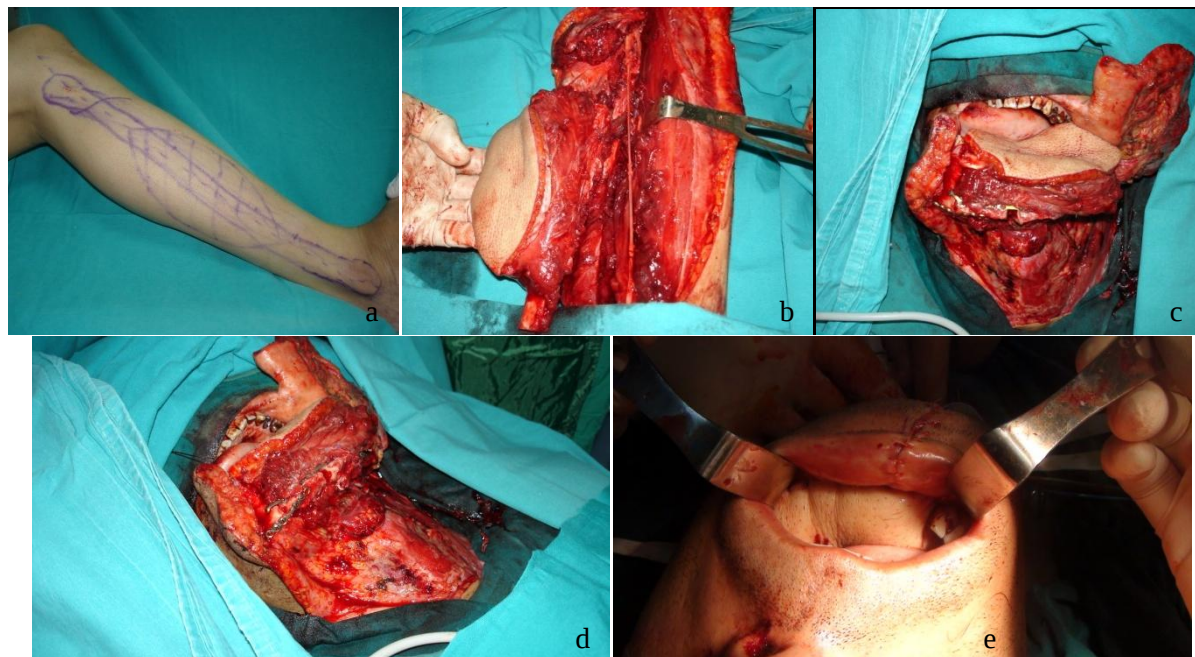


Figure 3a: Planning of the fibula osteomusculocutaneous flap **3b:** Harvesting of the flap **c:** Insetting the skin island of the flap **d:** Two osteotomies were performed on the flap to create the neoangulus of the mandible **e:** Early postoperative result

Complications

All of the free flaps survived. Neither mortality nor major morbidity was developed. None of the flaps required reexploration for

anastomotic thrombosis or hematoma. The surgical complication rate was 18,2%. This included haematoma formation under the neck

flaps (9,1%, n=1), and graft infection at the donor area of the fibula flap (9,1%, n=1).

Discussion

The versatility of free tissue transfers allows reconstruction of most complex defects; however, it carries significant risks, including longer operative times, donor site morbidity, recipient site complications and free flap failure, and longer hospital stays. As a result, careful consideration and evaluation is necessary prior to reconstruction. Several variables dictate donor site selection including tissue composition, extent of defect, distance from recipient vessels, and surgeon preference.

The most commonly utilized flap in our series was the RFFF. In 1981, Yang et al⁶ were among the first to use the radial forearm flap in head and neck surgery, and this RFFF is nowadays a workhorse in reconstructive head and neck surgery. The RFFF along with the anterolateral thigh flap (ALT) can be considered the workhorses for reconstructing upper aerodigestive tract defects⁷. It is commonly used for tongue, floor of mouth, lip and hard palate reconstruction. Its greatest advantage is the thin and pliable nature of the flap ideal for intraoral soft tissue lining defects. Its ease of harvest and long pedicle (about 20 cm) with large caliber vessels makes it popular with beginners. It can be harvested by two-team approach. Other advantages are the presence of large diameter superficial veins (cephalic or basilic) and deep venous system (the venae comitantes). Studies have shown that the smaller venae comitantes give reliable venous outflow but due to their smaller caliber, anastomosis is difficult compared to the cephalic vein⁸. There still is a debate regarding which is the dominant venous system. Ichinose et al.⁹ used Doppler to demonstrate the venae comitantes to be dominant. They theorized that interruption of small superficial venous channels draining into cephalic vein during flap harvest would force venous drainage more into the deep system. In our series we used a more clinical way of judgment. After flap harvest, the artery was anastomosed first and venous return was noted from both the superficial and deep systems. Whichever had a faster outflow was used for anastomosis.

Bianchi et al.¹⁰ and Kesting et al.¹¹ reported several advantages of the ALT flap for head and neck defects, including versatility, short harvesting time, and donor site morbidity. However, Kesting et al.¹¹ reported that intra-operative arterial spasms occurred more often in the case of the ALT free flap than in the case of RFFF.

Because of its safety, versatility, and predictable anatomy, the VRAM has become a work horse flap for reconstruction throughout the body and within the head and neck region¹². It has an unparalleled safety record with the lowest vessel thrombosis and flap failure rates¹³. The flap has a lengthy vascular pedicle for anastomosis to either side of the neck and the large caliber of the inferior epigastric vessels makes microsurgical coaptation straightforward. Primary donor-site closure for very large VRAMs can be achieved without the need for mesh or an additional skin graft. The remote location from the head and neck region saves operative time by permitting simultaneous flap elevation while the ablative portion of the procedure is performed. Patients with oropharyngeal cancer have generalized cachexia in addition to soft tissue deflation from neck dissections and prior radiation. Although native neck tissues are generally thin, the extra volume provided by both the rectus muscle and subcutaneous tissue of the VRAM fills this contour deformity, replaces unstable irradiated tissues, and provides coverage of the large neck vessels.

Fibula MFF was first introduced for OMF reconstruction by Hidalgo and is now considered as the gold standard for mandibular reconstruction¹⁴. The advantages of fibula include the length of bone available (around 25-30 cm), which permits multiple osteotomies and provides adequate pedicle length even for maxillary reconstruction. The peroneal artery and vein are usually of good quality and caliber and ideal for anastomosis to the neck vessels. Due to the distance from the recipient site, two team approach can be used thus greatly reducing operative time.

Our study has several limitations. First, the sample size of our study was small compared to that of the other studies on this topic. Second, we could not evaluate the outcomes in terms of functional aspects and

patients satisfaction.

Radical resection of tumors of the head and neck with immediate reconstruction by microsurgical free tissue transfer followed by adjuvant radiation therapy provides the best possible chance for cure and functional and social rehabilitation of the patient.

Conflict of Interest: None

References

1. Nakatsuka T, Harii K, Asato H, et al. Analytic review of 2372 free flap transfers for head and neck reconstruction following cancer resection. *J Reconstr Microsurg* 2003; 19:363–368. discussion 369
2. Rinaldo A, Shaha AR, Wei WI, Silver CE, Ferlito A. Microvascular free flaps: a major advance in head and neck reconstruction. *Acta Otolaryngol* 2002; 122:779–784
3. Seidenberg B, Hurwitt ES. Immediate reconstruction of the cervical esophagus by a revascularized isolated jejunal segment. *Surg Forum* 1958; 9:413–416
4. Rosenthal E, Carroll W, Dobbs M, Scott Magnuson J, Wax M, Peters G. Simplifying head and neck microvascular reconstruction. *Head Neck* 2004; 26:930–936
5. Disa JJ, Cordeiro PG. Mandible reconstruction with microvascular surgery. *Semin Surg Oncol* 2000; 19:226–234
6. Yang GF, Chen PJ, Gao YZ, et al. Forearm free skin flap transplantation: a report of 56 cases. 1981. *Br J Plast Surg* 1997;50:162Y165
7. Lueg EA. The anterolateral thigh flap: Radial forearm's "big brother" for extensive soft tissue head and neck defects. *Arch. Otolaryngol Head Neck Surg* 2004;130:813-8
8. Lim YS¹, Kim JS¹, Kim NG¹, Lee KS¹, Choi JH¹, Park SW². Free Flap Reconstruction of Head and Neck Defects after Oncologic Ablation: One Surgeon's Outcomes in 42 Cases. *Arch Plast Surg* 2014 Mar;41(2):148-52
9. Ichinose A¹, Terashi H, Nakahara M, Sugimoto I, Hashikawa K, Nomura T, Ogata N, Yokoo S, Tahara S. Do multiple venous anastomoses reduce risk of thrombosis in free-flap transfer? Efficacy of dual anastomoses of separate venous systems. *Ann Plast Surg* 2004 Jan;52(1):61-3
10. Bianchi B, Ferri A, Ferrari S, et al. The free anterolateral thigh musculocutaneous flap for head and neck reconstruction: one surgeon's experience in 92 cases. *Microsurgery* 2012; 32:87-95
11. Kesting MR, Holzle F, Wales C, et al. Microsurgical reconstruction of the oral cavity with free flaps from the anterolateral thigh and the radial forearm: a comparison of perioperative data from 161 cases. *Ann Surg Oncol* 2011;18:1988-94
12. Matros E, Cordeiro P. Single-Stage Reconstruction of Composite Central Neck Defects With the Double-Island Vertical Rectus Abdominis Musculocutaneous Flap. *Ann Plast Surg* 2011;66: 164–167
13. Kroll SS, Schusterman MA, Reece GP, et al. Choice of flap and incidence of free flap success. *Plast Reconstr Surg* 1996;98:459–463
14. Urken ML, Buchbinder D, Weinberg H, Vickery C, Sheiner A, Parker R, et al. Functional evaluation following microvascular oromandibular reconstruction of the oral cancer patient: A comparative study of reconstructed and non reconstructed patients. *Laryngoscop* 1991;101:935-50

First-line cisplatin plus bolus 5- Fluorouracil combination in patients with locally advanced and metastatic esophageal cancer (Izmir Oncology Group Study)

Lokal ileri ve metastatik özefagus kanserli hastalarda ilk hat bolus 5-Fluorourasil sisplatin kombinasyonu (İzmir Onkoloji Grubu Çalışması)

Murat Akyol, Yüksel Küçükzeybek, Umut Varol, İbrahim Yıldız, Suna Çokmert, İbrahim Vedat Bayoğlu, Yaşar Yıldız, Lütfiye Demir, Alper Can, Ahmet Dirican, Ahmet Alacacioğlu, Mustafa Oktay Tarhan
İzmir Katip Çelebi Üniversitesi Atatürk Eğitim Ve Araştırma Hastanesi, izmir

Received: 10/03/2015 Accepted: 19/05/2015 Doi: 10.5505/aot.2015.92408

ÖZET

Amaç: Sitotoksik kemoterapi, lokal ileri ve metastatik özefagus kanserinin standart tedavisidir. Biz bu çalışmada lokal ileri ve metastatik özefagus skuamoz hücreli kanserde birinci basamakta sisplatin ve kısa süreli infüzyonel 5-florourasil (5-FU) kombinasyonunun yararlarını ve yan etkilerini değerlendirdik.

Yöntem: Bu çalışmada, retrospektif olarak aralık 2006 ve temmuz 2013 tarihleri arasında sisplatin ve kısa süreli infüzyonel 5-florourasil (5-FU) kombinasyonu ile tedavi edilen daha önceden tedavi almamış lokal ileri veya metastatik özefagus skuamoz hücreli kanserli hastaları değerlendirdik. Kemoterapi rejimi olarak sisplatin 75 mg/m² d1 (1-3-saat infüzyon), kalsiyum lökoverin 60 mg/m² d1-2 ve 5-FU 500 mg/m² d1-2 (15-dakika infüzyon) 14 günde bir uygulandı.

Bulgular: Hastaların 14'ü (%51.9) erkek ve 13'ü (%48.1) kadın olup ortalama yaş 57 (39-80) idi. ECOG performans skoru 20 (%77) hastada 0 veya 1 iken diğer hastalarda 2 olarak bulundu. Tanı anında 10 hasta uzak metastaza sahipken 17 hasta lokal ileri hastalığa sahipti. Hastalar medyan 4 kür kemoterapi aldı. Tüm yanıt oranı %44.4'tü. (8 hastada parsiyel yanıt, 4 hasta komplet yanıt) ve 7 (%25.9) hasta stabil hastalığa sahipti. Hastalık kontrol oranı %70.3'tü. Hastaların medyan progresyonsuz sağkalımı 6.2 (%95 CI: 5.13 7.28) ve medyan genel sağkalımı 11.1 (%95 CI: 7.77-14.5) aydı. Hastaların % 40.7'sinde grade 3-4 nötropeni ve % 11.1'inde grade 3-4 trombositopeni saptandı.

Sonuç: Sisplatin ve kısa süreli infüzyonel 5-florourasil (5-FU) kombinasyonu ilaç infüzyonu için kateter gerektiren infüzyonel rejime alternative bir tedavi olarak düşünülebilir.

Anahtar Kelimeler: Özefagus kanseri, lokal ileri, metastatic, sisplatin, 5-florourasil

ABSTRACT

Objective: Cytotoxic chemotherapy is the basic treatment for locally advanced and metastatic esophageal cancer. We evaluated the benefits and side effects of the first-line short-term infusional 5- Fluorouracil (5-FU) and cisplatin combination regimen in patients with locally advanced and metastatic esophageal squamous cell cancer.

Methods: We retrospectively reviewed the untreated locally advanced or metastatic squamous cell esophageal cancer patients treated with short-term infusional 5-FU and cisplatin combination between December 2006 and July 2013. Chemotherapy regimen was administered as; cisplatin 75 mg/m² on day 1 (1-3-h infusion), ca-leucovorin 60 mg/m² d1-2 and 5-FU 500 mg/m² d1-2 (15-min infusion) every 14 days.

Results: There were 14 (51.9%) male and 13 (48.1%) female patients. The median age was 57 (range, 39-80) years. Twenty patients had an Eastern Cooperative Oncology Group performance status of 0 to 1 (77%), while the rest had PS of 2 (23%). At first diagnosis, 10 patients had distant metastases and 17 patients had localized disease. In total, 27 patients were treated with a median of four cycles. The overall response rate was 44.4% (8 partial responses, 4 complete responses) and 7 patients (25.9%) had stable disease. The disease control rate was 70.3%. Median progression free survival was 6.2 (95% CI: 5.13 7.28) months and median overall survival was 11.1 (95% CI: 7.77-14.5) months. Among the patients, 40.7% of them had grade 3-4 neutropenia, 11.1% of those patients had grade 3-4 thrombocytopenia.

Conclusion: Short-term infusional 5-FU and cisplatin combination regimen can be considered as an alternative treatment to an infusion regimen in which a catheter is necessary for the drug infusion.

Key words: Esophageal cancer, locally advanced, metastasis; cisplatin; 5- Fluorouracil



Introduction

Esophageal cancer is among the main causes of cancer death worldwide because of its extremely aggressive nature and poor survival rate. Approximately half of the patients with localized esophageal cancer die within the first 2 years following tumor resection due to progression to metastatic disease. Cancer of the esophagus typically occurs in one of two forms; upper two-thirds is a squamous cell carcinoma (SCC) and lower one-third is an adenocarcinoma. It is assumed that there are complete differences between esophageal adenocarcinomas and squamous cell cancer, such as the treatment protocol and prognosis.(1,2,3)

Cytotoxic chemotherapy is the most effective treatment modality for esophageal cancer patients with metastatic disease.(4) Grunberger et al. have showed that palliative chemotherapy can prolong the survival of metastatic esophageal cancer patients, relieve their symptoms and improve their quality of life. Nevertheless, no optimizing chemotherapy regimen has been developed for either locally advanced or metastatic disease and especially for squamous cell cancer (SCC) histology.(5) Numerous single agents and combination chemotherapy regimens have been evaluated in patients with metastatic carcinoma of the esophagus and combination therapies have been shown to be superior to monotherapies. Cisplatin-based combinations are well reported to show high response rates (15%-53%) and median survival durations range from 3.2 to 9.8 months. Cisplatin in combination with various drugs like bleomycin, vinorelbine and etoposide were tested.(6,7,8,9) However, the combination of cisplatin plus 5-Fluorouracil (5-FU) has been one of the most commonly used regimens in both metastatic and localized esophageal cancer due to its activity and well-established toxicity profile. Currently, cisplatin and infusional 5-FU regimen is considered to be standard therapy for the first-line treatment of metastatic esophageal cancer patients in many centers.(10,11,12) Addition of taxanes or anthracyclins to combination regimens can provide a statistically significant improvement in esophagogastric adenocarcinoma subtype. But the efficacy of triplet regimens in squamous subtype is not clear.(13,14)

In particular, many studies regarding infusional 5-FU regimens in gastrointestinal

and head-neck cancers showed more frequent catheter-related complications (infection and venous thrombosis).(15,16) So, we aimed to investigate the efficiency of short-term infusion of 5-FU and cisplatin combination in previously untreated patients with metastatic esophageal squamous cell cancer.

Materials and Methods

Patients

The data of 27 patients diagnosed with locally advanced or metastatic esophageal squamous cell cancer and presenting at the Medical Oncology Outpatient Clinic of Izmir Katip Celebi University Ataturk Training and Research Hospital between December 2006 and July 2013 were evaluated retrospectively. We included the patients treated with short-term infusional 5-FU and cisplatin combination in previously untreated locally advanced or metastatic esophageal squamous cell cancer, because they could not be treated with the 5-day infusion due to catheter-associated problems and social issues. Other inclusion criteria were Eastern Cooperative Oncology Group (ECOG) performance score (PS) of 0 to 2 (17) and adequate hepatic, renal, and marrow function (leukocyte count $> 3000/\text{L}$, absolute neutrophil count $> 1500/\text{uL}$, platelet count $\geq 100,000/\text{L}$, total bilirubin ≤ 1.5 times the institutional upper limits of normal and creatinine $\leq 1.5 \text{ mg/dL}$).

Treatment Plan

Chemotherapy regimen was administered as; cisplatin 75 mg/m^2 on day 1 (1-3-h infusion), ca-leucovorin 60 mg/m^2 d1-d2 and 5-FU 500 mg/m^2 d1-d2 (15-min infusion). Cisplatin was given with pre- and post-hydration and furosemide-induced diuresis. The regimen was repeated every 14 days. Before chemotherapy, standard premedication procedures were performed. Dose modifications were made according to nadir count of previous cycles. Cisplatin dose was reduced by 25% and 5-FU by 50% in case of leukocyte count $< 1 \times 10^9/\text{L}$ or platelet nadir $< 5 \times 10^9/\text{L}$. Cisplatin was stopped if serum creatinine $> 3 \text{ mg/dL}$ or creatinine clearance $< 40 \text{ mL/min}$.

Response Evaluation and Toxicity

Baseline tumor assessment was performed in all patients via abdominopelvic computed tomography (CT) and magnetic resonance imaging, and chest CT to rule out



other metastases. Radiological assessment was repeated every 8-10 weeks or every four-six cycles of therapy until progressive disease (PD) or cessation of chemotherapy. If a patient's disease was in response or stable at the time of treatment withdrawal, the patient was observed every 6-8 weeks until PD.

Progression free survival (PFS) was the investigated primary endpoint, which was defined as the time from the start of first-line cisplatin plus 5-FU treatment to the first documentation of progression. First documentation of progressive disease was based on the definition of PD in the RECIST (Response Evaluation Criteria in Solid Tumors 1.1) guidelines (18) and death as a result of any cause in the absence of previously documented PD. We censored the last clinical visit data for patients that died without known progression. Response duration was measured from the day of its initial documentation until confirmed disease progression and overall survival (OS) was measured from the initiation of treatment to death or to the last follow-up assessment. Patients were evaluated for hematological and nonhematological toxicities and were graded according to the National Cancer Institute (NCI) Common Toxicity Criteria, version 3.0 (19).

Statistical Analysis

The primary objective was the activity evaluated as overall response rate (ORR) (complete + partial response). PFS and OS were calculated using the Kaplan-Meier method. The SPSS software (ver. 15.0) was used for statistical analysis. Quantitative data are presented as the means, standard errors, medians, minimums and maximums; the results of qualitative analyses are presented as frequencies and percentages.

Results

Patients

We retrospectively reviewed the data of 27 patients with a diagnosis of locally advanced or metastatic esophageal squamous cell cancer presenting. There were 14 (51.9%) male and 13 (48.1%) female patients. The median age was 57 (range, 39-80) years. Twenty patients had an ECOG PS of 0 to 1 (77%), while the rest had PS of 2 (23%). Nearly half of the patients (n:13, 48%) had moderate differantation, 2 patients had well differantation, 9 patients had poor

differantation and 3 patient could not be evaluated. At first diagnosis, 10 patients had distant metastases and 17 patients had localized disease. Primer tumor localizations were upper esophagus in 14 (51.9%) patients, middle esophagus in 9 (33.3%) patients and lower esophagus in 4 (14.8%) patients. Patient characteristics are shown in *Table 1*.

Table 1. Patient characteristics and treatment details

Clinical findings	No. of patients	%
<i>Age (years)</i>		
Median	57	
Range	39-80	
<i>ECOG Performance status</i>		
0	10	(38.5)
1	10	(38.5)
2	6	(23.0)
<i>Tumor Differantation</i>		
Well	2	(8.3)
Moderate	13	(54.2)
Poor	9	(37.5)
<i>Primary tumor location</i>		
Upper	14	(51.9)
Middle	9	(33.3)
Lower	4	(14.8)
<i>Stage at first diagnosis</i>		
Localised	17	(63.0)
Metastatic	10	(37.0)
<i>Metastatic sites</i>		
0 or 1	18	(66.0)
≥2	9	(33.0)
Treatment		
<i>Prior surgery</i>		
No surgery	13	(48.1)
R0	11	(40.8)
R1-2	3	(11.1)
<i>Prior radiotherapy</i>		
No radiotherapy	16	(59.3)
Neoadjuvant	5	(18.5)
Primary definitive	3	(11.1)
Adjuvant	3	(11.1)
<i>Time from surgery to metastasis</i>		
Median, month	14.7	
Range	2-70	

ECOG PS= Eastern Cooperative Oncology Group performance status

Treatment Modalities

The median number of chemotherapy courses for the entire group was four (range, 2



to 12). Fourteen patients had previous surgery while 11 patients had previous radiotherapy before metastatic disease. Only 3(11.1%) of 11 patients had adjuvant radiotherapy for R1-R2 resection after surgery while 5(18.5%) patients had radiotherapy as neoadjuvant treatment. None had received prior chemotherapy for metastatic disease.

Response Rates and Toxicity

The overall response rate (ORR) was 44.4% (8 partial responses, four complete responses). Seven patients (25.9%) had stable disease and the disease control rate was 70.3%. Response rates to treatment are shown in Table 2. The most common reason for treatment withdrawal was disease progression.. The most common grade 3-4 toxicities were neutropenia. While 40.7% of the patients had grade 3-4 neutropenia, 11.1% of those patients had grade 3-4 thrombocytopenia. The most common non-hematologic toxicities were nausea/vomiting and less commonly mucositis. There was no treatment-related death. Table 3 lists the common treatment-related toxicities.

Table 2. Objective response, clinical benefit and disease control rates

Response	No. of patients	%
Objective response	12	44.4
Complete response	4	14.8
Partial response	8	29.6
Stable disease for ≥ 3 months	7	25.9
Disease control rate	19	70.3

Table 3. Hematologic and non-hematologic toxicity profiles.

Toxicity	Grade 1-2		Grade 3-4	
	No.of patients	(%)	No.of patients	(%)
<i>Hematological</i>				
Anemia	20	(74.1)	1	(3.7)
Nötropenia	10	(37)	11	(40.7)
Thrombocytopenia	4	(14.8)	3	(11.1)
<i>Non-hematological</i>				
Mukocyt mucositis	9	(33.3)	2	(7.4)
Nause/vomiting	14	(51.9)	3	(11.1)
Diarrhea	3	(11.1)	0	(0)

Survival Analysis

Median follow-up was 15.0 months (range, 3-95 months). Median time from operation to the first development of metastases was 14.7 months (range, 2-70 months). Median PFS was 6.2 months (95% CI: 5.13-7.28) and median OS was 11.1 months (95% CI: 7.77-14.5). The PFS curve is shown in Figure 1 and the OS curve in Figure 2. By the time the data were reviewed, 22 patients (81.5%) had died and 23 patients (85.2%) had progressed.

Figure 1. Progression-free survival curve of the metastatic esophagus cancer patients treated with first-line cisplatin plus 5-FU

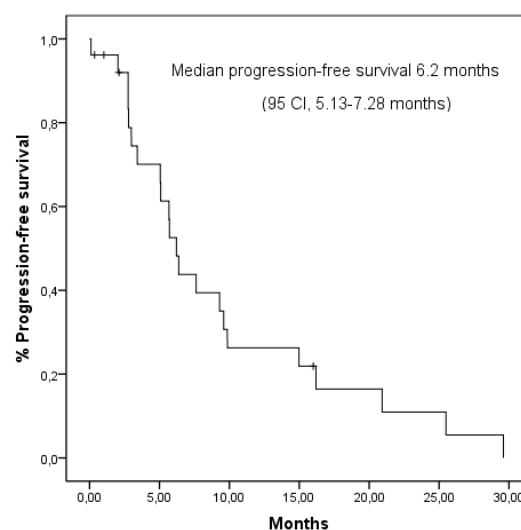
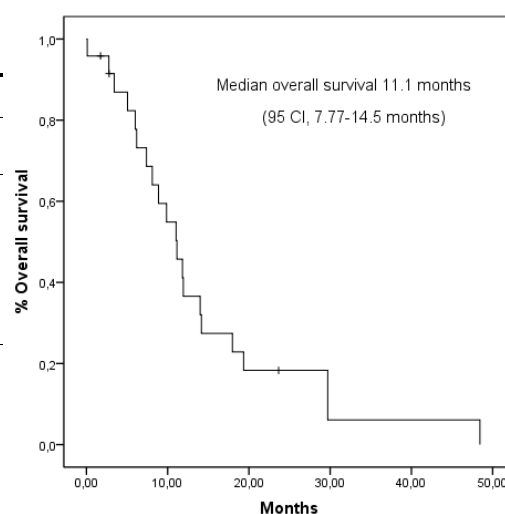


Figure 2. Overall survival curve of the metastatic esophagus cancer patients treated with first-line cisplatin plus 5-FU



Discussion

The role of chemotherapy has been poorly investigated in patients with advanced esophageal cancer. When we reviewed the literature, we found that trials relevant to chemotherapy have poor quality. Because they included small number of patients and the histologic types of esophageal cancer was not (adenocarcinoma and SCC) taken into account. (20,21) Although combination chemotherapies seem superior to monotherapies, the gain in response might be counterbalanced by a decreased tolerability or an increased toxicity. Therefore, even now, the benefit of chemotherapy in patients with disseminated disease is far from being proven and the prognosis of patients with advanced esophageal carcinoma is still poor. (22)

Currently, cisplatin and 5-FU combination is considered the standart regimen for patients with esophageal carcinoma. In a phase 2 study, H.Bleiberg et al. investigated 88 patients with locally advanced or metastatic squamous cell carcinoma of the oesophagus and treated them with cisplatin 100 mg/m² combined with 5-FU at a dose of 1000 mg/m² as a continuous infusion from days 1-5 (Arm A) or with cisplatin alone (Arm B) every 3 weeks. The response rate was 35% in Arm A and 19% in Arm B. The median duration of survival was 33 weeks and 28 weeks for Arm A and Arm B, respectively. Haematological and non-haematological toxicities were more frequent and more severe in Arm A. Grade 3-4 neutropenia was observed in 14% of patients and vascular trombotic events occurred in 9% patients. (22) Kies et al. and Ajani et al. have both reported high response rates of about 60% for resectable or localized tumors with cisplatin and 5-FU combination. However, Iizuka et al reported a response rate of only 35.9% with the same combination for patients with metastatic, recurrent, or bulky unresectable esophageal cancer. (23,24)

Jacqueline et al. in a phase 3 randomized study, compared the efficacy and toxicity of cisplatin plus bolus 5-FU versus infusional 5-FU as a first-line treatment in 232 patients with advanced esophageal, gastric and pancreatic cancer. Among the patients, only 38 of them were esophageal cancer while 19 had squamous cell histology. Most of the patients were gastric and pancreatic cancer. In this study, at first cycle these patients received

either FP (arm A: 5-FU 800 mg/m²/d in continuous infusion 5 days and cisplatin 100 mg/m² on day 1 or 2), or FLP (arm B: LV, 100 mg/m²/d in bolus 5 days, followed by 5-FU 350 mg/m²/d in 1 h infusion 5 days and cisplatin 100 mg/m² on day 1 or 2). Efficacy in terms of tumor response and survival was similar in two arms, showing an objective response rate of 18.6% in arm A vs. 15% in arm B, an overall median survival of 24 weeks in arm A vs. 24.7 in arm B ($p = 0.83$) and a median progression-free survival of 12.4 weeks vs. 12.1 in arms A and B ($p = 0.91$), respectively. Grade 3-4 neutropenia was observed %35.1 in arm B vs. %33.1 in arm A (12).

In another phase II study, 30 patients with unresectable, locally advanced or metastatic squamous cell or adenocarcinoma of the esophagus used folinic acid 200 mg/m²/d, 5-FU 300 mg/m²/d, and cisplatin 20 mg/m²/d intravenously for 5 days every 4 weeks. Two of 13 patients with squamous cell carcinoma had a complete response. Six other patients (3 SCC) had a partial response with a median duration of 9 months for an overall response rate of 27%. Further 6 patients (20%) had stable disease. Grade 4 neutropenia occurred in 6 patients (20%), with 5 requiring antibiotics for associated fever. Other grade 4 toxicities were nausea and vomiting, anemia, and thrombocytopenia occurred in one each (20).

In our study, the overall response rate was 44.4% (8 partial responses, 4 complete responses). Seven patients (25.9%) had stable disease. The disease control rate was 70.3%. Median PFS was 6.2 (95% CI: 5.13-7.28) months and median OS was 11.1 (95% CI: 7.77-14.5) months. Among the patients, 40.7% of them had grade 3-4 neutropenia, 11.1% of those patients had grade 3-4 thrombocytopenia. According to our results and the previous reports, short-term infusional 5-FU and cisplatin combination in previously untreated locally advanced or metastatic esophageal squamous cell cancer were seem to be similar with continuous infusional 5-FU in terms of median OS and PFS. However, grade 3-4 toxicity rates were more frequent than infusional 5-FU except for grade 3-4 non-hematological adverse effects. When treatment-related toxicities of infusional and



bolus 5-FU-containing regimens were compared in advanced-stage gastrointestinal and head-neck cancer, bolus 5-FU regimens appear to have a higher rate of hematologic toxicities, while gastrointestinal toxicities (diarrhea, vomiting, etc.) were seen less frequently.(15,25,26) As a result, this combination appears to be an active and convenient regimen for advanced esophageal cancer, resulting in prolonged remission and survival in some patients.

Despite the consideration of infusional chemotherapy as standard regimen for the treatment of esophageal cancer, there is a main problem with these regimens. This is the necessity for a central venous catheter and ambulatory infusion pump. Many studies regarding infusional 5-FU regimens in gastrointestinal and head-neck cancers showed more frequent catheter-related complications (infection and venous thrombosis).(15,16) So, thrombosis and catheter infections are major problems with infusion regimens. Deaths due to thrombosis around the central catheter have been reported. For example, a major drawback to the ECF (Epirubicin, cisplatin, 5-FU) regimen used in advanced esophagogastric adenocarcinoma is the need for a central venous line. In this randomized trial, central venous line complications occurred in 15 percent of those receiving ECF.(13)

Since this regimen carries a high risk for febrile neutropenia, it can be managed with primary prophylactic granulocyte colony-stimulating factor. Nevertheless, short-term infusional 5-FU and cisplatin combination regimen can be considered an alternative treatment to an infusion regimen due to similar survival outcome of the patients.

Conflict of Interest: None

References

1. Jemal A, Siegel R, Xu J, Ward E: Cancer statistics, 2010. *CA Cancer J Clin*, 60: 277–300, 2010.
2. Thorban S, Roder JD, Nekarda H, Funk A, Siewert JR, Pantel K: Immunocytochemical detection of disseminated tumor cells in the bone marrow of patients with esophageal carcinoma, 88: 1222-1227, 1996.
3. Thrift AP, Pandeya N, Whiteman DC: Current status and future perspectives on the etiology of esophageal adenocarcinoma. *Front Oncol*, 2: 11, 2012.
4. Leichman L, Berry BT: Experience with cisplatin in treatment regimens for esophageal cancer. 18: 64-72, 1991.
5. Grünberger B, Raderer M, Schmidinger M, Hejna M: Palliative chemotherapy for recurrent and metastatic esophageal cancer. *Anticancer Res*, 27: 2705-2714, 2007.
6. Kelsen D, Hilaris B, Coonley C, Chapman R, Lesser M, Dukeman M, Heelan R, Bains M: Cisplatin, vindesine, and bleomycin chemotherapy of local-regional and advanced esophageal carcinoma. *Am J Med*, 75: 645-652, 1983.
7. Dinwoodie WR, Bartolucci AA, Lyman GH, Velez-Garcia E, Martelo OJ, Sarma PR: Phase II evaluation of cisplatin, bleomycin, and vindesine in advanced squamous cell carcinoma of the esophagus. a Southeastern Cancer Study Group Trial. *Cancer Treat Rep*, 70: 267-270, 1986.
8. Spiridonidis CH, Laufman LR, Jones JJ, Gray DJ, Cho CC, Young DC: A phase II evaluation of high dose cisplatin and etoposide in patients with advanced esophageal adenocarcinoma. *Cancer*, 78: 2070-2077, 1996.
9. Conroy T, Etienne PL, Adenis A, Ducreux M, Paillot B, Oliveira J, Seitz JF, Francois E, Van Cutsem E, Wagener DJ, Kohser F, Daamen S, Praet M, Gorlia T, Baron B, Wils J: European Organisation for Research and Treatment of Cancer Gastrointestinal Tract Cancer Cooperative Group. Vinorelbine and cisplatin in metastatic squamous cell carcinoma of the oesophagus: response, toxicity, quality of life and survival. *Ann Oncol*, 13: 721, 2002.
10. Etienne MC, Bernard S, Fischel JL, Formento P, Gioanni J, Santini J, Demard F, Schneider M and Milano G: Dose reduction without loss of efficacy for 5-fluorouracil and cisplatin combined with folinic acid. In vitro study on human head and neck carcinoma cell lines. *Br J Cancer*, 63: 372-377, 1991.
11. Lacave AJ, Baron FJ, Anton LM, Estrada E, De Sande LM, Palacio I, Esteban E, Gracia JM, Buesa JM, Fernandez OA: Combination chemotherapy with cisplatin and 5-fluorouracil 5-day infusion in the therapy of



advanced gastric cancer: a phase II trial. *Ann Oncol*, 2: 751-754, 1991.

12. Duffour J, Bouché O, Rougier P, Milan C, Bedenne L, Seitz JF, Buecher B, Legoux JL, Ducreux M, Vetter D, Raoul JL, François E, Ychou M: Safety of cisplatin combined with continuous 5-FU versus bolus 5-FU and leucovorin, in metastatic gastrointestinal cancer. *Anticancer Res*, 26: 3877-3883, 2006.

13. Webb A, Cunningham D, Scarffe JH, Harper P, Norman A, Joffe JK, Hughes M, Mansi J, Findlay M, Hill A, Oates J, Nicolson M, Hickish T, O'Brien M, Iveson T, Watson M, Underhill C, Wardley A, Meehan M: Randomized trial comparing epirubicin, cisplatin, and fluorouracil versus fluorouracil, doxorubicin, and methotrexate in advanced esophagogastric cancer. *J Clin Oncol*, 15: 261, 1997.

14. Ajani JA, Fodor MB, Tjulandin SA, Moiseyenko VM, Chao Y, Cabral Filho S, Majlis A, Assadourian S, Van Cutsem E: Phase II multi-institutional randomized trial of docetaxel plus cisplatin with or without fluorouracil in patients with untreated, advanced gastric, or gastroesophageal adenocarcinoma. *J Clin Oncol*, 23: 5660-5667, 2005.

15. Hitt R, Paz-Ares L, Brandáriz A, Castellano D, Peña C, Millán JM, Calvo F, Ortiz de Urbina D, López E, Alvarez-Vicent JJ, Cortés-Funes H: Induction chemotherapy with paclitaxel, cisplatin and 5-fluorouracil for squamous cell carcinoma of the head and neck: long-term results of a phase II trial. *Ann Oncol*, 13: 1665-1673, 2002.

16. Hansen RM, Ryan L, Anderson T, Krzywda B, Quebbeman E, Benson A 3rd, Haller DG, Tormey DC: Phase III study of bolus versus infusion fluorouracil with or without cisplatin in advanced colorectal cancer. *J Natl Cancer Inst*, 15: 88: 668-674, 1996.

17. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP: Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol*, 6: 649-655, 1982.

18. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J: New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*, 45: 228-247, 2009.

19. Trotti A, Colevas AD, Setser A, Rusch V, Jaques D, Budach V, Langer C, Murphy B, Cumberlin R, Coleman CN, Rubin P: CTCAE v3.0: development of a comprehensive grading system for the adverse effects of cancer treatment. *Semin Radiat Oncol*, 13: 176-181, 2003.

20. Warner E, Jensen JL, Cripps C, Khoo KE, Goel R, Kerr IA, Bjarnason GA, Fields AL, Hrinco A: Outpatient 5-fluorouracil, folinic acid and cisplatin in patients with advanced esophageal carcinoma. *Acta Oncol*, 38: 255-259, 1999.

21. Ajani JA: Contribution of chemotherapy in the treatment of carcinoma of the esophagus: Results and commentary. *Semin Oncol*, 21, 474-482, 1994.

22. Bleiberg H, Conroy T, Paillot B, Lacave AJ, Blijham G, Jacob JH, Bedenne L, Namer M, De Besi P, Gay F, Collette L, Sahmoud T: Randomised phase II study of cisplatin and 5-fluorouracil (5-FU) versus cisplatin alone in advanced squamous cell oesophageal cancer. *Eur J Cancer*, 33: 1216-1220, 1997.

23. Kies MS, Rosen ST, Tsang TK, Shetty R, Schneider PA, Wallemark CB, Shields TW: Cisplatin and 5-fluorouracil in the primary management of squamous esophageal cancer. *Cancer*, 60: 2156-2160, 1987.

24. Ajani JA, Ryan B, Rich TA, McMurtrey M, Roth JA, DeCaro L, Levin B, Mountain C: Prolonged chemotherapy for localised squamous carcinoma of the oesophagus. *Eur J Cancer*, 28: 880-884, 1992.

25. Jeong J, Jeung HC, Rha SY, Im CK, Shin SJ, Ahn JB, Noh SH, Roh JK, Chung HC: Phase II study of combination chemotherapy of 5-fluorouracil, low-dose leucovorin, and oxaliplatin (FLOX regimen) in pretreated advanced gastric cancer. *Ann Oncol*, 19: 1135-1140, 2008.

26. Pfister DG, Bajorin D, Motzger R, et al: Cisplatin, fluorouracil, and leucovorin. Increased toxicity without improved response in squamous cell head and neck cancer. *Arch Otolaryngol Head Neck Surg*, 120: 89-95, 1994.



Colon Cancer and Glioblastoma Multiforme Co-occurrence at an Early Age; A Case Report

Erken Yaşta Kolon Kanseri ve Glioblastome Multiforme Birlikteliği; Olgu Sunumu

Fatma Buğdaycı Başal¹, Umut Demirci¹, Ahmet Şiyar Ekinci², Muzaffer Altundağ³, Levent Gürses¹, Ferit Aslan¹, Ayşe Demirci¹, Necati Alkış¹

¹Dr. A. Y. Ankara Onkoloji Eğitim Araştırma Hastanesi, Tıbbi Onkoloji Kliniği, Ankara, Türkiye

²Dr. A. Y. Ankara Onkoloji Eğitim Araştırma Hastanesi, Radyasyon Onkolojisi Kliniği, Ankara, Türkiye

³Dışkapı Yıldırım Beyazıt Eğitim Araştırma Hastanesi, Beyin Cerrahi Kliniği, Ankara, Türkiye

Dergiye Ulaşma Tarihi: 26/12/2014 Dergiye Kabul Tarihi: 13/01/2015 Doi: [10.5505/aot.2015.36349](https://doi.org/10.5505/aot.2015.36349)

ÖZET

Kolon kanseri ve beyin tümörü birlikteliği klinikte karşımıza Muir-Torre Sendromu, Turcot Sendromu, Cowden Sendromu ya da Gardner Sendromu olarak çıkabilir. Turcot Sendromu multiple adenomatöz kolon polipleri ile santral sinir sisteminin (SSS) primer tümörünün birlikte görüldüğü DNA tamir genlerinde mutasyonlarla seyreden nadir bir hastalıktır. Biz bu olguda polipozis zemininde gelişen kolon kanseri tanısından üç yıl sonra glioblastome multiforme (GBM) tanısı alan fakat genetik çalışmada Turcot Sendromu desteklenemeyen genç bir kadın hastayı sunduk.

Anahtar Kelimeler: Kolon kanseri, Glioblastome multiforme; Turcot Sendromu

ABSTRACT

The co-occurrence of colon cancer and brain tumor can be observed as Muir-Torre syndrome, Turcot syndrome, Cowden syndrome or Gardner's syndrome, in clinical practice. Turcot syndrome is an uncommon disease with mutations in DNA repair genes that consist of multiple adenomatous colon polyps and central nervous system (CNS) tumor. We report a case of a young woman presents with polyposis related colon cancer who develops glioblastoma multiforme (GBM) three years after the diagnosis which cannot be explained with Turcot Syndrome by genetic studies.

Key words: Colon cancer, Glioblastoma multiforme; Turcot's Syndrome

Giriş

Kolon kanseri ve beyin tümörü birlikteliği klinikte karşımıza bazı sendromlarla çıkar. Muir-Torre Sendromu (sebasöz neoplazm, keratoakantom, viseral malignite, beyin tümörü), Turcot Sendromu (polipozis koli, beyin tümörü), Cowden Sendromu (serebellumda displastik gangliositom ve kolonda hamartomatöz polipler) ya da Gardner Sendromu (polipozis koli, osteom, mezenkimal tümör, kraniofarenjiom) bu iki kliniğin birlikte görüldüğü sendromlardır (1-4). Literatürde Muir-Torre Sendromu ile Turcot Sendromu'nun çakıştığı olgular bildirilmiştir (1,5).

Turcot Sendromu multiple adenomatöz kolon polipleri ile santral sinir sisteminin (SSS) primer tümörünün birlikte görüldüğü

nadir bir hastalıktır (6). İlk olarak 1949'da Crail tarafından tanımlanmış ve 1959'da J. Turcot ve ark. tarafından beyin tümörü ve polipozis coli birlikteliği olan iki kardeşte 'Turcot's Sendromu' şeklinde rapor edilmiştir (7). Tanı alan hastalar genellikle 10-20 yaş aralığındadır (7,8). Turcot sendromunun genetik temeli karmaşık olup klinik ve genetik olarak çeşitli tiplerde kliniğe yansıyabilir. Literatürde yaklaşık 150 vaka bulunmaktadır (9-11). Biz bu olguda polipozis zemininde gelişen kolon kanseri tanısından üç yıl sonra glioblastome multiforme (GBM) tanısı alan genç bir kadın hastayı sunduk.

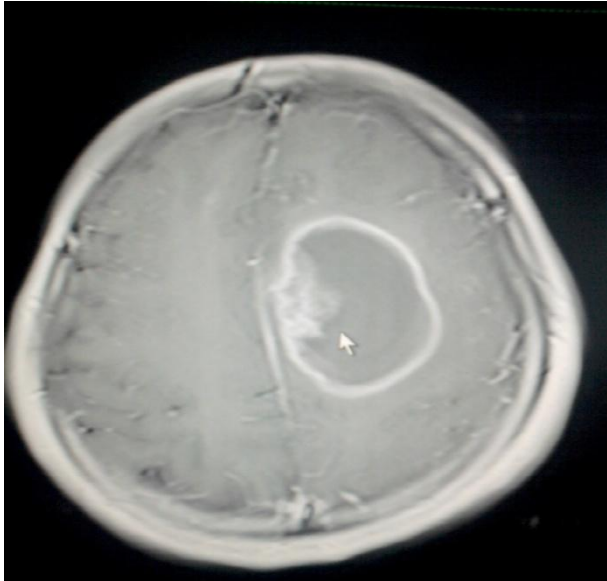
Olgu Sunumu

Yirmi iki yaşında kadın hasta Haziran 2011 yılında karın ağrısı nedeni ile yapılan

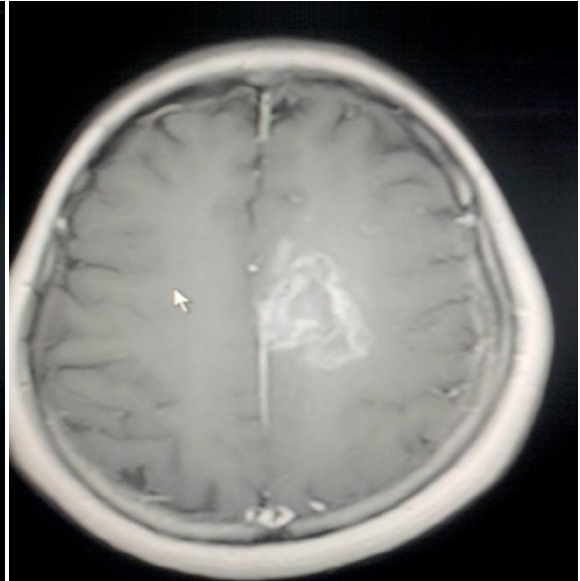
kolonoskopisinde çekumda, transvers, inen, sigmoid kolonlarda ve rektosigmoid bölgede multipl sayıda polip saptanmıştı. Total kolektomi sonrasında multipl odakta iyi diferansiye adenokarsinom, çok sayıda tübülovillöz adenom ve 10 adet reaktif lenf nodu saptanmış ve adjuvan FUFA (5FU+ Folinik asit) tedavisi uygulanmıştı. Remisyonda izlenen hasta Aralık 2013'te sağ üst extremitede kuvvet kaybı gelişmesi üzerine dış merkezde çekilen beyin manyetik rezonans görüntülemesinde (MRG) sol frontal lobda 5.5 cm'lik kitle saptanmış (Resim 1) ve biyopsi yapılmış. Tanısal olmayan biyopsi sonrası fokal epileptik nöbet geçiren hasta başka bir merkeze başvurmuş. Gros total olarak çıkartılan kitle (Resim 2) patolojisi GBM olarak raporlanan hasta idame tedavisi için hastanemize başvurdu. Özgeçmişinde kolon kanseri olan hastanın bir kız kardeşinin de beyin tümörü nedeniyle kaybedildiği öğrenildi.

Hastanın fizik muayenesinde sırtında akne benzeri lezyonları ve gövdede ve kollarda maküler kahverengi olmayan koyu renkli alanları vardı. Hastanın radyoterapi eş zamanlı temozolamid tedavisi sonrası idame temozolamid tedavisi tamamlandı. Hasta radyolojik ve klinik olarak progresyonsuz izlenmektedir.

Hastanın polipozis koli ve GBM tanıları birlikte ele alındığında Turcot Sendromu akla gelmekteydi. Bu nedenle hastanın kolon operasyonuna ait patoloji preparatları mikrosatellit instabilite (MSI) açısından immunohistokimyasal olarak değerlendirildi. Çalışmada neoplastik hücreler MLH1, PMS2, MSH6 ile pozitif olup MSH2 ile belirgin boyanma saptanmadı. Kontrolünde de boyanma saptanmadığından MSH2 kayıp olarak değerlendirilmedi. Bu nedenle hastada DNA tamir genlerinin kaybına rastlanmadı.



Resim- 1; Tanı anında çekilen T1 transvers kesit



Resim- 2; Operasyon sonrası T1 transvers kesit

Tartışma

Olgumuz genç yaşta kolonda multipl polipler nedeniyle opere edilmesinin ardından iyi diferansiye adenokarsinom tanısı almış ve adjuvan tedavi sonrası remisyonda izlenirken GBM tanısı almıştır. Bu iki tümörün birlikteliği hastada Turcot Sendromu varlığını akla getirmektedir.

Hereditör nonpolipozis koli (HNPCC) DNA tamir genlerinin (Mismatch Repair

Genes; MMR) mutasyonundan kaynaklanır. HNPCC sıklıkla MSH2, MLH1 ve PMS2 genlerindeki mutasyondan kaynaklanır (9,12). Olguların %90'ında MSI görülür (9,13). MSH2 mutasyonu sıklıkla multipl tümör gelişimi ile ilişkilidir (14). Turcot sendromu modern literatürde beyin tümörü polipozis sendromu olarak bilinmektedir (9,11). Nadir bir hereditör hastalık olup HNPCC ve familiyal adenomatozis polipozisin (FAP) varyantları olarak görülür (12). Tip 1 ve tip 2 olmak üzere

iki farklı klinikte karşımıza çıkar. Tip 1 otozomal resesif geçişli olup, HNPC ve sıklıkla GBM olmak üzere beyin tümörleri birlikteliği ile görülür. Tip 2 ise otozomal dominant geçişli olup FAP ve medulloblastom birlikteliği ile görülür. Bu iki tip sendrom arasında kesin bir ayırım yoktur. Tip 1’de kolon poliplerinin sayısı 100’den azdır ve beyin tümörleri gliomlar şeklinde görülür. Tip 2 Turcot Sendromu’nda kolonda polipler yüzler hatta binlere ulaşmakta ve %20 vakada kolorektal kansere rastlanmaktadır. Beyinde medulloblastom %60 vakada görülür (9-11,15). Bu anlamda bizim olgumuz tip 1 Turcot Sendromu’nu akla getirmektedir fakat yapılan incelemede MMR genlerinde mutasyona rastlanmamıştır.

Kolonik ve serebral semptomlar aynı anda ortaya çıkabileceği gibi birbirini de takip edebilir. İlk semptom ortaya çıktıktan sonra beş yıl içinde diğer semptomlar kendini gösterir (7). Genellikle barsak lezyonları beyin tümörü tanısından bir yıl sonra başgösterir yada postmortem saptanır (6). Ayrıca kolon rezeksiyonundan 2-8 yıl sonra da SSS malignitesi ortaya çıkabilir (6,15). Bizim olgumuzda da kolon kanseri tanısı aldıktan üç yıl sonra serebral semptomlar ortaya çıkmıştır. Cinsiyet ve ırk eğilimi bilinmemektedir fakat 10-30 yaşları arasında görülür (6). Kliniğe yansıması spesifik değildir. Pigmente nevüs, kafeola, bazal hücreli karsinoma gibi deri bulguları görülür (9,11). Bizim olgumuzda da sırtta akne benzeri lezyonlar, gövde ve kollarda kahverengi olmayan koyu renkli makuler lezyonları mevcuttu.

Olgumuz tip 1 Turcot Sendromu kliniğine uyması ve aile hikayesinin olması itibarıyla genetik incelemeyi hak etmiş ilginç bir hastadır. Fakat Türkiye’den literatürde varolan herhangi bir Turcot olgusu olmadığı gibi bizim olgumuzda da Turcot Sendromu’nu destekleyecek MMR genlerine rastlanmamıştır. Yine de bu hasta grubu eşlik edebilen multipl tümörler nedeni ile yakın izlenmelidir.

Çıkar Çatışması: Yok

Kaynaklar

1. Grandhi R, Deibert CP, Pirris SM, Lembersky B, Mintz AH. Simultaneous Muir-Torre and Turcot's syndrome: A case report and review of the literature. *Surg Neurol Int* 2013; 4: 52
2. Park MD, Yeane GA, Hamilton RL, Mabold J, Urban N. Identifying Muir-Torre syndrome in a patient with glioblastoma multiforme. *Neuro Oncol* (August 2009) 11 (4): 452-455
3. Yuasa H, Motokishita T, Tokito S, Tokunaga M, Goto M. Lhermitte-Duclos disease associated with Cowden's disease-case report. *Neurol Med Chir* (Tokyo) 1997 Sep;37(9):697-700
4. Bozbuga M, Suslu HT, Hicdonmez T, Bayındır Ç. Primary cerebellopontine angle craniopharyngioma in a patient with Gardner syndrome. *Journal of Clinical Neuroscience* Volume 18, Issue 2, February 2011, Pages 300-301
5. Kleinerman R, Marino J, Loucas E. Muir-Torre Syndrome / Turcot Syndrome overlap? A patient with sebaceous carcinoma, colon cancer, and a malignant astrocytoma. *Dermatology Online Journal* 18 (5): 3
6. Radin DR, Fortgang KC, Zee CS, Mikity VG, Halls JM. Turcot syndrome: a case with spinal cord and colonic neoplasms. *AJR Am J Roentgenol* 1984 Mar;142(3):475-6
7. Ma S, Hu Y, Yang J, Zhou X. Turcot's syndrome associated with intestinal non-Hodgkin's lymphoma: case report and review of literature. *Clin Neurol Neurosurg* 2013 Feb;115(2):117-20
8. McLaughlin MR¹, Gollin SM, Lese CM, Albright AL. Medulloblastoma and glioblastoma multiforme in a patient with Turcot syndrome: a case report. *Surg Neurol* 1998 Mar;49(3):295-301
9. Ozerov SS, Zakharov IV, Talypov SR, Konovalov DM, Kisliakov AN. Turcot syndrome: Rare observation and literature review. *Zh Vopr Neirokhir Im N N Burdenko* 2013;77(3):49-53
10. Hamilton SR, Liu B, Parsons RE, Papadopoulos N, Jen J, et al. The molecular basis of Turcot's syndrome. *N Engl J Med* 1995 Mar 30;332(13):839-47
11. Paraf F, Jothy S, Van Meir EG. Brain tumor-polyposis syndrome: two genetic diseases? *JCO* Jul 1, 1997;2744-58
12. Lebrun C, Olschwang S, Jeannin S, Vandenbos F, Sobol H. Turcot syndrome confirmed with molecular analysis. *Eur J Neurol* 2007 Apr;14(4):470-2
13. De Vos M, Hayward BE, Picton S, Sheridan E, Bonthron DT. Novel PMS2 pseudogenes can conceal recessive mutations causing a distinctive childhood cancer syndrome. *Am J Hum Genet* 2004 May;74(5):954-64
14. Balaguer F, Cervantes A, Arnold D. Familial risk-colorectal cancer: ESMO Clinical Practice Guidelines. Balmaña J, ESMO Guidelines Working Group. *Ann Oncol* 2013 Oct;24 Suppl 6:vi73-80
15. Itoh H, Ohsato K, Yao T, Iida M, Watanabe H. Turcot's syndrome and its mode of inheritance. *Gut* 1979 May;20(5):414-9

Castleman Disease Localized On The Right And Left Buccal Mucosa

Sağ Ve Sol Bukkal Mukoza Yerleşimli Castleman Hastalığı

Caner Kılıç¹, Metin Kaya², Ela Cömert¹, Ümit Tunçel¹, Nazan Bozdoğan³

¹Ankara Onkoloji Eğitim Araştırma Hastanesi, Kulak Burun Boğaz Kliniği, Ankara, Türkiye

²Batman Devlet Hastanesi

³Ankara Onkoloji Eğitim Araştırma Hastanesi, Patoloji Kliniği, Ankara, Türkiye

Dergiye ulaşma tarihi: 15/11/2014, Dergiye kabul tarihi: 30/04/2015, Doi: [10.5505/aot.2015.72693](https://doi.org/10.5505/aot.2015.72693)

ÖZET

Castleman hastalığı (CH), en sık mediastende asemptomatik kitle olarak görülen lenfoproliferatif bir hastalıktır. Baş boyun bölgesinde ise en sık boyun da görülür. Oral kavite de yerleşimi nadirdir. Tedavisinde cerrahi eksizyon uygulanır. Bu makalede sağ ve sol yanak mukozasında, giderek büyüyen şişlik şikayeti ile tarafımıza başvuran ve histopatolojik tanısı castleman hastalığı- plazma hücreli tip olarak raporlanan, non hodgkin lenfoma (NHL) öyküsü olan hasta, literatür eşliğinde sunulmuştur.

Anahtar Kelimeler: Bukkal Mukoza, Castleman Hastalığı, Non hodgkin lenfoma

ABSTRACT

Castleman disease (CD) is a lymphoproliferative disorder that is most frequently seen as an asymptomatic mass in the mediastinum. Among the head and neck region, the neck is the most frequent localization. It is seldom localized in the oral cavity. Surgical excision is the primary choice of treatment. The current study presents a patient with previous non-Hodgkin Lymphoma (NHL) history, who was complaining of a mass gradually increasing in size beneath the right and left buccal mucosa and a histopathological diagnosis of Castleman disease – plasma cell type. The related literature is also reviewed.

Key words: Buccal Mucosa, Castleman Disease, Non Hodgkin Lymphoma

Introduction

Castleman disease (CD) is a lymphoproliferative disorder characterized by lymphoid tissue hyperplasia. It is also called angiomatous lymphoid hamartoma. Histopathologically, the disease is classified as hyalinic vascular, plasma cell, and mixed variants. The most frequent subtype is the hyalinic variant, which has a low recurrence rate. The plasma cell subtype is more aggressive and is concomitant with systemic diseases (1). It is most commonly localized in the mediastinum as an asymptomatic mass. Among the head and neck region, the neck is the most frequent localization (2). Chronic inflammation and immune insufficiency are responsible for the etiology and it is seen concomitantly with autoimmune diseases like pemphigus.³ Clinically, isolated or multicentric subtypes can be seen. Isolated subtypes generally are seen in younger patients and multicentric types in older patients. In the treatment, total or near total surgical excision can be performed according the localization (4). Radiotherapy may be used as an adjuvant or a mass reductive modality (5). We herein

report a patient with previous NHL history, who had CD lesions localized beneath right and left buccal mucosa. We present the treatment of this patient who shows a rare localization of the disease and a review of the literature as well.

Case Report

A 64-year-old male patient who had gradually growing masses in the oral cavity (beneath both sides the buccal mucosa) was admitted to the Ankara Oncology Teaching and Research Hospital Ear Nose Throat Department. The physical exam revealed rigid masses with smooth surfaces, and reduced mobility was observed under the right and left buccal mucosa (Figure 1). No other abnormalities were found.

Systemic signs such as fever and sweating were absent. Laboratory tests and viral markers were normal. Systemic physical exams were normal, as well. According to the patient's medical history,



he had received chemotherapy almost nine years before due to diffuse B cell NHL. He underwent lymph node excision in his neck 4.5 years prior and the specimen revealed plasma cell type CD. Radiological examination was natural.

Horizontal incisions were made on the mucosa transorally above the masses to diagnose and treat the patient. Minor salivary glands under the mucosa were lateralized and masses with smooth surfaces adhered to the surrounding tissue were observed.

The mass under the left buccal mucosa and near total excision of the mass under the right buccal mucosa were totally excised. The histopathological examination of both specimens revealed Castleman disease with plasma cell subtype (Figure 2). Neither adjuvant radio nor chemotherapy was recommended by oncology departments. During the three-year follow up, no recurrence was occurred.

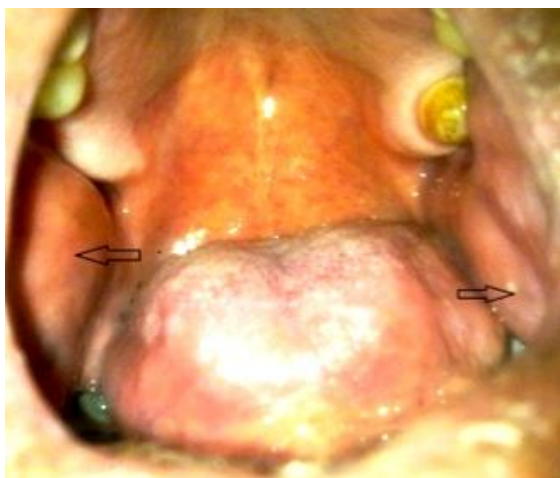


Figure 1: Masses under the right and left buccal mucosa.

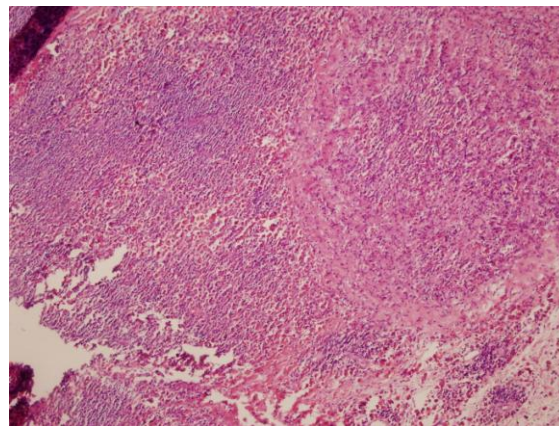


Figure 2: Castleman disease with plasma cell subtype

Discussion

Castleman disease was first described in a patient as an isolated mediastinal mass. It is also called angiofollicular lymph node hyperplasia, giant lymph node hyperplasia, lymph node hamartoma, and benign giant lymphoma. It is seen equally among the genders and more frequently in young adults (1). The etiology is not clearly identified. However, it may be seen concomitantly with other disorders such as NHL, multiple myeloma, B cell lymphoma, Kaposi's sarcoma (6). It was reported that viral infections such as HHV-8, HIV, EBV.⁷ The patient presented herein received treatment for NHL nine years prior, and he is still in remission.

Depending on clinical presentation, the disease can also be divided into isolated or multicentric subtypes. The multicentric type is generally seen with other systemic diseases and shows progress more aggressively (5). Histopathologically, CD is also classified into three different subtypes as vascular, plasma cell, and mixed (1). The plasma cell type accounts for almost 10% of the cases, is generally multicentric, and is associated with systemic symptoms such as fever, sweating, elevated sedimentation rate, anemia, and thrombocytopenia. Although the current patient's lesions were multicentric, and histopathologically of the plasma cell type, he did not present systemic signs.

Castleman disease that occurs in the head and neck region, is most frequently seen in the neck, and it was reported to be rarely seen in the parotis, mouth floor, and oral cavity, as well (2). One study in the literature



reported a study of 14 patients with CD in the neck, in which the mass was found unilaterally and at level II all the patients (8). Karakoc et al. reported that in a patient with dysphagia, a postoperative pathological specimen revealed CD, which was thought to be parapharyngeal schwannoma preoperatively (9). In a patient who had been followed-up for cervical mass and treated with preoperative embolization due to enhanced peripheral vascularization in the MRI, the postoperative specimen showed CD (10). Deshmukh et al. reported that a patient who had been diagnosed with squamous cell carcinoma of the tongue with stage T1N3M0 had undergone cervical dissection. After the dissection, the specimen revealed CD, so the authors accepted the stage of the disease as T1N0M0 (11). These studies suggest that CD in the neck localized laterally may mimic many different disorders (2). Three years ago, the current patient underwent cervical node biopsy at level II and the specimen showed CD plasma cell subtype.

CD localized in the oral cavity is rarely described. There is only one case of a well-defined submucosal mass unilaterally beneath the buccal mucosa in literature (12). The current case was admitted to our department with asymptomatic masses localized under the right and left buccal mucosa. A case with masses with such localization is presented for the first time in the literature.

Histopathological confirmation is needed for the definitive diagnosis. Fine needle aspiration biopsy has no diagnostic value, and the diagnosis is made by incisional or excisional biopsy. Total or near total excision should be performed for the treatment (4). Corticosteroids should be added in the therapy of patients with systemic symptoms. Due to autoimmunity being blamed for the etiology, cytotoxic drugs or immunomodulators such as interferon and intravenous immunoglobulin are used (13). The recurrence rate is high in the plasma subtype, and thus, chemotherapy and radiotherapy (RT) can be added. It was reported that a partial or complete response can be obtained in the treatment of CD with 40-50 Gy. doses of radiotherapy. In the same study, the authors claimed that response rate of the RT in patients with the plasma cell type was better than the other types due to higher tumoral activity of the plasma cell type (14).

Although Castleman disease has good prognosis with surgery, long term recurrences

are reported in literature. Total excision was performed in the treatment of a patient with CD plasma cell variant, and recurrence occurred 11 months later. Re-excision and chemotherapy was given for the recurrence (15). We performed total excision for the left and near total excision for the right buccal masses in the treatment. During the three-year follow-up, neither recurrence nor additional systemic symptoms occurred.

Early diagnosis is very important in Castleman disease, especially in the multicentric and plasma cell subtypes, due to accompanying systemic disorders with high mortality, potential of malignant transformation and high recurrence rates. CD, localized under buccal mucosa like in the current case, should be remembered in the differential diagnosis of asymptomatic masses in the oral cavity and the physician should be aware of concomitant disorders.

References

1. Gangopadhyay K, Mahasin ZZ, Kfoury H. Castleman disease (giant lymph node hyperplasia). Arch Otolaryngol Head Neck Surg 1997;123(10):1137-9.
2. Markou KD, Goudakos JK, Psillas G, Antoniadis A, Karasmanis I, Vital V, Nicolaou A. Castleman's disease of the neck: report of a case and review of the literature. B-ENT.2009;5(3):189-93.
3. Uskul B, Ertugrul M, Selvi A, Mihmanli A, Zindanci I, Turker H. A rare association: Castleman's disease and pemphigus vulgaris .Tuberk Toraks. 2005;53(2):172-6
4. Bowne WB, Lewis JJ, Filippa DA, Niesvizky R, Brooks AD, Burt ME, et al. The management of unicentric and multicentric Castleman's disease. Cancer 1999;85(3):706-17.
5. Vries I, MS van Acht M, BJ Demeyere T, LM Lybeert M, Zoete J.P, Nieuwenhuijzen G. Neoadjuvant radiotherapy of primary irresectable unicentric Castleman's disease: a case report and review of the literature. Radiation Oncology 2010;5:7
6. Maslovsky I, Uriev L, Lugassy G. The heterogeneity of Castleman disease: report of five cases and review of the literature. Am J Med Sci 2000;320(4):292-5.
7. Gomes H, Huyett P, Laver N, Wein RO. A unique presentation of Epstein-Barr virus-associated Castleman's disease. Am J Otolaryngol 2013;34(3):262-4.
8. Chen YF, Zhang WD, Sun CZ, Ouyang D, Chen WK, Luo RZ, Wu MW. Clinical features and outcomes of head and neck castleman's disease. J Oral Maxillofac Surg 2012;70(10):2466-79.
9. Zawawi F, Varshney R, Haegert DG, Daniel SJ. Castleman's Disease: a rare finding in a pediatric neck. Int J Pediatr Otorhinolaryngol 2014;78(2):370-2



10. Karakoc O, Kilic E, Ilica T, Tosun F, Hidir Y. Castleman disease as a giant parapharyngeal mass presenting with dysphagia. *J Craniofac Surg* 2011;22(6):54-7.
11. Sanchez-Ros-Sanchez A, Infante-Cossio P, Gonzalez-Garcia A, Borrero-Martin JJ. Preoperative embolization for the treatment of cervical Castleman disease. *J Craniofac Surg* 2012;23(3):257-9.
12. Deshmukh M, Bal M, Deshpande P, Jambhekar NA. Synchronous squamous cell carcinoma of tongue and unicentric cervical Castleman's disease clinically mimicking a stage IV disease: a rare association or coincidence? *Head Neck Pathol* 2011;5(2):180-3.
13. Maruyama S, Hao N, Cheng J, Horino K, Ohnishi M, Fukushi M, Fujii M, Saku T. Castleman's disease of the buccal mucosa: report of a case and review of the literature of head and neck cases. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2002;93(3):305-10.
14. Bowne WB, Lewis JJ, Filippa DA, Niesvizky R, Brooks AD, Burt ME, et al. The management of unicentric and multicentric Castleman's disease: a report of 16 cases and a review of the literature. *Cancer* 1999; 85(3):706-17.
15. de Vries IA, Van Acht MM, Demeyere T, Lybeert ML, de Zoete JP, Nieuwenhuijzen GA. Neoadjuvant radiotherapy of primary irresectable unicentric Castleman's disease: a case report and review of the literature. *Radiat Oncol* 2010;2:5-7.



İris nevi and melanomas: Distinguishing parameters

İris nevüsleri ve melanomları: Ayırt edici parametreler

Reşat Duman¹, Nilay Duman², Rahmi Duman³, Mustafa Doğan¹

¹Afyon Kocatepe Üniversitesi, Tıp Fakültesi, Göz Hastalıkları Ana Bilim Dalı, Afyonkarahisar

²Afyon Kocatepe Üniversitesi, Tıp Fakültesi, Dermatoloji Ana Bilim Dalı, Afyonkarahisar

³Bursa Şevket Yılmaz Eğitim Ve Araştırma Hastanesi, Göz Hastalıkları Ana Bilim Dalı, Bursa

Dergiye Ulaşma Tarihi: 18/03/2015 Dergiye Kabul Tarihi: 30/05/2015 Doi: 10.5505/aot.2015.77487

ÖZET

İris melanomlarının çoğu daha önce var olan iris nevüsleri üzerinden gelişmektedir. İris melanomlarının enükleasyon, metastaz ve fonksiyonel kayba neden olma riskleri nedeniyle erken tanılar oldukça önemlidir. İris nevüsünden melanom gelişimini kestirecek klinik parametrelerin farkında olunması melanom gelişimi açısından riskli nevüs grubunun belirlenmesini ve iris melanomların erken tespitini kolaylaştıracaktır. Bu derlemede iris nevüslerinin ve melanomlarının klinik özellikleri ve ayırt edici klinik parametreler sunuldu. Böylelikle bu hastalara klinik yaklaşımda yardımcı olunması amaçlandı.

Anahtar Kelimeler: iris, nevüs, melanom.

ABSTRACT

Most of the iris melanomas arise from pre-existing iris nevi. Early diagnosis of iris melanomas is quite important because of potential risk of enucleation, metastasis and functional loss. Being aware of the clinical parameters predicting the development of melanoma from pre-existing nevus will help determining the hazardous nevus group and early diagnosis of iris melanomas. In this review, clinical features of iris nevi and melanomas and distinguishing clinical parameters were presented. Thus, helping in the clinical management of such patients were aimed.

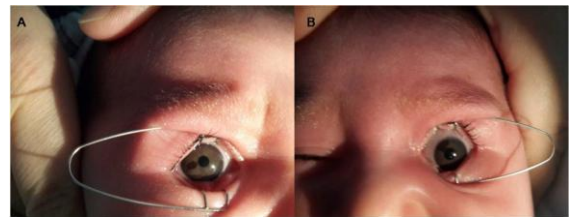
Key words: iris, nevus, melanoma.

İris nevüsleri

Normal nüfusta göz içi lezyonları değerlendirildiğinde iris nevüsleri sık görülen tanılardan birisidir. İris nevüsleri toplumun %4-6' sında görülür.¹ Çocukluktaki iris lezyonlarının %25'ini, genç erişkinlerde % 36'sını ve orta ve ileri yaş erişkinlerdeki iris lezyonlarının %47'sini oluşturur.² İris nevüsleri nadiren doğuştan mevcut iken sıklıkla ergenlik sonrası belirginleşerek tanı alır (Resim 1). Çoğunlukla beyaz ırkta ve mavi-gözlü bireylerde, sıklıkla 5.dekatta tespit edilir. Her iki cinsiyette de ortaya çıkabilse de son serilerde kadınlarda biraz daha yüksek oranda bildirilmiştir.³

İris nevüsleri irisin herhangi bir kısmını tutabilse de sıklıkla alt kadranda ortaya çıkar. Şekilleri, boyutları ve pigmentlenme özellikleri olgudan olguya değişiklik gösterir. Tekil ya da çoklu; yassı veya nodüler lezyonlar şeklinde ortaya çıkabilirler, küçük ve iyi sınırlı

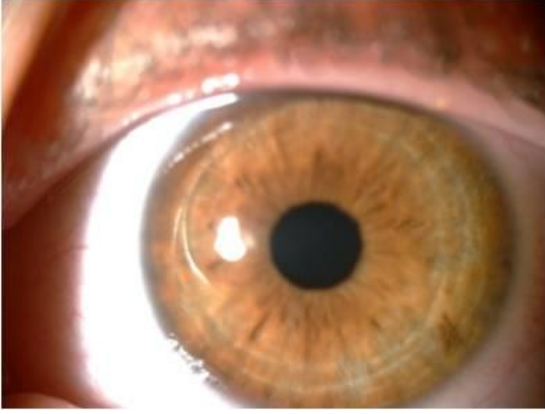
olabilecekleri gibi, büyük ve yaygın olabilirler (Resim 2).



Resim 1. Bebek olguda doğuştan mevcut çift taraflı iris nevüsü.

İris nevüsleri sıklıkla pigmentlidirler, nadiren amelanotik olabilirler.¹ Yaygın lezyonlar tüm sektörü ya da tüm irisi tutabilir, genellikle doğumsal oküler melanositozlu hastalarda ortaya çıkar, heterokromiye neden olabilir, iris nevüs sendromunda izlenebilir.





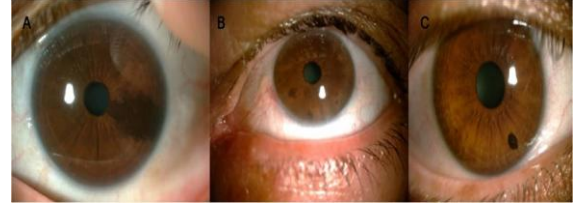
Resim 2. İris kenarında yer alan küçük tekil nevüs.

İris nevüs sendromu (Cogan-Reese sendromu); iridokorneal endotelial sendrom spektrumu içinde yer alırken, yaygın nevüs ve buna eşlik eden diğer iris anomalileri (çoklu nodüller, ektropiyon uvea, vb) ve tek taraflı glokom ile karakterizedir.⁴ Bir diğer iris nevüs tipi tapioca nevüstür. Bu tip nevüslerde, yüzey çoklu nodüler görünümündedir, tapioca bitkisinin köklerine benzediği için bu isimlendirme kullanılmıştır.⁵ Bir diğer iris nevüs tipi melanositomdur. Melanositomer, klinik olarak daha yoğun ve daha derin pigment içerir, çoğunlukla koyu kahve-siyah granüler yüzeye sahip nodüler lezyonlar olarak ortaya çıkar, belirgin bir damarlanma artışı göstermez. Melanositomer kendiliğinden nekroze olabilir, bunun sonucunda çevreye pigment ekimi olabilir ve trabeküler ağda tıkanma sonucu ikincil glokom gelişebilir. Melanositomer zamanla malign dönüşüm gösterebilir.⁶

Genel olarak, iris nevüslerinin çapı 3 mm'den, kalınlığı 1 mm'den küçüktür.¹ Yakın zamanlı bir seride pupile yakın lezyonların daha büyük olduğu ve daha uzamış ve üçgen şekilli olduğu, pupile uzak lezyonların ise daha küçük ve yuvarlak olduğu bildirilmiştir (Resim 3).⁷ İris nevüslerinin histopatolojisinde yüzeysel iris stromasında melanosit çoğalması izlenir, hücreler sıklıkla iğsi tiptedir. Epiteloid hücrelerin baskın olduğu olgularda melanomla karışabilir.⁸

İris nevüslerinde belirgin bir damar artışı izlenmez.¹ Sıklıkla pupil tepkilerinde bozukluk oluşmaz.¹ İris nevüslerinde sektör katarakt, iridokorneal açığı tutulumu, pupile yakın yerleşimli lezyonlarda pupiller kenarda hafif bozulma ve ektropiyon uvea gelişimi ve zamanla yavaş büyüme izlenebilir, bunlar

eskiden düşünüldüğünün aksine her zaman malign dönüşümü düşündürmez.¹



Resim 3. A: Pupile yakın yerleşimli, büyük ve uzamış nevüs, B, C: Pupile uzak yerleşimli küçük ve yuvarlak hatlı nevüs.

İris nevüslerinin üzerinden melanom gelişme riski kesin olarak bilinmemektedir. Farklı çalışmalarda oranlar %2-5 olarak bildirilmiştir.^{3,9} 1611 iris nevüsü içeren yakın zamanlı bir seride olguların 27'sinde (%2) melanom gelişmiştir ve bu ortalama 69 ayda (aralık 4-214 ay, ortanca 46 ay) izlenmiştir.³ Ayrıca bu seride, Kaplan-Meier analizi ile iris nevüsünden melanom gelişme riskinin 10 yılda %4, 15 yılda %8 ve 20 yılda %11 olduğu gösterilmiştir.³ Genel olarak bazal çapın 3 mm'den fazla olması, damarlanmanın artışı, tümörün hızla büyümesi, göz dışına yayılım, siliyer cisim tutulumu ve eşlik eden ilaç tedavilerine dirençli glokomun varlığı melanom gelişimini akla getirmelidir.¹ Yakın zamanda Shields ve ark.³ iris nevüsünden melanom gelişimini öngörücü faktörler olarak ABCDEF kuralını önermiştir. Bu kural;
A: Age young (40 yaşından küçük olma),
B: Blood (hyphema) (hifemanın varlığı),
C: Clock hour inferior (saat 4-9 arası altta yerleşim),
D: Diffuse (yaygın lezyon varlığı),
E: Ectropion uvea (ektropiyon uvea varlığı) ve
F: Feathery margins (tüylü sınır varlığı) olarak belirlenmiştir. Bu kriterleri taşıyan nevüsleri olan hastalarda melanom riski daha yüksek olduğu için, tümör büyümesini değerlendirmek için daha yakın klinik takip önerilmektedir.

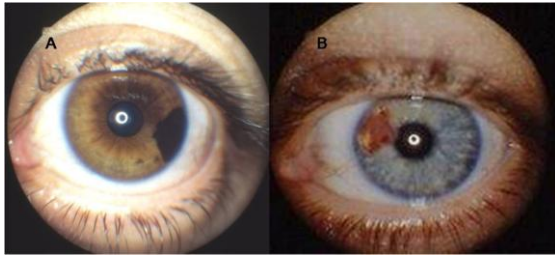
İris melanomları

İris melanomları oldukça nadir görülen tümörlerdir, tüm üveal melanomların %2-10'unu oluşturur.^{10,11} Çalışmalardaki tahmin edilen yıllık sıklığı milyonda 0.4-0.9'dur.¹² İris melanomlarının sıklığı son yıllarda artış



göstermiştir.^{12,13} Bu artışın güneş ışınlarına bağlı olduğu düşünülmektedir.¹⁴

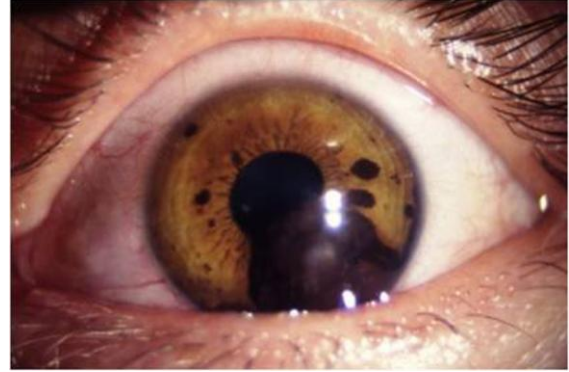
İris melanomları de novo ortaya çıkabileceği gibi, çoğunlukla daha önce var olan iris nevüsleri üzerinden gelişir.¹⁵ Cinsiyet ayrımı yapmaz, her yaşta ortaya çıkabilse de sıklıkla 40-50 yaşlarda tanı alır.¹⁶ Çoğunlukla beyaz ırkta ve açık renkli irislerde ortaya çıkar.¹⁶ Her iki gözde benzer oranlarda izlenir.¹² İris melanomları, sınırlı veya yaygın lezyonlar olarak ortaya çıkabilir.⁸ Zamanla büyüme gösterir, iris stromasının yerini değiştirir ve ikincil glokoma, katarakta, belirgin damar artışına veya ektropion uveaya neden olabilir.¹⁷ Sınırlı lezyonlar sıklıkla alt kadranda pigmentli nodüler lezyonlar şeklinde ortaya çıkar.¹² Yaygın lezyonlar ise edinilmiş heterokromi şeklinde tek taraflı koyu iris görünümüne neden olur.⁸ İris melanomları sıklıkla kahverengidir ancak pigmentasyon özellikleri olgudan olguya değişiklik gösterebilir, lezyonlar çok renkli veya amelanotik de olabilir (Resim 4).^{10,12}



Resim 4. A: Pigmente iris melanomu. B: Pigmentsiz iris melanomu (Resimler Dr. İlhan Günalp'a ait olup, onun izniyle kullanılmıştır).

Lezyonlarda sıklıkla damar artışı izlenir.¹⁰ Ortalama tümör çapı 6.2 mm, ortalama kalınlık 2.3 mm'dir.¹² İris melanomları pupil sınırında, orta zonda yerleşebilir, ya da pupilden çevre irise kadar uzanabilir, uydu lezyonlar şeklinde yayılım gösterebilir (Resim 5).¹⁰ Önde ön kamaraya doğru arkada ise arka kamaraya doğru büyüyebilir, silier cismi lokal ya da yaygın olarak tutabilir, arkada bu büyüme lens tarafından sınırlandırılır ve bu USG'de aslan pençesi görünümüne sebep olur.¹⁸ İris melanomlarının histopatolojik incelemesinde iğsi, epitelooid veya hem epitelooid hem de iğsi melanom hücreleri izlenebilir. Literatür olgularının yarısından fazlasında iğsi hücreler bildirilmiştir.¹⁰ Epitelooid hücre tipi veya karışık hücreli tip daha saldırgan biçimlerle

ilişkilendirilmiştir.^{12,15,18} Yaygın melanomlar, genellikle epitelooid tiptedir ve sınırlı lezyonlara kıyasla daha saldırgan klinik seyre sahiptir ve metastaz riski daha yüksektir.^{15,18}



Resim 5. Saat 4 ile 6 arasında yerleşim gösteren iris melanomu ve uydu lezyonları (Resim Dr. İlhan Günalp'a ait olup, onun izniyle kullanılmıştır).

İris melanomlarının çeşitli klinik tipleri mevcuttur. Tapioca melanomların yüzeyi çoklu nodüler görünüme sahiptir. Bir diğer iris melanom tipi trabeküler ağ melanomudur (halka melanom). Bu melanom sadece trabeküler ağı tutar, kütle oluşumundan ön kamara açısı etrafında yaygın yayılım gösterir ve tek taraflı glokomla ortaya çıkar.⁸

İris melanomlarının olası komplikasyonları arasında hifema, glokom, katarakt, metastaz ve ölüm yer alır.^{6,8,10} Glokom tümör ekimine, açılı kapanmasına veya yeni damar oluşumuna bağlı gelişebilir. Yaygın ve halka melanomlarda ikincil glokom riski daha yüksektir.^{8,15,18} Bu glokom sıklıkla ilaç tedavilerine dirençlidir ve optik diskte ağır derecede çukurlaşma ve fonksiyonel kayba neden olabilir.^{18,19}

İris melanomlarının metastaz oranları farklı çalışmalarda 5 yılda %3-11, 10 yılda %5-9 ve 20 yılda %10-11 arasında bildirilmiştir.^{10,12,20,21} Yaygın melanom varlığında, tümör kalınlığı fazla ise, eşlik eden glokom varlığında, arka tümör sınırı açı veya iris köküne ulaşmışsa, tümör göz dışına uzanım gösteriyorsa ve lezyona daha önce bir cerrahi işlem uygulanmışsa metastaz riski artmıştır.^{18,19,21} İris melanomlarının koroid ve siliyer cisim kaynaklı diğer uveal melanomlara göre daha iyi seyirli olduğu bilinmektedir.¹² Daha iyi klinik seyrin daha düşük biyolojik aktiviteye veya tümör çapına bağlı olduğu düşünülmektedir.¹² Shields ve ark.²⁰ 8033 uveal melanomu dahil ettikleri çalışmalarında iris melanomlarının ortalama çapının ve



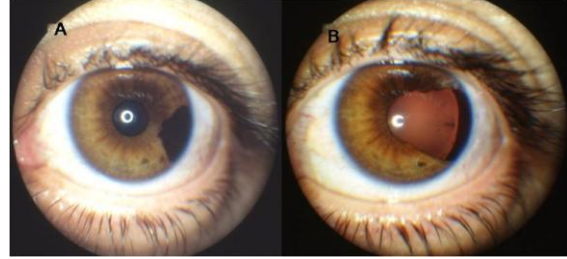
kalınlığının(5.5 mm/2.1 mm) koroidal melanoma (11.0 mm/4.5 mm) ($P<0.01$) ve siliyer cisim melanomuna (11.0 mm/6.0 mm) ($P<0.001$) kıyasla anlamlı olarak daha az olduğunu ve artan kalınlığın artmış metastaz riski ile uyumlu olduğunu göstermişlerdir. İris melanomlarında mortalite oranları melanom hücre tipi, melanom evresi, metastaz varlığı ve siliyer cisim tutulumu olup olmasına göre %0-11 arasında değişir.²² Metastaz varlığında, evre ileri ise, hücre tipi epitelioid hücre/epitelioid+iğsi hücre karakterinde ise ve siliyer cisim tutulmuşsa mortalite artış göstermektedir.²² Yaşın prognoz üzerine etkisi tartışmalıdır.¹² Bazı serilerde çocuklardaki uveal melanomların daha iyi prognoza sahip olduğu gösterilmiştir.²⁰ Shields ve ark.¹² 317 olguluk serilerinde çocuklardaki iris melanomlarında tümör boyutunun, açıl tutulumunun ve ikincil glokom gelişiminin erişkinlere kıyasla anlamlı olarak daha az olduğunu gösterdiler de metastaz ve mortalite açısından yaşa göre bir farklılık tespit etmemişlerdir.

İris melanomlarında evrelendirme için 2009 Amerika Birleşik Kanseri Komitesi evrelendirme sistemi kullanılmaktadır.²³ Buna göre irise sınırlı tümör T1, siliyer cisim veya koroide uzanan tümör T2, ek olarak skleraya uzanım gösteren tümör T3, ve sklera dışı uzanım gösteren tümör T4 olarak kabul edilmektedir. Metastazsız sağkalım T1 tümörler için 100%, T2 tümörlerde %90, T3 ve T4 tümörlerde %50'dir.^{6,10}

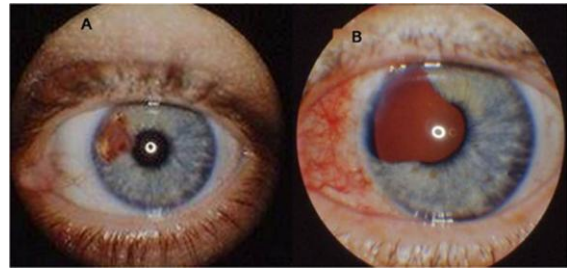
İris nevüslerinin ve melanomlarının tanısı genellikle klinikle konur. Bu lezyonlar gonyoskopi ile ayrıntılı olarak incelenmeli ve belli zaman aralıklarında fotoğraflanarak boyutları takip edilmelidir. Tümörün arka sınırlarını değerlendirmede transluminasyon testi de kullanılabilir. Karanlıkta ışık kaynağı ile transkonjonktival veya transkorneal olarak gözün aydınlatılmasıyla tümör sınırları görülebilmektedir. Şüpheli vakalarda malign-benign ayrımı için, iris floresan anjiyografi, ultrason biyomikroskopi (UBM), transluminasyon testi, ön segment optik koherens tomografi ve ince iğne aspirasyon biyopsisi kullanılabilir.¹ Ayırıcı tanıda; iris kistleri, yabancı cisimler, medülloepitelyoma ve leiomyoma gibi tümörlerin yanısıra metastatik kitleler de akılda tutulmalıdır.¹⁶

İris melanomunda tedavi yaklaşımı eğer tümör küçükse, saat 3-4 arasında

yerleşimli ise ve çevreye ekilmediyse cerrahi rezeksiyondur (iridektomi). Açıya yayılan tümörlerde iridosiklektomi tercih edilir (Resim 6, 7).²⁴ Cerrahideki amaç tümörü tamamen çıkarmak ve nükse ya da metastaza neden olabilecek tümör hücrelerini geride bırakmamaktır. Cerraha veya cerrahi tekniğe bağlı olarak kalıntı tümör, yerel nüks ve metastaz oranları sırasıyla %3-7, %2-14 ve %0-9 arasında değişir.¹⁶ Cerrahi sonrası nüks ortalama 45 ayda gelişir.¹⁶ Tümör büyükse ve çevreye ekilmişse, cerrahi sonrası histopatolojik olarak cerrahi sınırlar tutulmuşsa, klinik olarak kalıntı tümör mevcutsa veya takipte yerel nüks izlenmişse radyoterapi uygulanabilir.^{16,24} Radyoterapi radyoaktif bir plakla (plak brakiterapisi) veya dışsal ışın (proton radyoterapisi) şeklinde uygulanabilir.^{24,25} Kontrol edilemeyen glokom varlığında veya hızlı büyüme gösteren tümör varsa ve radyoterapi uygulanamıyorsa enükleasyon önerilmektedir.²⁴ Yaşam beklentisinin çok düşük olduğu ve komorbiteleri yüksek hastalarda sadece gözlem de uygun tedavi yaklaşımı olabilmektedir.¹⁶



Resim 6. İridosiklektomi ile tedavi edilen iris melanomu (Resimler Dr. İlhan Günalp'a ait olup, onun izniyle kullanılmıştır).



Resim 7. İridosiklektomi ile tedavi edilen iris melanomu (Resimler Dr. İlhan Günalp'a ait olup, onun izniyle kullanılmıştır).

Sonuçta iris melanomlarının sağkalım açısından prognozu iyi olsa da enükleasyon, metastaz ve fonksiyonel kayba neden olma riskleri nedeniyle erken tanılar önemlidir. İris melanomlarının çoğu daha önce var olan iris nevüsleri üzerinden gelişmektedir. Klinik



takipte yukarıda ele aldığımız kriterlerin kullanılması riskli nevüslerin belirlenmesi ve melanomların erken tespitini kolaylaştıracaktır.

Çıkar Çatışması: Yok

Teşekkür

Bilgilerini ve melanom hasta resimlerini bizimle paylaşan, bu derlemenin yazılma sürecinde bizden desteğini esirgemeyen sayın hocamız Prof. Dr. İlhan Günalp'a teşekkürlerimizi sunarız.

Kaynaklar

1. Kiratli H. Head and Neck: Iris Hamartomas. Atlas Genet Cytogenet Oncol Haematol. 2010; 14: 83-6.
2. Shields CL, Kancherla S, Patel J, et al. Clinical survey of 3680 iris tumors based on age at presentation. Ophthalmology. 2012; 119: 407-14.
3. Shields CL, Kaliki S, Hutchinson A, et al. Iris nevus growth into melanoma: analysis of 1611 consecutive eyes: the ABCDEF guide. Ophthalmology. 2013; 120: 766-72.
4. Ozdemir Y, Onder F, Coşar CB, Usubütün A, Kural G. Clinical and histopathologic findings of iris nevus (Cogan-Reese) syndrome. Acta Ophthalmol Scand. 1999; 77: 234-7.
5. Hassenstein A, Bialasiewicz AA, von Domarus D, Schäfer H, Richard G. Tapioca melanomas of the iris: immunohistology and report on two cases. Graefes Arch Clin Exp Ophthalmol. 1999; 237: 424-8.
6. Shields CL, Shields PW, Manalac J, Jumroendarasame C, Shields JA. Review of cystic and solid tumors of the iris. Oman J Ophthalmol. 2013; 6: 159-64.
7. Schwab C, Zalaudek I, Mayer C, et al. New insights into oculodermal nevogenesis and proposal for a new iris nevus classification. Br J Ophthalmol. 2014 Oct 30 [Epub ahead of print].
8. Jerry A, Shields JA, Shield CL. Intraocular Tumors: An Atlas and Textbook (2nd ed). Philadelphia; Lippincott Williams & Wilkins; 2008: 2; 14.
9. van Klink F, de Keizer RJ, Jager MJ, Kakebeeke-Kemme HM. Iris nevi and melanomas: a clinical follow-up study. Doc Ophthalmol. 1992; 82: 49-55.
10. Khan S, Finger PT, Yu GP, et al. Clinical and pathologic characteristics of biopsy-proven iris melanoma: a multicenter international study. Arch Ophthalmol. 2012; 130: 57-64.
11. Krohn J, Dahl O. Incidence of iris melanoma in western Norway. Acta Ophthalmologica. 2008; 86: 116-7.
12. Shields CL, Kaliki S, Shah SU, Luo W, Furuta M, Shields JA. Iris melanoma: features and prognosis in 317 children and adults. J AAPOS. 2012; 16: 10-6.
13. Jensen OA. Malignant melanoma of the iris. A 25-year analysis of Danish cases. Eur J Ophthalmol. 1993; 3: 181-8.
14. Michalova K, Clemett R, Dempster A, Evans J, Allardyce RA. Iris melanomas: are they more frequent in New Zealand? Br J Ophthalmol. 2001; 85: 4-5.

15. Millodot M, Hendler K, Pe'er J. Iris melanoma: a case report and review. Ophthalmic Physiol Opt. 2006; 26: 120-6.
16. McLaughlin JP, Fung AT, Shields JA, Shields CL. Iris melanoma in children: Current approach to management. Oman J Ophthalmol. 2013; 6: 53-5.
17. Shields JA, Sanborn GE, Augsburger JJ. The differential diagnosis of malignant melanoma of the iris. A clinical study of 200 patients. Ophthalmology. 1983; 90: 716-20.
18. Singh AD, Damato BE. Iris melanoma. In: Singh AD, Damato BE, eds. Clinical Ophthalmic Oncology (2nd ed). London; Springer; 2014: 137-158.
19. Demirci H, Shields CL, Shields JA, Eagle RC Jr, Honavar SG. Diffuse iris melanoma: a report of 25 cases. Ophthalmology. 2002; 109: 1553-60.
20. Shields CL, Furuta M, Thangappan A, et al. Metastasis of uveal melanoma millimeter-by-millimeter in 8033 consecutive eyes. Arch Ophthalmol. 2009; 127: 989-98.
21. Shields CL, Shields JA, Materin M, Gershenbaum E, Singh AD, Smith A. Iris melanoma: riskfactors for metastasis in 169 consecutive patients. Ophthalmology. 2001; 108: 172-8.
22. Geisse LH, Robertson DM. Iris melanoma. Am J Ophthalmol. 1985; 99: 638-48.
23. Edge SB, Byrd DR, Compton CC, et al. AJCC Cancer Staging Manual (7th ed). New York; Springer; 2009: 547-59.
24. Kanski JJ, Bowling B. Clinical Ophthalmology a systematic approach (7th ed). Philadelphia; Elsevier Saunders; 2011: 487-8.
25. Shields CL, Shah SU, Bianciotto CG, Emrich J, Komarnicky L, Shields JA. Iris melanoma management with iodine-125 plaque radiotherapy in 144 patients: impact of melanoma-related glaucoma on outcomes. Ophthalmology. 2013; 120: 55-61.



Primary Cardiac Angiosarcoma: A Case Report

Primer Kardiyak Anjiosarkoma: Bir Olgu Sunumu

Ayşe Gök Durnalı¹, Ayşe Yüksel², Muzaffer Bedri Altundağ³, Murat Vural⁴, Berna Öksüzöğlü¹, Necati Alkış¹

¹Dr.A. Y. Ankara Onkoloji Eğitim ve Araştırma Hastanesi, Tıbbi Onkoloji Kliniği, Ankara, Türkiye

²Ankara Onkoloji Eğitim ve Araştırma Hastanesi, Kardiyoloji Kliniği, Ankara, Türkiye

³Ankara Onkoloji Eğitim ve Araştırma Hastanesi, Radyasyon Onkolojisi Kliniği, Ankara, Türkiye

⁴Ankara Numune Eğitim ve Araştırma Hastanesi, Radyoloji Kliniği, Ankara, Türkiye

Dergiye Ulaşma Tarihi:26/02/2015 Dergiye Kabul Tarihi:28/05/2015 Doi: 10.5505/aot.2015.92400

ÖZET

Primer kardiyak anjiosarkoma, kötü prognozlu nadir bir hastalıktır. Açık kardiyak cerrahi operasyon olan ve sağ atriumda kardiyak anjiosarkoma tanısı alan 34 yaşında erkek hasta tıbbi onkoloji bölümüne başvurdu. Tümörün tam küratif rezeksiyonu mümkün olmamıştı ve hastaya postoperatif dönemde 6 siklus kombinasyon kemoterapi rejimi (doksorubisin ve mesna korumasıyla ifosfamid) verildi. Hastada 8 ay boyunca stabil hastalık mevcuttu ve progresyon sonrasında ikinci sıra kemoterapi (paklitaksel) başlandı, ancak hasta tanıdan 15 ay sonra kaybedildi. Kardiyak anjiosarkoma olgularının çoğunda küratif rezeksiyonlar mümkün olmadığından daha ileri tedavi seçeneklerine son derece ihtiyaç vardır.

Anahtar Kelimeler: Kardiyak anjiosarkoma, Kemoterapi

ABSTRACT

Primary cardiac angiosarcoma is a rare disease with poor prognosis. A 34-year-old male patient who underwent an open cardiac surgery and diagnosed as cardiac angiosarcoma on the right atrium was admitted to the medical oncology department. Complete curative resection of the tumor was not possible and postoperatively 6 cycles of combination chemotherapy regimen (ifosfamide with mesna protection and doxorubicin) was given. Patient had stable disease for 8 months, and after progression a second-line chemotherapy (paclitaxel) was started but he died after 15 months of diagnosis. Since curative resections are not possible in most of the cardiac angiosarcoma cases, further treatment options are desperately needed.

Key words: cardiac angiosarcoma, chemotherapy

Introduction:

Most of the malignant neoplasms located in the heart are metastatic tumors. Primary cardiac tumors are quite rare, and only 25% of them are malignant (1, 2). One of the malignant primary neoplasm of the heart, namely cardiac angiosarcoma originates from the mesenchymal tissue and endothelial subepicardium. It occurs more frequently in young middle-aged patients and its prognosis is very poor (3, 4). We have reported a patient with this disease and our treatment outcomes.

Case Report:

A 34-year-old man was admitted to the medical oncology department with the diagnosis of cardiac angiosarcoma. In his past

history, approximately one month ago, he was admitted to emergency department with chest pain, massive pleural effusion was detected on chest X-ray, and chest computerized tomography (CT) showed a mass in the right atrium. The chest tube was inserted and he underwent an open cardiac surgery. On exploration, pericardium was sticky and enclosed by vascular structures, there was a mass with irregular borders on the right atrium extending to the right ventricle, and invasion to the right pleura. Since complete curative resection was not possible, partial resection was undertaken. Pathological examination of resected material was reported as well-differentiated angiosarcoma with vascular invasion, 4x3 cm in size, and there was 9 mitosis per 10 high power field (HPF) and

eventually surgical margins were tumor-positive.

Cardiac magnetic resonance imaging (MRI), taken after admission to medical oncology department, revealed a mass, 81x55 mm in size, invading the anterior wall of right ventricle, protruding into the cavity of right ventricle with the suspicion of invasion to tricuspid valve and right atrium and aorta (Figure 1).

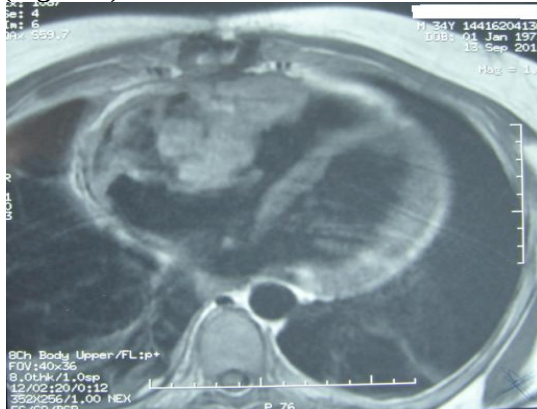


Figure 1: Magnetic resonance imaging taken after cardiac surgery revealed a mass, 81x55mm in size, invading the anterior wall of right ventricle.

Transthoracic echocardiography confirmed a semi mobile mass 50x40mm in size in the right atrium (Figure 2).



Figure 2: Transthoracic echocardiography showed a semi mobile mass 50x40mm in size in the right atrium

Abdominal ultrasonography was normal. A combination chemotherapy regimen used for other soft tissue sarcomas (ifosfamide 1800mg/m²/day on 1-5 days, with mesna protection, doxorubicin 60mg/m²/day on day 1, every 3 weeks), was started, and after the 1st cycle, febrile neutropenia developed and chemotherapy doses were reduced by 20% at the following cycles. After 3 cycles of

chemotherapy, there was a minimal regression on MRI findings and 3 more cycles were given. After 6 cycles, MRI and echocardiography revealed stable disease. Positron Emission Tomography (PET-CT) showed increased uptake of fluorodeoxyglucose only on right ventricular region. He was consulted to the heart surgery clinics for a second operation, however no more curative operation was considered to be possible. He was consulted with the radiotherapy clinics and radiotherapy was not indicated. About 5 months later, there was progression on cardiac MRI findings and chest CT showed metastatic nodules, 2 cm in diameter. With these findings second line chemotherapy (paclitaxel 175mg/m²/day on day 1, every 21 days) was started. After 3 cycles of paclitaxel chemotherapy, minimal regression was achieved, but after 6 cycles, clinical findings and imaging findings showed progression. Due to cardiac and respiratory failure, the patient died 45 days after the last chemotherapy cycle and 15 months after the initial diagnosis.

Discussion:

Primary cardiac angiosarcoma is seen infrequently, accounting for less than 10% of all primary cardiac tumors (5). It is seen mostly in right side of the heart and in young to middle-aged patients (3,4). Symptoms vary according to the size and site of the tumor: chest pain, cough, syncope, dyspnea, lung edema, arrhythmia, peripheral edema, dizziness are the most common symptoms (3,4,6,7,8). Transthoracic echocardiography and computed tomography (CT) are the useful tools for initial evaluation and suggestion of diagnosis, and MRI is helpful in preoperative differential diagnosis (8,9). Diagnosis of cardiac angiosarcoma is often confirmed by the resection of the tumor. Because of the fragility of the tumor, myocardial biopsy is not recommended. In the presented case, CT was used for the initial evaluation; and cardiac MRI and echocardiography for the evaluation of residual tumor and chemotherapy responses. Because of the rarity of this disease, there has been no standard treatment guideline. If possible, extensive surgical resection of tumor is considered as the best curative management (10,11). In some cases, radiotherapy after surgery was reported to improve outcomes

(2,10). There are insufficient data about the role of adjuvant chemotherapy. Chemotherapy regimens containing doxorubicin, ifosfamide, cisplatin and paclitaxel have been tried (6,12,13, 14). For advanced disease doxorubicin and weekly paclitaxel seem to provide some improvement in progression free survival (14). Several phase II trials have been published investigating vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitors such as sorafenib, imatinib, pazopanib, sunitinib and anti-vascular endothelial growth factor (VEGF) antibody, bevacizumab, demonstrated that some angiosarcoma patients had response or durable disease stabilization on these agents (14, 15, 16). One of these phase II studies, sorafenib showed limited antitumor activity in pretreated patients only, for both visceral and superficial angiosarcoma, with short duration of tumor control (16). Further studies are needed to confirm these findings and to identify which patients will benefit from these agents.

Whatever the chosen treatment modality, the prognosis of cardiac angiosarcoma is poor and the median survival is between 3 to 12 months. Surgical excision of the tumor may be associated with better survival increasing up to 21 months (10). If surgical resection is not possible, median survival is approximately 6 months (7,17). In one case report of a metastatic patient, multimodality palliative treatment with neoadjuvant and adjuvant chemotherapy and surgery improved survival (18). The patient presented herein had minimal symptomatic disease for about 8 months with multimodality treatment including incomplete resection and chemotherapy.

In conclusion, primary cardiac angiosarcoma is a rare and aggressive tumor with poor prognosis. For treatment options; surgical resection should be considered first and chemotherapy and radiotherapy may be indicated for palliative purposes.

Conflict of interest: None

References:

1. Reynen K: Frequency of primary tumors of the heart. *Am J Cardiol.* 1996; 77: 107
2. Moggio RA, Pucillo AL, Schechter AG, Pooley RW, Sarabu MR, Reed GE: Primary cardiac tumors: diagnosis and management in 14 cases. *NY State Med J Med.* 1992; 92: 48-52
3. Naka N, Ohsawa M, Tomita Y, Kanno H, Uchida A, Aozasa KI: Angiosarcoma in Japan: a review of 99 cases. *Cancer.* 1995;75: 989-996
4. Ge Y, Ro JY, Kim D, et al. Clinicopathologic and immunohistochemical characteristics of adult primary cardiac angiosarcomas: analysis of 10 cases. *Ann Diagn Pathol.* 2011;15(4): 262-7
5. Dennig K, Lehmann G, Richter T: An angiosarcoma in the left atrium. *N Engl J Med.* 2000;342:443-444.
6. Pezzuto A, Gencarelli G, Martone L, Bruno P, Mariotta S: Primary cardiac angiosarcoma in a young woman. *Case Rep Oncol.* 2010;3:24-29
7. Gong Y, Hong T, Chen M, Huo Y: A right heart angiosarcoma with rapidly progressing hemorrhagic pericardial effusion. *Intern Med.* 2011;50: 455-458
8. Castilla-Cabanes E, Pascual-Calleja I, Roncales-Garcia Blanco F, del Rio-Ligori A: Clinical variations of cardiac sarcoma. *Rev Esp Cardiol.* 2009;62: 823-824
9. Di Bela G, Gaeta M, Patane L, Lentini S: Tissue characterization of a primary cardiac angiosarcoma using magnetic resonance imaging. Letter to editor. *Rev Esp Cardiol.* 2010; 63(11): 1382-3
10. Poole GV, Meredith JW, Brejer R: Surgical implications in malignant cardiac disease. *Ann Thor Surg.* 1983;36: 484-491
11. Erpolat OP, Icli F, Doğan OV, et al. Primary cardiac angiosarcoma: a case report. *Tumori.* 2008;94: 892-897
12. Sarrejeant JM, Butany J, Cusimano RJ: Cancer of the heart: epidemiology and management of primary tumors and metastasis. *Am J Cardiovasc Drugs.* 2003;3: 407-421
13. Ram Prabu MP, Thulker S, Ray R, Bakhshi S. Primary cardiac angiosarcoma with good response to paclitaxel. Letter to editor. *J Thorac Oncol.* 2011;6(10): 1778-1779
14. Penel N, Maréchal S, Robin YM, Hohenberger P. Angiosarcoma: state of the art and perspectives. *Crit Rev Oncol Hematol.* 2011 Nov;80(2):257-63
15. Park MS, Ravi V, Araujo DM. Inhibiting the VEGF-VEGFR pathway in angiosarcoma, epithelioid hemangioendothelioma and hemangiopericytoma / solitary fibrous tumor. *Curr Opin Oncol.* 2010 Jul;22(4):351-5
16. Ray-Coquard I, Italiano A, Bompas E, et al. Sorafenib for patients with advanced angiosarcoma: a phase II Trial from the French Sarcoma Group (GSF/GETO). *Oncologist* 2012;17(2):260-6
17. Simpson L, Kumar SK, Okuno SH, et al Malignant primary cardiac tumors: review of a single institution experience. *Cancer.* 2008;112: 2440-2446.
18. Pigott C, Welker M, Khosla P, Higgins RS: Improved outcome with multimodality therapy in primary cardiac angiosarcoma. *Nat Clin Pract Oncol.* 2008;5: 112-115

Role of RDW and MPV in Diagnosis of Colorectal Polyps and Carcinoma: A Case-Control Study

Kolorektal Polip ve Karsinom Tanısında RDW ve MPV'nin Rolü: Vaka-Kontrol Çalışması

Mustafa Cengiz¹, Abdurrahman Şahin², Kamil Özdil³, Hacı Mehmet Sökmen³

¹Dr. A. Y. Ankara Onkoloji Eğitim Ve Araştırma Hastanesi, Gastroenteroloji Bölümü, Ankara, Türkiye.

²Fırat Üniversitesi Tıp Fakültesi, Gastroenteroloji Bölümü, Elâzığ, Türkiye.

³Ümraniye Eğitim Ve Araştırma Hastanesi, Gastroenteroloji Bölümü, İstanbul, Türkiye.

Dergiye Ulaşma Tarihi:28/04/2015 Dergiye Kabul Tarihi:28/05/2015 Doi: [10.5505/aot.2015.96268](https://doi.org/10.5505/aot.2015.96268)

ÖZET

Giriş ve Amaç: Ortalama trombosit hacmi (MPV) kırmızı kan hücresi dağılım genişliği (RDW) testleri rutin tam kan sayımında bulunan basit testlerdir. İnflamasyon, MPV ve RDW değerlerinde değişiklikler yapabilir. Bu çalışmada KRK, adenom ve sağlıklı kontrollerin MPV ve RDW değerlerini karşılaştırmayı amaçladık.

Yöntem ve Gereçler: KRK veya irritabl barsak hastalığı şikâyetleri nedeniyle kolonoskopik tarama yapılan vakaların MPV ve RDW değerleri geriye dönük olarak değerlendirilmiştir. Kolonoskopi ve histopatolojik bulgularına göre hastalar KRK, adenom ve normal kontrol grubu olmak üzere 3 ayrı gruba ayrıldı. Sonrasında adenom grubu displazi ve villöz komponent varlığına göre yüksek olasılıklı prekanseröz ve düşük olasılıklı prekanseröz olarak 2 alt gruba ayrıldı.

Bulgular: Çalışmaya ardışık toplam 602 hasta alındı. Bunlardan KRK grubunda (n=130)'si, adenom grubunda (n=241)'si ve normal kolonoskopik bulguları olan (n=233)'si hasta kontrol grubundaydı. KRK grubunda diğer gruplara nazaran hemoglobin, MCV değerleri daha düşükken trombosit sayıları daha yüksek bulundu (P<0.001). MPV ortanca değerleri KRK, adenom ve kontrol grupları arasında karşılaştırıldığında sırasıyla (7,51-7,91-7,90 ve P<0,001). Ayrıca RDW median değerleri gruplara arasında (15,7-14,6-14,4 ve P<0,001) istatistiksel olarak anlamlı bulundu. Adenom alt grupları karşılaştırıldığında düşük-yüksek olasılıklı gruplar arasında sadece RDW açısından istatistiksel anlamlı fark tespit edildi (14,4-14,8,ve P=0.02). MPV değerleri açısından gruplar arasında fark bulunamadı (7,89-8,04 ve P>0.05).

Tartışma ve Sonuç: Kolonoskopik taramaya alınacak vakalarda RDW ve MPV değerleri dikkate alınmalıdır.

Anahtar Kelimeler: Adenom, Karsinom, MPV, RDW

ABSTRACT

Introduction: Mean platelet volume (MPV) and red cell distribution width (RDW) are simple tests in routine complete blood count. We aimed to evaluate RDW and MPV values of patients with colorectal carcinoma (CRC), adenoma and healthy controls.

Methods: The MPV and RDW values of participants who underwent colonoscopic examination for CRC screening or irritable bowel syndrome related symptoms were evaluated retrospectively. Patients were divided into three groups as CRC group, adenoma group and control group according to colonoscopic and histopathological findings. Patients with adenomas were separated into two subgroups according to dysplasia and villous component as high probable precancerous (HPP) and low probable precancerous (LPP) groups.

Results: A total of consecutive 602 participants were enrolled into the study. There were n=130 patients in CRC, n=241 patients adenoma group and n=233 in control group. The CRC group had lower hemoglobin levels, MCV values and higher platelet count compared to adenoma group and control group. The median MPV values of CRC group (7.51) were lower than adenoma group (7.91) and control group (7.90) (P<0.001, for both). The median RDW value of CRC group (15.7) was significantly higher than adenoma group (14.6) and controls (14.4) (P=0.01, for both). Adenoma subgroups comparison reveals that the only different parameter was RDW between LPP and HPP (14.4 vs. 14.8, P=0.02). The MPV values are similar in both groups (7.89 vs. 8.04, P>0.05).

Discussion and Conclusion: The RDW and MPV values should be taken into consideration in patients who underwent colonoscopic screening.

Key words: Adenoma, carcinoma, MPV, RDW

Giriş

Kolorektal kanser (KRK) dünyada kanser ilişkili morbidite ve mortalitenin en sık nedenlerinden biridir (1). Kanserlerin %95'inden fazlası adenomatöz polipten orijin alır. KRK'lerin büyük bir çoğunluğu normal görünümlü mukozadan adenoma, displazi ve nihai olarak karsinoma geçiş gösteren sıralı yolakla meydana gelir. Genelde 50 yaşından sonra adenomatöz polipler sıklıkla görülmekle beraber poliplerin büyük bir çoğunluğu adenokarsinoma ilerlemez (2). Yüksek evre displazi ve önemli villöz komponent gibi bazı histolojik özelliklerin nihai kanser oluşmasını tahmin etmede değerleri vardır. KRK tanısının erken konması kanser ilişkili mortaliteyi azaltmakta ve sağkalımı arttırmaktadır. Ayrıca KRK taraması bazılarının prekanseröz özellikleri olabilecek poliplerin tespit edilmesinde ve çıkarılmasında önem arz etmektedir. Bu bulguların doğrultusunda kolonoskopik takip önerilmektedir. KRK taraması için gaitada gizli kan, kolonoskopik veya radyolojik prosedürler uygulanmaktadır. Ancak KRK taraması için yaygın bir şekilde kabul gören herhangi bir kan testi bulunmamaktadır.

Kırmızı kan hücreleri (RBC), beyaz kan hücreleri ve trombositleri içeren dolaşımdaki kan hücrelerinin sayılıp şekillendirilmesi için elektronik analiz cihazları kullanılmaktadır. Toplam hücre sayımı yapılmasının yanı sıra bu cihazlar ayrıca ortalama hücre hacmini ve hücre boyutunun dağılımını tahmin etmede kullanılmaktadırlar. Kırmızı hücre dağılım genişliği (RDW) eritrosit popülasyonunun değişkenliğinin ölçüsüdür (3). Artmış RDW retikülositlerin dolaşıma olgunlaşmadan salınmasına neden olan bir sürü hastalıkta görülebilir. Aneminin ayırıcı tanısının yanı sıra yükselmiş RDW değerleri kalp yetmezliği, kardiyovasküler olaylar, çölyak hastalığı ve inflamatuvar barsak hastalığı aktivitesi ile ilişkili bulunmuştur (4). Ayrıca RDW'deki artışların artmış inflamatuvar markırlarla ilişkili olduğu bulunmuştur (5,6).

Trombositler; koagülasyonda, inflamasyonda, trombozda ve aterosklerozda önemli rol oynayan çok

sayıda cisimleri üretir ve salgılarlar. Ortalama trombosit hacmi (MPV) inflamasyonu gösteren ve en geniş olarak çalışılan moleküllerden biridir. Trombosit sayısı ve MPV birbiriyle ters ilişkilidir böylelikle toplam trombosit kütlesi yaklaşık olarak sabit kalmaktadır (7). Yüksek MPV belirlenmiş değişik önemli risk faktörleri ile ilişkili bulunmuştur ve kardiyovasküler, serebrovasküler hastalıklar ve arteriyel ve venöz tromboza neden olan düşük evre inflamasyonla ilişkilidir. Yüksek evre inflamasyonla ilişkili olan romatoid artrit veya Ailevi Akdeniz Ateş (FMF) ataklarında düşük MPV değerleri tespit edilmiştir (8). Literatürde kanser hastalarının RDW değerlerini araştıran az sayıda çalışma bulunmaktadır (9, 10). Ayrıca kanser hastalarının MPV değerlerini araştıran çalışmaların sayısı daha da azdır (11). Öyle ki bu çalışmalarda hem Kürk'le hasta sayısı az hem de sağlıklı kontrollerle karşılaştırma yapılmamıştır. Ayrıca literatürde kolon adenomlarının RDW ve MPV değerleri hakkında veri bildiğimiz kadarıyla bulunmamaktadır.

Bu çalışmada amacımız; KRK tanısı alan hastalar veya kolon polipi olan hastaların RDW ve MPV değerlerinin normal sağlıklı kontrollerin değerleriyle karşılaştırılmasıdır. Ayrıca alt grup analizde düşük ve yüksek derece displazili adenomları olan hastaların değerlerini karşılaştırmayı amaçladık.

Gereç ve Yöntem

Hastalar:

Bu retrospektif çalışmaya KRK taraması veya irritabl barsak hastalığı şikayetleri nedeniyle total kolonoskopi yapılan hastalar alındı. Vakalar kolonoskopik ve histopatolojik bulgularına göre KRK grubu, adenom grubu ve normal kontrol olmak üzere 3 ayrı gruba ayrıldı. Hastaların demografik özellikleri, kolonoskopi yapılma nedenleri, yaş, cinsiyet, eski tıbbi hikaye ve kolonoskopi işlemi esnasında laboratuvar testleri binası önlemek için hastaların bulgularından haberdar olmayan klinisyen tarafından veri tabanına kaydedildi. Kolonoskopi

işlemeden önce hastaların onayı alındı. Vakaların demografik ve klinik bilgileri analiz edildi. Kanseri olan hastalar anemi durumuna bakılmaksızın çalışmaya alındı. Öncesinde KRK nedeniyle opere olan ve kolonoskopik takip için işlem yaptıran hastalar çalışmadan dışlandı. Tam kan sayım (CBC) değerleri tanı anında ve herhangi bir kan ürünü replasmanı yapılmadan elde edilen kanlardan çalışıldı.

Kolon polipi olan hastalar histopatolojik olarak displazi derecesine ve villöz komponent varlığına göre 2 ayrı alt gruba ayrıldı; yüksek olasılıklı prekanseröz (yüksek dereceli displazi veya villöz adenom) ve düşük olasılıklı prekanseröz (tübüler/tübülövilöz adenom ve düşük derece displazi). Kolonoskopi esnasında birden fazla polip tespit edildiğinde derecesi en yüksek olan displazi ile villöz komponenti olan polip çalışmaya alındı. Kolonoskopide polip tespit edilen veya kolonoskopik bulguları normal olan vakaların son 3 ayda var olan CBC değerleri çalışmaya dahil edilmiştir. Kronik diyare veya demir eksikliği anemisi etiyojisini aydınlatmak için kolonoskopi yapıp işlemde normal veya polip tespit edilen hastalar yanlış sonuçları engellemek için dışlanmıştır.

Bütün gruplar için, RDW veya MPV değerlerini etkileyecek diyabet, tiroit disfonksiyonu, inme, tromboembolik olaylar, kalp yetmezliği, kardiyovasküler olaylar ve inflamatuvar bozuklukları gibi kronik rahatsızlığı olan hastalar çalışmadan dışlanmıştır. Ayrıca hem RDW hem de MPV değerlerine ulaşamayan hastalar çalışmadan dışlanmıştır.

Laboratuvar testleri:

Hemoglobin (HB), mean corpuscular volume (MCV), RDW, trombosit sayısı, beyaz küre (WBC) ve MPV değerleri Advia 2120 (Siemens Healthcare Diagnostics Inc., Tarrytown, New York, USA) cihazı kullanılarak tespit edilmiştir. Ayrıca RDW hesaplaması (standart sapma (SD)/MCV X 100%) denklemi kullanılarak yapılmıştır.

İstatistiksel analizler:

İstatistiksel analizler SPSS 21. Versiyonu kullanılarak yapıldı. Değişkenler normal

dağılıp dağılmadığını araştırmak için görsel (histogram, olasılık plotları) ve analitik metotlar (Kolomogorov-Smirnov/Shapiro-Wilk's testleri) kullanıldı. Normal dağılım gösteren değişkenler için ortalama ve standart sapma kullanılırken normal dağılmayan değişkenler için ortanca ve aralık değerleri verildi. Normal dağılım gösteren değişkenler 3 grup arasında karşılaştırılınca varyans analiz ile değerlendirme yapıldı ve bonferroni düzeltmesi Student T testi ile yapıldı. Normal dağılmayan değişkenler için Kruskal Wallis testleri ve Bonferroni düzeltmesi Mann-Whitney U testi kullanılarak yapıldı. Ayrıca düşük derece ve yüksek derece displazi grupları arasında parametreler Man Whitney U testi kullanılarak değerlendirildi. P değeri için 0,05'ten küçük olan değerler istatistiksel olarak anlamlı kabul edildi.

Sonuçlar

Bu çalışmaya toplamda 602 ardışık vaka alındı. Vakalar KRK grubu, adenom grubu ve normal kontrol olmak üzere 3 ayrı gruba ayrıldı. Karsinom grubunda 130 hasta varken bunların %57,7'si erkekti. Toplamda 241 adenom hastasının %64,5'i erkek hastalardan oluşuyordu. Ayrıca kolonoskopisi normal olan 233 sağlıklı vaka çalışmada yer aldı. KRK grubunda bulunan vakaların yaşları diğer her iki gruptan daha büyüktü ve fark istatistiksel olarak anlamlıydı (P<0.001). Cinsiyet açısından gruplar arasında istatistiksel olarak anlamlı farklılık yoktu.

Karsinom grubunda diğer her iki gruba nazaran daha düşük HB ve MCV değerleri bulunurken trombosit değerleri daha yüksek bulundu ve farklılık istatistiksel olarak anlamlıydı (Bütün değişkenler için P<0,001). Trombosit sayısı adenom grubunda sağlıklı gruba göre daha düşüktü (P=0.03) ayrıca MCV değerleri daha yüksekti (P=0,03). MPV değerleri karşılaştırıldığında karsinom, adenom ve sağlıklı grupların değerleri sırasıyla 7,51 (5,6-11,1)-7,91 (5,89-13,70)-7,90 (5,89-18,60) olarak tespit edildi. Karsinom ve adenom grupları ve karsinom

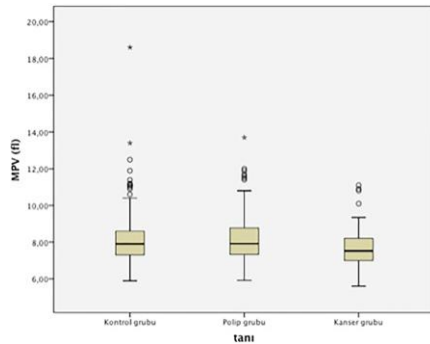
ile kontrol grupları arasında MPV açısından anlamlı istatistiksel fark bulunurken ($P<0,001$). Polip grubu ile kontrol grubu arasında istatistiksel anlamlı fark bulunamadı ($P>0,05$). Ayrıca ortanca RDW değerleri açısından gruplar karşılaştırıldığında KRK grubunda adenom grubuna göre daha yüksek değerler tespit edildi. (15,7 ile 14,6 ve $P<0,001$). Ayrıca KRK grubu ile kontroller arasında da RDW açısından

istatistiksel anlamlı fark bulundu (15,7 ile 14,4 ve $P<0,001$). Ancak adenom grubu ile kontrol grubu arasında anlamlı fark bulunamadı (14,6 ile 14,4 ve $P>0,05$). Çalışmaya alınan vakaların klinik özellikleri ve laboratuvar değerlerinin karşılaştırılması Tablo 1’de özetlenmiştir. Ayrıca MPV ve RDW değerlerinin gruplar arasında karşılaştırılması sırasıyla Şekil 1 ve Şekil 2’de gösterilmiştir.

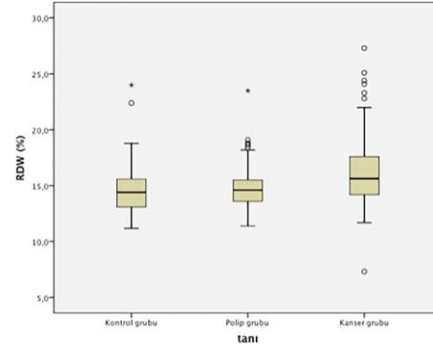
Tablo 1: Vakaların klinik özellikleri ve laboratuvar değerlerinin karşılaştırılması

	Kontrol grubu	Adenom grubu	Karsinom grubu	P değeri
Yaş (yıl)	53,3 ±13,1	57 ±11,8	62,8 ± 12,8	<0.001
Cinsiyet Erkek (%)	136 (%58,6)	156 (%64,5)	75 (%57,7)	0.26
Hemoglobin ^a (g/dL)	13,8 (12,1-17,3)	14 (11,9-17,7)	11,8 (5,7-19,6)	< 0.001
Trombosit ^a (/mm ³ ×10 ³)	259 (125-509)	252 (122-526)	335 (98-822)	< 0.001
MPV ^a (fL)	7,9 (5,89-18,6)	7,91 (5,92-13,7)	7,51 (5,6-11,1)	< 0.001
RDW ^a (%)	14,4 (11,2-24)	14,6 (11,4-23,5)	15,7 (7,3-27,3)	< 0.001
MCV ^a (fL)	86,5 (62,9-97,5)	87,3 (66,9-99,3)	83,3 (63,4-98)	< 0.001

MCV: ortalama corpuscular hacim RDW: Kırmızı kan hücresi dağılım genişliği; MPV: Ortalama trombosit hacmi. (^a) Data median olarak temsil edilmiştir (range).



Şekil 1: Grupların MPV değerlerinin karşılaşı.



Şekil 2: Grupların RDW değerlerinin karşılaşı.

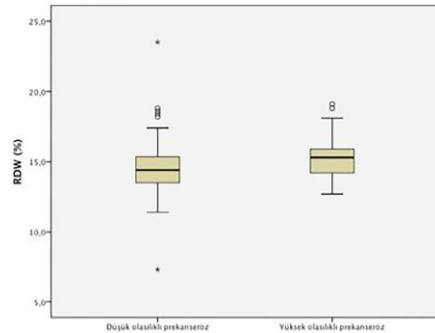
Polip grubu düşük olasılıklı prekanseröz ve yüksek olasılıklı prekanseröz olmak üzere 2 gruba ayrılmıştı. Düşük olasılık grubunda 148 hasta bulunurken yüksek olasılık grubunda 93 hasta bulunuyordu. Yaş açısından yüksek olasılık grubu daha yaşlı hastalardan oluşmaktaydı. Bu alt grupların demografik ve karakteristik özellikleri ve CBC sonuçlarının karşılaştırılması Tablo

2’ gösterilmiştir. RDW değerleri yüksek olasılık grubunda daha yüksek olmak üzere her iki grup arasında karşılaştırıldığında farklılık istatistiksel olarak anlamlı bulundu (14,4 ile 14,8 ve $P=0,02$). Bu karşılaştırma Şekilde 3’te gösterilmiştir. Ancak MPV değerleri gruplar arasında istatistiksel olarak anlamlı farklı değildi (7,89 ile 8,04 ve $P>0,05$).

Tablo 2: Polip alt grupların demografik ve laboratuvar özelliklerinin karşılaştırılması.

	Düşük derece grup	Yüksek derece grup	P değeri
Yaş (yıl)	55,2 ± 12,4	59,7 ± 10,3	< 0,001
Cinsiyet Erkek (%)	91 (86,1,5)	64 (68,8)	0,25
Hemoglobin ^a (g/dL)	14,2 (11,9-17,7)	13,9 (11,9-17,5)	0,47
Trombosit (/mm ³ x 10 ³)	251 (122-518)	252 (139-526)	0,81
MPV ^a (fL)	7,89 (6,5-11,9)	8,04 (5,92-13,7)	0,48
RDW ^a (%)	14,4 (11,4-23,5)	14,8 (12,7-19,1)	0,02
MCV ^a (fL)	87,1 (66,9-99,3)	87,3 (69,2-97,2)	0,81

MCV: ortalama corpuscular hacim RDW: Kırmızı kan hücresi dağılım genişliği; MPV: Ortalama trombosit hacmi. (^a) Data median olarak temsil edilmiştir (range).

**Şekil 3:** Polip alt gruplarının RDW değerlerinin karşılaştırılması

Tartışma

Bu çalışmada KRK grubu, adenom grubu ve kontrol gruplarının CBC parametrelerini karşılaştırdık ve sonuçta KRK hasta grubunda RDW değerlerinde artış izlenirken MPV değerlerinde düşüş olduğu tespit edildi. Kolonik poliplerin ise CBC parametreleri üzerine ciddi bir etkileri olmadığı görüldü. Polip özelliğine göre tek anlamlı farklılık RDW değerlerinde tespit edildi.

Aşkar veya gizli gastrointestinal sistem kanamaları KRK en önemli bulgularından biridir. Gastrointestinal kanama ve demir eksikliği anemisi erkeklerde ve menopoz sonrası kadınlarda kolorektal değerlendirme için 2 önemli endikasyondur. Gastrointestinal sistemden kronik kan kaybı demir eksikliği anemisi yapar öyle ki demir eksikliği anemisine bağlı olarak KRK hastalarında HB ve MCV değerleri düşük bulunurken RDW ve trombosit değerleri yüksek bulunur. Bizim sonuçlarımız bu gerçeğe uyuşmaktadır. Ayrıca Spell ve ark'ının yaptığı bir çalışmada RDW değerlerinin sağ kolon kanserlerinde yüksek derecede

sensitif ve spesifik olduğu tespit edilmiş. Bu çalışmada kontrol grubunda %12'lik bir RDW yüksekliği tespit edilmişken KRK grubunda bu oran %69 olarak bulunmuş. Sağ taraf KRK, sol taraf KRK ve kontrol gruplarının ortalama RDW değerleri sırasıyla 16,8- 15- 13,3 olarak bulunmuş. İlginç olarak CBC'nin diğer parametreleri (HB, MCV) ile RDW'nin kombinasyonunda tek başına RDW'nin sensitivite ve spesifitesini artıramamıştır. Eritrosit hacmindeki değişkenlik aşkar anemiden önce ortaya çıkmaktadır ve normal CBC ile birlikte artmış RDW erken demir eksikliği anemisinin iyi sensitif ve spesifik bir belirteçidir (9). Ayrıca demir eksikliğini tespit etmekte artmış RDW diğer laboratuvar testlerinden daha duyarlıdır (12).

Yapılan bazı çalışmalarda tıbbi checkup için başvuran hastalarda anemi durumundan bağımsız olarak RDW değerlerinin inflamatuvar markırlarla (yüksek sensitif C reaktif protein (CRP) ve eritrosit sedimentasyon hızı (ESR)) ilişkili olduğu bulunmuştur (5, 13). İnflamasyonun eritropoez ve dolaşımdaki eritrosit yarı ömrü üzerindeki etkisi anizositoza neden olup RDW değerlerinde artışa neden olabilmektedir (14). Yapılan bir çalışmada RDW değerlerindeki 1 SD artışın kanser mortalitesinde %28'lik bir artışla ilişkisi olduğu tespit edilmiştir. İlginç olarak RDW'nin mortalite ile olan ilişkisi inflamasyonun varlığına bağımlı değildi (6). Bizim çalışmamızda kanser bağımlı inflamasyon ve kronik hastalık anemisi anemi durumu ve artmış RDW durumu ile ilişkili olabilir.

Dolaşımdaki küçük ve büyük yapıdaki trombositlerin sınıflandırılmasında sistemik

inflamasyonun şiddeti değerlendirilmelidir (8). Artmış MPV düzeyleri genelde vasküler risk faktörleri, immün trombositopenik durumlar, düşük derece inflamatuvar durum ve edinsel dev trombosit bozukluklarla ilişkilidir. Düşük MPV değerleri ise sitotoksik tedavi sonrası kemik iliği aplazisi, hipersplenizm, reaktif trombositosis yüksek dereceli inflamasyon ve Wiskott-Aldrich sendromu ile ilişkilidir (15). Kanser bir sürü proinflamatuvar sitokin salgılandığı sistemik inflamatuvar bir bozukluktur. Birkaç proinflamatuvar sitokin kemik iliğindeki hematopoetik hücrelerin maturasyonuna etki ederek hematopoetik hücrelerin dolaşıma salgılanmasına neden olur. Yüksek derece inflamasyonla ilişkili durumlar (aktif inflamatuvar barsak hastalığı, Romatoid Artrit, FMF atağında) genel olarak dolaşımdaki küçük trombositlerle ve düşük MPV değerleri ile ilişkili iken aynı durumlar remisyonda iken veya anti-inflamatuvar ilaç kullanımı dolaşımdaki daha büyük trombositlerle ve daha yüksek MPV değerleri ile ilişkilidir (8). Yüksek derece inflamasyon MPV ile negatif ilişkilidir. Adenomdan karsinom gelişimi malign hücrelerin mukozal tabakayı geçmesi ve sonuç olarak sistemik yüksek inflamatuvar durum oluşması ile sonuçlanır. Öyle ki KRK hastalarında düşük MPV değerleri beklenen bir durumdur.

Bu çalışmada MPV'nin KRK ve adenom ile olan ilişkisini araştırdık ve kolon poliplerinin MPV üzerine önemli bir etkinliği olmadığı sonucuna vardık ancak düşük MPV değerleri KRK ile ilişkiliydi. Yapılan bir çalışmada Bevacizumab tedavisi alan metastatik KRK hastalarında MPV değerlendirilmiş (11). Bu çalışmada bulunan ortalama MPV değerleri bizim sonuçlardan daha yüksek olarak bulunmuş. Öyle ki bu çalışmadaki hastaların çoğu opere olmuş ve metastatik KRK olarak sınıflandırılmış. Bizim daha düşük MPV değerlerini bulmamızın bir nedeni de hastaların opere olmadan ve tanı konar konmaz değerlerine bakılması nedeniyledir. Öyle ki metastatik KRK hastalarının bir kısmında kitle rezeke edilmediği için değerlendirme aşamasında lezyondan salınan bazı sitokinler megakaryosit ve MPV değerlerini

etkilemiştir. Ayrıca biz çalışmamızda opere olmuş ve takip kolonoskopi olan hastaları dışladığımız için bizim değerler daha düşük olarak bulundu. Böylelikle bizim sonuçlarımızla KRK'nin net olarak MPV üzerine olan etkisi net ve açık olarak tespit edilmiş olmaktadır. Adenom ve kontrol grupları karşılaştırıldığında anlamlı fark bulamadık ayrıca düşük-yüksek olasılık prekanseröz adenomlar arasında da istatistiksel anlamlı fark bulunmadı. Bu sonuç gösteriyor ki; polipi olan hastalarda polipin özelliğinden bağımsız olarak mukoza tabakasına sınırlanmış düşük derece inflamasyon MPV değerlerine etki etmemektedir. Öte yandan prekanseröz derecesi ile RDW arasında ilişki tespit edildi. Düşük derece inflamasyon RDW değerlerini etkilerken MPV değerleri etkilenmemektedir. İnflamasyonun mukozanın ötesine geçmesiyle trombositosis ve MPV düşüşü meydana gelmektedir.

Çalışmamızın bazı kısıtlamaları mevcuttu şöyle ki; retrospektif dizayn olması, nispeten özellikle adenom grubunda düşük hasta sayısı varlığı olarak sayılabilir. Ayrıca retrospektif dizayndan dolayı polip çapı değerlendirilemedi. Ancak polip çapı hem yapan kişiye bağlıdır hem de genelde yaklaşık olarak değerlendirildiği için sağlıklı sonuç vermeyecektir. Kişiler arasındaki bu değişkenliğin etkisinden kurtulmak için polip boyutu ile değerlendirme subjektif olabileceği için çalışmada değerlendirilmemiştir. Ayrıca biz bu çalışmada KRK hastaların tanı anındaki CBC değerlerini değerlendirdik ilerde prospektif olarak tanı anında, operasyon sonrası ve kemoradyoterapi sonrası değerlendirme yapılması hastalık trendinde bu markerlerin rolünü daha iyi bildirecektir.

Sonuç olarak, KRK hastalarında MPV değerleri düşük olarak bulunurken displazi ve adenomun villöz komponenti varlığı RDW değerlerini arttırmaktadır. Bu çalışmanın sonuçlarına göre, kolonoskopik tarama yapılacak hastalarda RDW ve MPV değerleri dikkate alınmalıdır. Kanser ve inflamasyonun kemik iliği dolaşımdaki hematopoetik hücreler üzerine etkilerini

araştırmak için randomize kontrollü ve prospektif çalışmalara ihtiyaç vardır.

Çıkar Çatışması: Yok

Kaynaklar:

1. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer* 2010; 127: 2893-2917
2. Levin B, Lieberman DA, McFarland B, Andrews KS, Brooks D, Bond J et al. Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps, 2008: a joint guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology. *Gastroenterology* 2008; 134: 1570-1595
3. Dixon LR. 1997. The complete blood count: physiologic basis and clinical usage. *J Perinat Neonatal Nurs* 1997; 11: 1-18
4. Song CS, Park DI, Yoon MY, Seok HS, Park JH, Kim HJ et al. Association between red cell distribution width and disease activity in patients with inflammatory bowel disease. *Dig Dis Sci* 2012; 57: 1033-1038
5. Lippi G, Targher G, Montagnana M, Salvagno GL, Zoppini G, Guidi GC. Relation between red blood cell distribution width and inflammatory biomarkers in a large cohort of unselected outpatients. *Arch Pathol Lab Med* 2009; 133: 628-632
6. Perlstein TS, Weuve J, Pfeffer MA, Beckman JA. Red blood cell distribution width and mortality risk in a community-based prospective cohort. *Arch Intern Med* 2009; 169: 588-594
7. Bath PM, Butterworth RJ. Platelet size: measurement, physiology and vascular disease. *Blood Coagul Fibrinolysis* 1996; 7: 157-161
8. Gasparian AY, Ayyazyan L, Mikhailidis DP, Kitas GD. Mean platelet volume: a link between thrombosis and inflammation? *Curr Pharm Des* 2011; 17: 47-58
9. Spell DW, Jones DV, Jr., Harper WF, David Bessman J. The value of a complete blood count in predicting cancer of the colon. *Cancer Detect Prev* 2004; 28: 37-42
10. Baicus C, Caraiola S, Rimbas M, Patrascu R, Baicus A. Utility of routine hematological and inflammation parameters for the diagnosis of cancer in involuntary weight loss. *J Investig Med* 2011; 59: 951-955
11. Mutlu H, Berk V, Karaca H, Erden A, Aslan T, Akca Z. Treatment regimen with bevacizumab decreases mean platelet volume in patients with metastatic colon cancer. *Clin Appl Thromb Hemost* 2012; 18: 546-548
12. Van Zeben D, Bieger R, van Wermeskerken RK, Castel A, Hermans J. Evaluation of microcytosis using serum ferritin and red blood cell distribution width. *Eur J Haematol* 1990; 44: 106-109
13. Lappe JM, Horne BD, Shah SH, May HT, Muhlestein JB, Lappe DL et al. Red cell distribution width, C-reactive protein, the complete blood count, and mortality in patients with coronary disease and a normal comparison population. *Clin Chim Acta* 2011; 412: 2094-2099
14. Weiss G, Goodnough LT. Anemia of chronic disease. *N Engl J Med* 2005; 352: 1011-1023
15. Aksoy S, Kilickap S, Hayran M, Harputluoglu H, Koca E, Dede DS ve ark. Platelet size has diagnostic predictive value for bone marrow metastasis in patients with solid tumors. *Int J Lab Hematol* 2008; 30: 214-219.

The utility of diffusion-weighted imaging in differentiation of papillary and clear cell subtypes of renal cell carcinoma

Renal Hücreli Kanserde Difüzyon Ağırlıklı MR Görüntüleme Kullanılarak Papiller ve Şeffaf Hücreli Subtiplerin Ayırt Edilmesi

Hale Çolakoglu Er¹, Elif Peker², Ayşe Erden², Erdem Öztürk³

¹Şehitkamil Devlet Hastanesi, Radyoloji Bölümü, Gaziantep, Turkey

²Ankara Üniversitesi Tıp Fakültesi, Radyoloji Ana Bilim Dalı, Ankara, Turkey

³Ankara Üniversitesi Tıp Fakültesi, Üroloji Ana Bilim Dalı, Ankara, Turkey

Received: 22/12/2014 Accepted: 18/02/2015 Doi: [10.5505/aot.2015.25238](https://doi.org/10.5505/aot.2015.25238)

ÖZET

Amaç: Bu çalışmadaki amacımız, papiller tip ile şeffaf hücreli renal hücreli kanser alt tiplerini ayırt etmede difüzyon ağırlıklı görüntülemenin yararlılığını belirlemektir.

Yöntem: Papiller tip ve şeffaf hücreli tip renal kanseri olan toplam 16 olgu retrospektif olarak değerlendirilmiştir. İnceleme 3 Tesla alan gücüne sahip manyetik rezonans cihazında gerçekleştirilmiştir. Renal kitle konturları T2 ağırlıklı görüntülerden de faydalanılarak sınırlanmış ve kistik-nekrotik dejenerasyon alanları dışarıda kalacak şekilde elle çizilen ilgi alanı (freehand ROI) kullanılarak kitlelerin solid komponentlerinin $b=50 \text{ sn/mm}^2$ ve $b=1000 \text{ sn/mm}^2$ DAG'lerde görünür difüzyon katsayı (apparent diffusion coefficient =ADC) değerleri ve ortalama sinyal intensite (SI) değerleri ile böbreğin normal parankiminin ortalama sinyal intensite (SI) değerleri ölçülmüştür. Normal parankimin sinyal intensite değerlerinin ölçümü için ROI kortikomedüller bileşmeye yerleştirilmiştir.

Bulgular: Ortalama ADC değeri papiller RHK' larda $(0.991 \pm 0.143 \times 10^{-3} \text{ mm}^2/\text{sn})$ şeffaf hücreli RHK'lardan istatistiksel olarak anlamlı derecede düşüktü $(1.296 \pm 0.277 \times 10^{-3} \text{ mm}^2/\text{sn})$ ($p<0.05$). Ayrıca papiller RHK grubunda, $b=1000 \text{ sn/mm}^2$ DAG'lerde ölçülen ortalama SI değerleri (22.8 ± 6.3) , normal parankimden (43.4 ± 14.8) ; şeffaf hücreli RHK grubunda $b=50 \text{ sn/mm}^2$ DAG'lerde ölçülen ortalama SI değerleri (102 ± 27.5) , normal parankimden (138.8 ± 33) istatistiksel olarak farklıydı ($p<0.05$).

Sonuç: Papiller ve şeffaf hücreli kanser subtiplerinin ayırt edilebilmesinde difüzyon ağırlıklı görüntüleme faydalı bir yöntem olabilir. Papiller hücreli kanserlerin sınırları, $b=1000 \text{ sn/mm}^2$; şeffaf hücreli kanserlerin sınırları ise $b=50 \text{ sn/mm}^2$ DAG'lerde daha net olarak seçilebilmektedir. Bulgularımızın desteklenmesi için daha geniş hasta serisini kapsayan çalışmalara gereksinim vardır.

Anahtar Kelimeler: Renal hücreli kanser; magnetik rezonans görüntüleme; difüzyon ağırlıklı görüntüleme; görünür difüzyon katsayısı.

ABSTRACT

Objective: To determine the utility of diffusion-weighted imaging (DWI) in differentiation of papillary and clear cell subtypes of renal cell carcinoma (RCC).

Methods: A total of 16 patients with papillary RCC and clear cell RCC were enrolled in this retrospective study. Patients underwent MRI with a 3.0-Tesla wholebody system (MAGNETOM Verio, Siemens, Erlangen, Germany) using a standard body matrix coil. Apparent diffusion coefficient (ADC) values and signal intensity (SI) values at $b=50 \text{ s/mm}^2$ $b=1000 \text{ s/mm}^2$ DWI of solid components of the renal masses and SI values of normal renal parenchyma were measured. A freehand ROI was drawn around the peripheral margin of the tumor on the diffusion images excluding the cystic or necrotic portions, while referring to the T2-weighted conventional images for verification of lesion boundaries. To measure SI values of normal renal parenchyma, ROIs were placed on the normal corticomedullary junction.

Results: Mean ADC value was statistically significantly lower in papillary RCC $(0.991 \pm 0.143 \times 10^{-3} \text{ mm}^2/\text{s})$ than in that of clear cell RCC $(1.296 \pm 0.277 \times 10^{-3} \text{ mm}^2/\text{s})$. For the papillary RCC group, there was statistically significant difference ($p<0.05$) between mean SI values of normal parenchyma (22.8 ± 6.3) and lesion (43.4 ± 14.8) at $b=1000 \text{ s/mm}^2$ DWI; for the clear cell RCC group there was statistically significant difference ($p<0.05$) between mean SI value of normal parenchyma (138.8 ± 33) and lesion (102 ± 27.5) at $b=50 \text{ s/mm}^2$ DWI.

Conclusion: For discrimination of papillary and clear cell subtypes of RCC, DWI seems to be a useful method. The boundaries of papillary RCC can be more clearly perceived on $b=1000 \text{ s/mm}^2$ and that of clear cell RCC on $b=50 \text{ s/mm}^2$ DWI. However, more extensive research on a larger series of patients are needed to support our findings.

Key words: renal cell carcinoma, magnetic resonance imaging, diffusion weighted imaging, apparent diffusion coef

Introduction

The most common renal malignancy is renal cell carcinoma (RCC) originates from the renal

parenchyma. The global incidence of RCC has increased over the past twenty years by 2% per year (1). The most common subtypes include



clear cell RCC (70% of RCC cases), papillary RCC (10–15%), and chromophobe RCC (5%) (2,3).

Diffusion-weighted imaging (DWI) is a magnetic resonance imaging (MRI) technique based on the molecular mobility of water (4). On DWI, lesions with dense cellularity and poor interstitium that restrict the mobility of water molecules exhibit high signal intensity (5). The apparent diffusion coefficient (ADC) allows for quantification of diffusivity, which is shown to be restricted in the majority of malignancies due to higher cellularity compared to surrounding tissue. The measurable data obtained by DWI can give opinion about the nature of the lesions in various parts of the body and help to characterize them without using intravenous contrast medium (6).

Characterization of the renal tumors before operation is necessary for clinical decision and evaluation of prognosis (3). Recent studies on MRI of the renal tumors showed that ADC values obtained by DWI may provide a new quantitative data for differentiating benign tumors from the malignant ones and may help identifying pathologic subtypes of the neoplasms (7,8). The aim of this study was to determine the utility of DWI in discrimination of papillary and clear cell subtypes of RCC.

Materials and Methods

Patients

A total of 29 patients with renal mass underwent dynamic renal MRI using 3.0 Tesla system in our radiology department between October 2012 and November 2014 were retrospectively analyzed. Thirteen patients were excluded for absence of histopathologic results. Sixteen patients (14 male, 2 female; age range, 37-75 years, mean 58 years) whose histopathological data were available were included to the study. Nine patients had clear cell RCC, 7 patients had papillary type RCC.

MR techniques

The patients underwent MRI at 3.0 Tesla whole-body system (Magnetom Verio, Siemens) using standard body matrix coil. The imager operates with a maximum gradient strength of 45 mT/m and a slew rate of 200 mT/m/s in all three directions. Conventional

MR images and DW images were acquired during the same procedure. The MR imaging examination consisted of coronal T2-weighted half-Fourier single-shot turbo spin-echo (HASTE) multi breathhold images, axial T2-weighted turbo spin-echo (TSE) BLADE images, axial T2-weighted images with fat saturation, axial dual echo T1-weighted gradient-echo images, axial DW images, and axial 3D fat suppressed T1-weighted gradient echo (VIBE: Volume Interpolated Breathhold Examination) images. All pulse sequence parameters used in this study are listed in detail in Table 1.

After the acquisition of precontrast routine sequences for renal MR imaging, DW images with three different b values (50,400, and 1000 s/mm²) were obtained in the axial plane using a single-shot multi-slice echoplanar imaging (EPI) sequence with spectral adiabatic inversion recovery fat suppression and the following parameters: repetition time/echo time, 5500/75 ms; EPI factor,122; field of view, 380×296 mm; matrix size,128×102; slice thickness, 5.0 mm; distance factor, 20%; averages, 4; reduction factor, 2; and receiver bandwidth, 2442 Hz/Px. The acquisition time for the DWI was 4min and 24 seconds.

Image interpretation

The ADC maps were automatically generated by using a monoexponential decay model including all three b-values at Siemens Software Version syngo MR B17. ADC values and signal intensity of normal renal parenchyma and solid components of the renal masses were determined as follows: Freehand (ROI)s covering the tumor was defined for the lesions detected on the diffusion images, while referring to the T2-weighted conventional sequence for verification of lesion boundaries. Diffusion-weighted images with $b = 50 \text{ s/mm}^2$ was used for the mixed cystic and solid lesions and $b=1000 \text{ s/mm}^2$ DWI was selected for the evaluation of solid lesions. On each slice, the high signal intensity of tumor boundaries was traced manually and ROIs were copied to the corresponding ADC map to measure ADC values. To measure SI values of normal renal parenchyma, ROIs were placed in the normal corticomedullary junction of the kidney. Signal intensities of normal kidney and papillary RCC were measured on $b=1000 \text{ s/mm}^2$ diffusion



images. Signal intensities of normal kidney and clear cell RCC was measured on b=50

s/mm² diffusion images.

Table 1. Pulse sequence parameters

	T2-weighted HASTE	T2- weighted TSE BLADE	T1- weighted GE (In-opp phase)	DWI EPI b=50, 400,1000 s/mm ²	T1-weighted 3D GE VIBE (dynamic)
Parameter					
Matrix (fr x p)	320x224	320x256	320x224	128x102	320x224
Slice thickness (mm)	5.0	7.0	5.0	5.0	3.0
Distance factor	20%	20%	20%	20%	20%
TR (ms)	1400	2500	206	5500	3.92
TE (ms)	93	89	TE (i) 2.46 TE (o) 6.15	75	1.39
Flip angle (degree)	180	140	70	-	9
Fat suppression		SPAIR	-	SPAIR	Q-fat sat
Reduction factor	2	2	2	2	2
NEX	1	1	1	4	1
Number of slices	30	30	35	25	64 (per phase)
FoV (mm)	380x380	380x380	380x224	380x296	380x308
Plane	Coronal	Transvers	Transvers	Transvers	Transvers
Band width (Hz/Px)	446	300	280	2442	400
Breathing control	Breath hold	Navigator	Breath hold	Free//Navigatr	Multibreath hold
Acquisition time (min:s)	0:42	4:32	0:40	4:24	1:08

Statistical analysis

Statistical analysis was performed using a commercially available software (Statistical Package for Social Sciences, version 15.0, SPSS Inc., Chicago, Illinois, USA). The results were reported as means±SD. The t test was used to compare the differences between mean ADC values obtained in papillary RCC and clear cell RCC groups. Also, significances of the differences between mean SI values at diffusion-weighted images with b = 50 s/ mm² of clear cell RCC and normal parenchyma were analyzed with t test. Significances of the differences between mean SI values at diffusion-weighted images with b = 1000 s/ mm² of papillary RCC and normal parenchyma were analyzed with paired t-test (paired samples t test). Significances of the differences between mean SI values at diffusion-weighted images with b = 400 s/ mm² of papillary RCC and normal parenchyma; clear cell RCC and normal parenchyma were analyzed with paired

t-test (paired samples t test). P values less than 0.05 were deemed to indicate a statistically significant difference.

Results

The mean ADC value was significantly lower in papillary RCC ($0.991 \pm 0.143 \times 10^{-3}$ mm²/s) than in that of clear cell RCC ($1.296 \pm 0.277 \times 10^{-3}$ mm²/s) ($p < 0.05$) (Fig 1). For the papillary RCC group, there was statistically significant difference ($p < 0.05$) between mean SI values of normal parenchyma (22.8 ± 6.3) and lesion (43.4 ± 14.8) at b=1000 s/mm² DWI; for the clear cell RCC group, there was statistically significant difference ($p < 0.05$) between mean SI values of normal parenchyma (138.8 ± 33) and lesion (102 ± 27.5) at b=50 s/mm² DWI. For the papillary RCC group, there was not statistically significant difference ($p > 0.05$) between mean SI values of normal parenchyma (62.5 ± 21.8) and lesion (75 ± 28.8) at b=400 s/mm² DWI. For the clear cell group, there was not statistically significant difference ($p > 0.05$) between mean SI values of normal parenchyma



(58.8 ± 9.4) and lesion (54.1 ± 15.4) at $b=400$ s/ mm^2 DWI.

The MRI findings of lesions are presented in Table 2. Examples of our cases is presented in Figs. 2 and 3.

Table 2. MRI findings of lesions

	T1- weighted GE	T2-weighted HASTE	T2- weighted TSE BLADE	DWI $b=50$ s/ mm^2	DWI $b=400$ s/ mm^2	DWI $b=1000$ s/ mm^2	ADC	T1-weighted 3D GE VIBE(dynamic)
1	Isointense	Hyperintense	Hyperintense	Isointense	Hyperintense	Hyperintense	Hypointense	Not performed
2	Isointense	Hypointense	Hypointense	Isointense	Hyperintense	Hyperintense	Hypointense	Not performed
3	Isointense	Hypointense	Hypointense	Isointense	Hyperintense	Hyperintense	Hypointense	Not performed
4	Iso-hypointense	Hypo-hyperintense	Hypo-hyperintense	Isointense	Hyperintense	Hyperintense	Hypointense	Not performed
5	Isointense	Hypointense	Hypointense	Isointense	Hyperintense	Hyperintense	Hypointense	Moderate enhancement
6	Isointense	Hypointense	Hypointense	Isointense	Hyperintense	Hyperintense	Hypointense	Moderate enhancement
7	Iso- hyperintense	Hypo-Hyperintense	Hypo-Hyperintense	Isointense	Hyperintense	Hyperintense	Hypointense	Not performed
8	Hypointense	Hypointense	Hypointense	Isointense	Hyperintense	Hyperintense	Hypointense	Not performed
9	Iso- hyperintense	Hypointense	Hypointense	Isointense	Hyperintense	Hyperintense	Hypointense	Moderate enhancement
10	Iso- hyperintense	Hypo-Hyperintense	Hypo-Hyperintense	Hypo-Hyperintense	Iso- hyperintense	Iso- hyperintense	Hypo-Hyperintense	Not performed
11	Iso-hypointense	Iso-hyperintense	Iso-hyperintense	Hypo-Hyperintense	Iso- hyperintense	Iso-hyperintense	Hypo-Hyperintense	Not performed
12	Hypointense	Hypo-Hyperintense	Hypo-Hyperintense	Hypo-Hyperintense	Iso- hyperintense	Iso-hyperintense	Hypo-Hyperintense	Not performed
13	Hypo-Hyperintense	Iso-hyperintense	Hypo-Hyperintense	Hypo-Hyperintense	Iso- hyperintense	Iso-hyperintense	Hypo-Hyperintense	Not performed
14	Hypo-Hyperintense	Iso-hypointense	Hipo-Hiperintens	Hypo-Hyperintense	Iso- hyperintense	Iso-hyperintense	Hypo-Hyperintense	Not performed
15	Iso-hypointense	Iso-hyperintense	Iso-hyperintense	Hypo-Hyperintense	Iso- hyperintense	Iso-hyperintense	Hypo-Hyperintense	Heterogen enhancement
16	Iso-hypointense	Iso-hyperintense	Iso-hyperintense	Hypo-Hyperintense	Iso- hyperintense	Iso-hyperintense	Hypo-Hyperintense	Heterogen enhancement



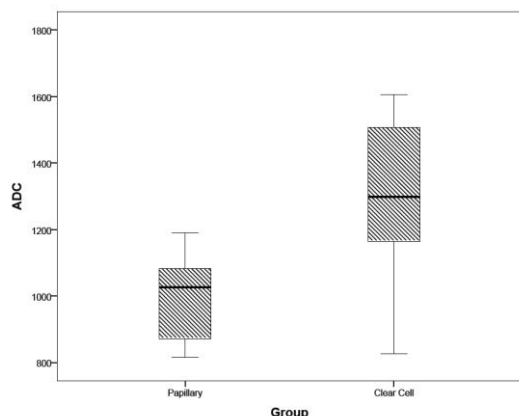


Figure 1. Graphic representation of the ADC values ($\times 10^{-3} \text{ mm}^2/\text{s}$) of papillary and clear cell RCC groups.

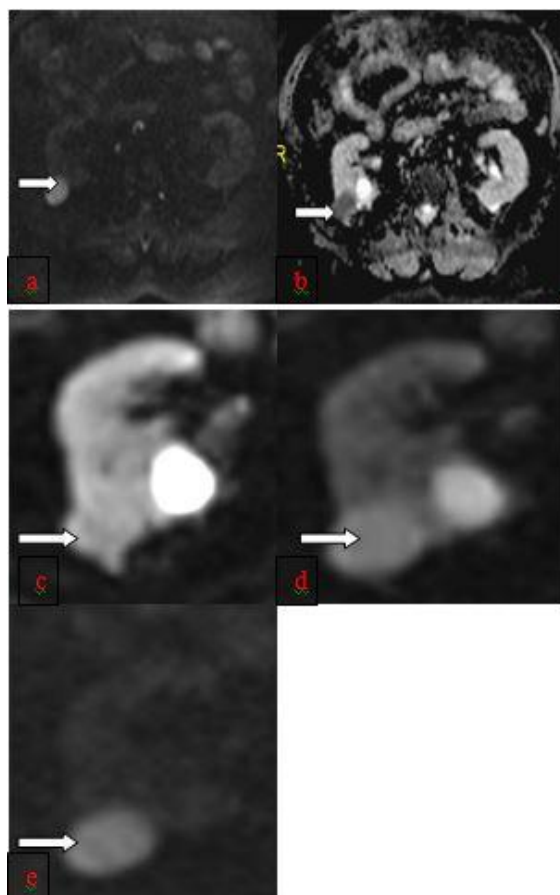


Figure 2. a–e. A 68 year-old-male with papillary RCC. Arrows show the tumor. (a) Axial DW imaging obtained with b value of 1000 s/mm^2 . Mean signal intensity value is measured 40. (b) ADC map shows that the ADC of the tumor is $0.90 \times 10^{-3} \text{ mm}^2/\text{s}$. (c) In DW images obtained with b value of 50 s/mm^2 the papillary RCC (showed with arrow) was hardly distinguishable from adjacent parenchyma (d) DW images obtained with b value of 400 s/mm^2 , (e) in DW images obtained with b value of 1000 s/mm^2 , the papillary RCC has

become more clearly visible by the suppression of the surrounding tissue.

Discussion

Recent studies suggested that DWI could provide comparable accuracy to contrast-enhanced MRI in identifying renal lesions (7,9). In our study, we found that the mean ADC value was statistically significantly lower in papillary RCC than in that of clear cell RCC. In a study conducted by Wang et al, clear cell RCCs demonstrated higher ADCs than papillary RCCs and chromophobic RCCs ; with b values of 0 and 800 s/mm^2 , papillary RCCs showed lower ADCs than chromophobic RCCs, while with b values of 0 and 500 s/mm^2 , no significant difference in ADC was seen between papillary RCCs and chromophobic RCCs (8). In the study of Paudyal et al, a significant difference in ADC values between clear cell carcinoma and non-clear cell carcinoma was found (10). Yu et al. presented that the ADC value was also statistically different between clear cell RCC and non-clear cell RCC, and between different grades of clear cell RCC except grade I vs II and grade III vs IV (11). Inci et al. found statistically significant difference with ADC values and b factors of 500 and 1000 in types of renal carcinoma, the mean ADC value of chromophobe cell carcinoma was significantly higher than that of papillary cell carcinoma and clear cell carcinoma (12). We did not evaluate chromophobe cell carcinoma, because we had only one patient with this subtype. Taouli et al. have reported that DW imaging can be used to characterize renal lesions; however, compared with contrast enhanced MR imaging, it is less accurate . Our study focused on the efficacy of DWI, the relationship between DWI and contrast enhanced MR imaging in differentiation of subtypes of renal cell carcinoma was not evaluated. In the study of Sandrasegaran et al, there was no significant difference between the ADCs of clear cell cancers and non-clear cell cancers (13). However, they used minimum ADC per lesion whereas we used mean ADC value.

A wide range in ADCs in subtypes of renal cell carcinoma has been reported in the literature: We found mean ADC value $0.991 \pm 0.143 \times 10^{-3} \text{ mm}^2/\text{s}$ in papillary RCC and $1.296 \pm 0.277 \times 10^{-3} \text{ mm}^2/\text{s}$ in clear cell RCC, which were different in the study of Yu et al ($1.053 \pm$



0.380 in papillary RCC and 1.469 ± 0.417 in clear cell RCC). This probably is caused by using different b values. The mean ADC values in our study were similar to the mean ADC values in the study of Inci et al. ($0.90 \pm 0.16 \times 10^{-3} \text{ mm}^2/\text{s}$ in papillary RCC and $1.23 \pm 0.13 \times 10^{-3} \text{ mm}^2/\text{s}$ in clear cell RCC). Zhang

et al. indicated that the ADC values measured with low b values showed high standard deviations (14).

In the study of Wang et al, higher b values than 800 s/mm^2 , such as 1000 s/mm^2 , were not selected because according to their experience, when a b value of 1000 sec/mm^2

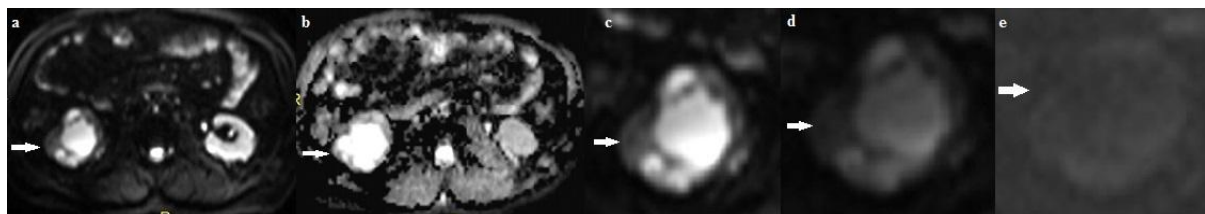


Figure 3. a–e. A 60 year-old-female with clear cell RCC. Arrows show the tumor with cystic and necrotic areas. (a) Axial DW imaging obtained with b value of 50 s/mm^2 . Mean signal intensity value is measured 98. (b) ADC map shows that the ADC of the tumor is $1.42 \times 10^{-3} \text{ mm}^2/\text{s}$. (c) In DW images obtained with b value of 50 s/mm^2 the clear cell RCC (showed with arrow) was clearly visible because of shining of cystic areas (d) DW images obtained with b value of 400 s/mm^2 (e) in DW images obtained with b value of 1000 s/mm^2 , the clear cell RCC was hardly distinguishable from adjacent parenchyma.

is used, the signal-to-noise ratio (SNR) of DW images decreases so significantly that part of the images cannot be evaluated. In our study, we used $b = 1000 \text{ s/mm}^2$ value because it seemed more appropriate for distinguishing RCC subtypes by using ADCs and we did not experience difficulties in analyzing images due to low SNR.

Different from the other studies, we also measured mean SIs on diffusion weighted images. For the papillary RCC group, there was statistically significant difference ($p < 0.05$) between mean SI value in $b = 1000 \text{ s/mm}^2$ values between normal parenchyma (22.8 ± 6.3 and lesion (43.4 ± 14.8). For the clear cell RCC group, there was statistically significant difference between mean SI value in $b = 50 \text{ s/mm}^2$ values between normal parenchyma (138.8 ± 33 and lesion (102 ± 27.5). This allows us to discriminate the lesion borders easily on $b = 1000 \text{ s/mm}^2$ diffusion images and on $b = 50 \text{ s/mm}^2$ diffusion images, respectively for papillary RCC and clear cell RCC.

In previous studies, investigators have evaluated the value of DWI in assessing the cellularity of renal masses. In the study of Squillaci et al, the mean ADC value of renal tumors did not significantly correlate with tumor cellularity (15). Rosenkrantz et al, have reported that ADC values, obtained with b

values 0 and 400 and 0 and 800 s/mm^2 , were lower among high-grade than among low-grade ccRCC (16).

Diffusion-weighted imaging has been limited due to its artifacts associated with respiratory motion, peristalsis and cardiac pulsations. Breath-hold EPI technique (17) which we also used in our study helps DWI to become feasible to cope such artifacts seen in abdomen imaging (18,19). Most of the recent studies on DWI usually performed with 1.5 T MRI system. In the present investigation, we used a 3-T MRI which had advantage of improved SNR compared to 1.5 T. However, comparative studies showed high correlation of the ADC values between both field strengths (20, 21).

Our study had some limitations. We assessed small number patients in our study. Further studies with a large number of populations are necessary to confirm our findings. Several factors such as ROI shape, partial-volume effects, MRI equipment, intraobserver variability affect the ADC measurements (22,23). Possible measurement errors due to above-mentioned factors may lead to misdiagnoses and should be taken into consideration when DWI is used to discriminate the RCC subtypes.

Conflict of Interest: None



References

1. National Cancer Institute. Surveillance, Epidemiology, and End Results Program. SEER stat fact sheets: kidney and renal pelvis cancer, 2013.
2. Nickerson ML, Jaeger E, Shi Y, Durocher JA, Mahurkar S, Zaridze D, et al. Improved identification of von Hippel-Lindau gene alterations in clear cell renal tumors. *Clin Cancer Res* 2008; 14:4726–34.
3. Crepel M, Jeldres C, Perrotte P, Capitanio U, Isbarn H, Shariat SF, et al. Nephron-sparing surgery is equally effective to radical nephrectomy for T1BN0M0 renal cell carcinoma: a population-based assessment. *Urology* 2010; 75:271–5.
4. Holdsworth SJ, Bammer R. Magnetic resonance imaging techniques: fMRI, DWI, and PWI. *Semin Neurol* 2008; 28:395–406.
5. Koh DM, Collins DJ. Diffusion-weighted MRI in the body: applications and challenges in oncology. *AJR Am. J. Roentgenol* 2007; 188:1622–35.
6. Elmi A, Hedgire SS, Covarrubias D, Abtahi SM, Hahn PF, Harisinghani M. Apparent diffusion coefficient as a non-invasive predictor of treatment response and recurrence in locally advanced rectal cancer. *Clin Radiol* 2013; 68:524–531.
7. Taouli B, Thakur RK, Mannelli L, Babb JS, Kim S, Hecht EM, et al. Renal lesions: characterization with diffusion-weighted imaging versus contrast-enhanced MR imaging. *Radiology* 2009; 251:398–407.
8. Wang H, Cheng L, Zhang X, Wang D, Guo A, Gao Y, et al. Renal cell carcinoma: diffusion-weighted MR imaging for subtype differentiation at 3.0 T. *Radiology* 2010; 257:135–43.
9. Kim S, Jain M, Harris AB, Lee VS, Babb JS, Sigmund EE, et al. T1 hyperintense renal lesions: characterization with diffusion-weighted MR imaging versus contrast-enhanced MR imaging. *Radiology* 2009; 251: 796–807.
10. Paudyal B, Paudyal P, Tsushima Y, Oriuchi N, Amanuma M, Miyazaki M, et al. The role of the ADC value in the characterisation of renal carcinoma by diffusion-weighted MRI. *British Journal of Radiology* 2010; 83:336–43.
11. Yu X, Lin M, Ouyanga H, Zhou C, Zhang H, et al. Application of ADC measurement in characterization of renal cell carcinomas with different pathological types and grades by 3.0 T diffusion-weighted MRI. *European Journal of Radiology* 2012; 81:3061–3066.
12. İnci E, Hocaoglu E, Aydin S, Cimilli T. Diffusion weighted magnetic resonance imaging in evaluation of primary solid and cystic renal masses using the Bosniak classification. *Eur J Radiol* 2012; 81:815–20.
13. Sandrasegaran K., Sundaram P., Ramaswamy R. Akisik FM, Rydberg MP, Lin C, et al. Usefulness of Diffusion-Weighted Imaging in the Evaluation of Renal Masses *AJR* 2010; 194:438–445 .
14. Zhang JL , Sigmund EE , Chandarana H , Rusinek H, Chen Q, Vivier PH, et al . Variability of renal apparent diffusion coefficients: limitations of the monoexponential model for diffusion quantification. *Radiology* 2010 ; 254: 783 – 792.
15. Squillaci E, Manenti G, Di Stefano F, Miano R, Strigari L, Simonetti G. Diffusion-weighted MR imaging in the evaluation of renal tumours. *J Exp Clin Cancer Res* 2004; 23:39–45.
16. Rosenkrantz AB, Niver BE, Fitzgerald EF, Babb JS, Chandarana H, Melamed J. Utility of the apparent diffusion coefficient for distinguishing clear cell renal cell carcinoma of low and high nuclear grade. *American Journal of Roentgenology* 2010; 195:344–51.
17. Müller MF , Edelman RR . Echo planar imaging of the abdomen . *Top Magn Reson Imaging* 1995 ; 7 : 112 – 119 .
18. Matoba M , Tonami H , Kondou T , Yokota H, Higashi K, Toga H, et al . Lung carcinoma: diffusion-weighted MR imaging—preliminary evaluation with apparent diffusion coefficient . *Radiology* 2007 ; 243: 570 – 577 .
19. Inan N , Arslan A , Akansel G , Anik Y, Sarisoy HT, Ciftci E, et al . Diffusionweighted imaging in the differential diagnosis of simple and hydatid cysts of the liver . *AJR Am J Roentgenol* 2007; 189: 1031–1036 .
20. Cornfeld DM, Weinreb JC. MR imaging of the prostate: 1.5T versus 3T. *Magn Reson Imaging Clin N Am* 2007; 15:433–48. 40.
21. Habermann CR, Gossrau P, Kooijman H, Graessner J, Cramer MC, Kaul MG, et al. Monitoring of gustatory stimulation of salivary glands by diffusion-weighted MR imaging: comparison of 1.5T and 3T. *AJNR Am J Neuroradiol* 2007; 28:1547–51.
22. Feuerlein S, Pauls S, Juchems MS, Stuber T, Hoffmann MH, Brambs HJ, et al. Pitfalls in abdominal diffusion-weighted imaging: how predictive is restricted water diffusion for malignancy. *AJR Am Roentgenol* 2009; 193:1070–1076.
23. Le Bihan D, Poupon C, Amadon A, Lethimonnier F. Artifacts and pitfalls in diffusion MRI. *J Magn Reson Imaging*. 2006; 24:478–88.



Intraoral Reconstruction with Microsurgical Free Flaps

Serbest Fleplerle Ağız İçi Defektlerinin Rekonstrüksiyonu

Hakan Uzun¹, Ozan Bitik², Ela Cömert³, Caner Kılıç³, Samet Özlügedik³, Ümit Tunçel³

¹Dr. A. Y. Ankara Oncology Training And Research Hospital, Plastic Reconstructive and Aesthetic Surgery, Ankara, Turkey

²Hacettepe University Faculty of Medicine, Department of Plastic Reconstructive and Aesthetic Surgery, Ankara, Turkey

³Dr. A. Y. Ankara Oncology Training And Research Hospital, Department of Otorhinolaryngology, Ankara, Turkey

Received: 29/04/2015 Accepted: 05/05/2015 Doi: [10.5505/aot.2015.02986](https://doi.org/10.5505/aot.2015.02986)

ÖZET

Amaç: Yazarlar, tek bir merkezde intraoral bölge için gerçekleştirilen serbest flep rekonstrüksiyonlarını değerlendirmeyi amaçlamışlardır.

Yöntemler: Baş boyun bölgesindeki defektlerin rekonstrüksiyonu için 4 yıllık süre içinde onbir tane serbest doku nakli gerçekleştirildi. Hastalar, defekt lokalizasyonu, uygulanan flepler, komplikasyonlar ve hastanede yatış süreleri açısından değerlendirildi.

Bulgular: Yedi hasta serbest radial önkol flebi ile, iki hasta serbest vertikal rektus abdominis muskulokütan flebi ile, bir hasta serbest transvers rektus abdominis muskulokütan flebi ile bir hasta da serbest fibula osteomuskulokütan flebi ile rekonstrükte edildi. Fleplerin hiçbirinde anastomozda tromboz veya hematoma nedeniyle reeksplorasyon yapılmadı. Flep kaybı görülmedi. Mortalite veya major morbidite ile karşılaşılmadı. Ortalama hastanede yatış süresi 21.1 gündü (11-25 gün).

Sonuç: Ağız içi defektlerinin rekonstrüksiyonu için multidisipliner yaklaşım desteklenmelidir. Uzun ameliyat süresi, donör alan morbiditesi ve mikrocerrahi başarısızlığı gibi riskleri olmasına rağmen serbest doku nakilleri birçok kompleks defektin onarımına olanak sağlamaktadır.

Anahtar Kelimeler: serbest flep; intraoral rekonstrüksiyon; mikrocerrahi.

ABSTRACT

Objective: The authors aimed to evaluate the outcomes of free flap reconstructions performed for intraoral region in a single center.

Methods: Eleven free flaps have been performed for defects of the head and neck over a 4-year period. The patients were evaluated in terms of defects, flaps performed, complications and hospital stays.

Results: Seven patients were reconstructed with radial forearm free flap, one patient was reconstructed with free transverse rectus abdominis musculocutaneous flap, two patients were reconstructed with free vertical rectus abdominis musculocutaneous flap and the remaining one was reconstructed with free fibula osteomuskulocutaneous flap. None of the flaps required reexploration for anastomotic thrombosis or hematoma. No flap failure occurred. We did not encounter any mortality or major morbidity. The average hospital stay was 21.1 days with a range from 11 to 25 days.

Conclusions: Multidisciplinary approach should be encouraged for the reconstruction of intraoral defects. The versatility of free tissue transfers allows reconstruction of most complex defects; although it carries significant risks, including longer operative times, donor site morbidity, recipient site complications and microsurgical failure, and longer hospital stays.

Keywords: free flap, head and neck oncology, intraoral reconstruction, microsurgery.

Introduction

Since the development of free tissue transfer and microsurgical techniques in the 1980s, microvascular free flap tissue transfers have largely become the gold standard for reconstruction of complex head and neck

defects¹⁻³. One distinct advantage of free tissue transfer is its utility (surface area, volume, vascularity, diversity of tissue type) when compared to local or regional tissue transfer. As a result, a large variety of defect dimensions and locations can be reconstructed, allowing for larger oncologic resections,

improved tissue coverage and lower patient morbidity.

Over time, there have been significant changes in reconstructive techniques, with gravitation towards a narrower set of donor sites and a reduction in complication rates^{4,5}. The selection and outcomes of free tissue transfers in head and neck reconstructions were evaluated in this study. Outcomes were based on donor and recipient site and indication for reconstruction. Despite the widespread use of this technique in the head and neck, not all free flap donor sites or recipient sites are equivalent. Furthermore, a single percentile to describe failure rates is misleading. We evaluated patients who presented for a microvascular free flap reconstruction of a complex head and neck defect in order to better understand the potential risks and benefits of each type of free tissue transfer.

Methods

Patient Selection

The patients who presented between March 2011 and April 2015 for a microvascular free flap reconstruction of a head and neck defect were included (n=11). The selection of the donor site depended on the defect (cutaneous, soft tissue, or bone), and surgeon preference. Demographic characteristics examined included: surgical indication, duration of hospital stay, and complications.

Results

Patient and Flap Characteristics

All of the patients were males with a mean age of 54. Indications for reconstruction

included defect following resection of a primary or recurrent malignancy (75%, n=6), a secondary reconstruction (25%, n=5). The distribution of microvascular free flaps used for reconstruction of the defects was as follows: radial forearm fasciocutaneous flap (RFFF) (63,6%, n=7), vertical rectus abdominis musculocutaneous (VRAM) flap (18,2%, n=2), transverse rectus abdominis musculocutaneous (TRAM) flap (9,1%, n=1), and free fibula osteomusculocutaneous flap (9,1%, n=1). Ipsilateral facial artery and its venae comitantes were used for microsurgical anastomosis. In one patient contralateral facial vessels were dissected. One patient who previously underwent bilateral neck dissection and radiotherapy required saphenous vein grafts due to the unavailability of facial vessels. Superior thyroid vessels were chosen for anastomosis in that case. One artery and one vein anastomosis were performed for each flap. Aside from rectus flaps, two-team approach was used. The average hospital stay was 21.1 days with a range from 11 to 25 days.

Defect Characteristics

All of the patients had squamous cell carcinoma. Two patients had cancers located on floor of the mouth (Figure 1). One patient had cancer located over the palatopharyngeal fold which extended to lateral and posterior parts of the tongue. They were reconstructed with free RFFF (Figure 2). Two patients underwent partial glossectomy and functional surgery with RFFF was contemplated. One patient underwent hemimandibulectomy and was reconstructed with free fibula osteomusculocutaneous flap (Figure 3). Four patients required release of adhesions between base of tongue and lower lip. Three rectus abdominis flaps and one RFFF were utilized to create new sulcus and lower lips.

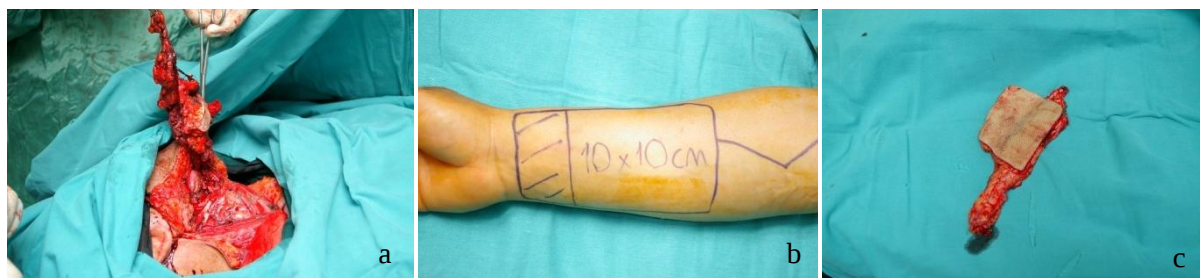


Figure 1a: The defect of the floor of the mouth just before the the specimen was resected en bloc **b:** Planning of the RFFF **c:** Harvested RFFF



Figure 2a: The 3D defect of the palatopharyngeal region, retromolar region and lateral part of the floor of the mouth exposing carotid vessels. **b:** Planning of the RFFF **c:** Insetting of the RFFF **d:** Postoperative 14th day appearance

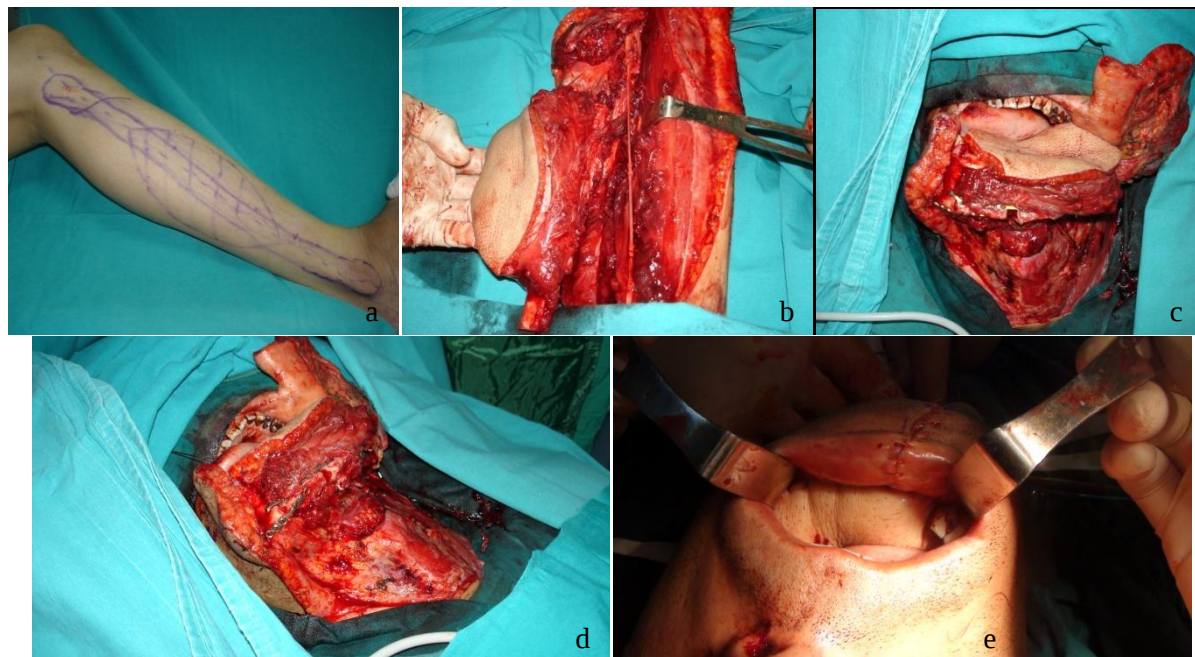


Figure 3a: Planning of the fibula osteomusculocutaneous flap **3b:** Harvesting of the flap **c:** Insetting the skin island of the flap **d:** Two osteotomies were performed on the flap to create the neoangulus of the mandible **e:** Early postoperative result

Complications

All of the free flaps survived. Neither mortality nor major morbidity was developed. None of the flaps required reexploration for

anastomotic thrombosis or hematoma. The surgical complication rate was 18,2%. This included haematoma formation under the neck

flaps (9,1%, n=1), and graft infection at the donor area of the fibula flap (9,1%, n=1).

Discussion

The versatility of free tissue transfers allows reconstruction of most complex defects; however, it carries significant risks, including longer operative times, donor site morbidity, recipient site complications and free flap failure, and longer hospital stays. As a result, careful consideration and evaluation is necessary prior to reconstruction. Several variables dictate donor site selection including tissue composition, extent of defect, distance from recipient vessels, and surgeon preference.

The most commonly utilized flap in our series was the RFFF. In 1981, Yang et al⁶ were among the first to use the radial forearm flap in head and neck surgery, and this RFFF is nowadays a workhorse in reconstructive head and neck surgery. The RFFF along with the anterolateral thigh flap (ALT) can be considered the workhorses for reconstructing upper aerodigestive tract defects⁷. It is commonly used for tongue, floor of mouth, lip and hard palate reconstruction. Its greatest advantage is the thin and pliable nature of the flap ideal for intraoral soft tissue lining defects. Its ease of harvest and long pedicle (about 20 cm) with large caliber vessels makes it popular with beginners. It can be harvested by two-team approach. Other advantages are the presence of large diameter superficial veins (cephalic or basilic) and deep venous system (the venae comitantes). Studies have shown that the smaller venae comitantes give reliable venous outflow but due to their smaller caliber, anastomosis is difficult compared to the cephalic vein⁸. There still is a debate regarding which is the dominant venous system. Ichinose et al.⁹ used Doppler to demonstrate the venae comitantes to be dominant. They theorized that interruption of small superficial venous channels draining into cephalic vein during flap harvest would force venous drainage more into the deep system. In our series we used a more clinical way of judgment. After flap harvest, the artery was anastomosed first and venous return was noted from both the superficial and deep systems. Whichever had a faster outflow was used for anastomosis.

Bianchi et al.¹⁰ and Kesting et al.¹¹ reported several advantages of the ALT flap for head and neck defects, including versatility, short harvesting time, and donor site morbidity. However, Kesting et al.¹¹ reported that intra-operative arterial spasms occurred more often in the case of the ALT free flap than in the case of RFFF.

Because of its safety, versatility, and predictable anatomy, the VRAM has become a work horse flap for reconstruction throughout the body and within the head and neck region¹². It has an unparalleled safety record with the lowest vessel thrombosis and flap failure rates¹³. The flap has a lengthy vascular pedicle for anastomosis to either side of the neck and the large caliber of the inferior epigastric vessels makes microsurgical coaptation straightforward. Primary donor-site closure for very large VRAMs can be achieved without the need for mesh or an additional skin graft. The remote location from the head and neck region saves operative time by permitting simultaneous flap elevation while the ablative portion of the procedure is performed. Patients with oropharyngeal cancer have generalized cachexia in addition to soft tissue deflation from neck dissections and prior radiation. Although native neck tissues are generally thin, the extra volume provided by both the rectus muscle and subcutaneous tissue of the VRAM fills this contour deformity, replaces unstable irradiated tissues, and provides coverage of the large neck vessels.

Fibula MFF was first introduced for OMF reconstruction by Hidalgo and is now considered as the gold standard for mandibular reconstruction¹⁴. The advantages of fibula include the length of bone available (around 25-30 cm), which permits multiple osteotomies and provides adequate pedicle length even for maxillary reconstruction. The peroneal artery and vein are usually of good quality and caliber and ideal for anastomosis to the neck vessels. Due to the distance from the recipient site, two team approach can be used thus greatly reducing operative time.

Our study has several limitations. First, the sample size of our study was small compared to that of the other studies on this topic. Second, we could not evaluate the outcomes in terms of functional aspects and

patients satisfaction.

Radical resection of tumors of the head and neck with immediate reconstruction by microsurgical free tissue transfer followed by adjuvant radiation therapy provides the best possible chance for cure and functional and social rehabilitation of the patient.

Conflict of Interest: None

References

1. Nakatsuka T, Harii K, Asato H, et al. Analytic review of 2372 free flap transfers for head and neck reconstruction following cancer resection. *J Reconstr Microsurg* 2003; 19:363–368. discussion 369
2. Rinaldo A, Shaha AR, Wei WI, Silver CE, Ferlito A. Microvascular free flaps: a major advance in head and neck reconstruction. *Acta Otolaryngol* 2002; 122:779–784
3. Seidenberg B, Hurwitz ES. Immediate reconstruction of the cervical esophagus by a revascularized isolated jejunal segment. *Surg Forum* 1958; 9:413–416
4. Rosenthal E, Carroll W, Dobbs M, Scott Magnuson J, Wax M, Peters G. Simplifying head and neck microvascular reconstruction. *Head Neck* 2004; 26:930–936
5. Disa JJ, Cordeiro PG. Mandible reconstruction with microvascular surgery. *Semin Surg Oncol* 2000; 19:226–234
6. Yang GF, Chen PJ, Gao YZ, et al. Forearm free skin flap transplantation: a report of 56 cases. 1981. *Br J Plast Surg* 1997;50:162Y165
7. Lueg EA. The anterolateral thigh flap: Radial forearm's "big brother" for extensive soft tissue head and neck defects. *Arch. Otolaryngol Head Neck Surg* 2004;130:813-8
8. Lim YS¹, Kim JS¹, Kim NG¹, Lee KS¹, Choi JH¹, Park SW². Free Flap Reconstruction of Head and Neck Defects after Oncologic Ablation: One Surgeon's Outcomes in 42 Cases. *Arch Plast Surg* 2014 Mar;41(2):148-52
9. Ichinose A¹, Terashi H, Nakahara M, Sugimoto I, Hashikawa K, Nomura T, Ogata N, Yokoo S, Tahara S. Do multiple venous anastomoses reduce risk of thrombosis in free-flap transfer? Efficacy of dual anastomoses of separate venous systems. *Ann Plast Surg* 2004 Jan;52(1):61-3
10. Bianchi B, Ferri A, Ferrari S, et al. The free anterolateral thigh musculocutaneous flap for head and neck reconstruction: one surgeon's experience in 92 cases. *Microsurgery* 2012; 32:87-95
11. Kesting MR, Holzle F, Wales C, et al. Microsurgical reconstruction of the oral cavity with free flaps from the anterolateral thigh and the radial forearm: a comparison of perioperative data from 161 cases. *Ann Surg Oncol* 2011;18:1988-94
12. Matros E, Cordeiro P. Single-Stage Reconstruction of Composite Central Neck Defects With the Double-Island Vertical Rectus Abdominis Musculocutaneous Flap. *Ann Plast Surg* 2011;66: 164–167
13. Kroll SS, Schusterman MA, Reece GP, et al. Choice of flap and incidence of free flap success. *Plast Reconstr Surg* 1996;98:459–463
14. Urken ML, Buchbinder D, Weinberg H, Vickery C, Sheiner A, Parker R, et al. Functional evaluation following microvascular oromandibular reconstruction of the oral cancer patient: A comparative study of reconstructed and non reconstructed patients. *Laryngoscop* 1991;101:935-50

First-line cisplatin plus bolus 5- Fluorouracil combination in patients with locally advanced and metastatic esophageal cancer (Izmir Oncology Group Study)

Lokal ileri ve metastatik özefagus kanserli hastalarda ilk hat bolus 5-Fluorourasil sisplatin kombinasyonu (İzmir Onkoloji Grubu Çalışması)

Murat Akyol, Yüksel Küçükzeybek, Umut Varol, İbrahim Yıldız, Suna Çokmert, İbrahim Vedat Bayoğlu, Yaşar Yıldız, Lütfiye Demir, Alper Can, Ahmet Dirican, Ahmet Alacacioğlu, Mustafa Oktay Tarhan
İzmir Katip Çelebi Üniversitesi Atatürk Eğitim Ve Araştırma Hastanesi, izmir

Received: 10/03/2015 Accepted: 19/05/2015 Doi: 10.5505/aot.2015.92408

ÖZET

Amaç: Sitotoksik kemoterapi, lokal ileri ve metastatik özefagus kanserinin standart tedavisidir. Biz bu çalışmada lokal ileri ve metastatik özefagus skuamoz hücreli kanserde birinci basamakta sisplatin ve kısa süreli infüzyonel 5-florourasil (5-FU) kombinasyonunun yararlarını ve yan etkilerini değerlendirdik.

Yöntem: Bu çalışmada, retrospektif olarak aralık 2006 ve temmuz 2013 tarihleri arasında sisplatin ve kısa süreli infüzyonel 5-florourasil (5-FU) kombinasyonu ile tedavi edilen daha önceden tedavi almamış lokal ileri veya metastatik özefagus skuamoz hücreli kanserli hastaları değerlendirdik. Kemoterapi rejimi olarak sisplatin 75 mg/m² d1 (1-3-saat infüzyon), kalsiyum lökoverin 60 mg/m² d1-2 ve 5-FU 500 mg/m² d1-2 (15-dakika infüzyon) 14 günde bir uygulandı.

Bulgular: Hastaların 14'ü (%51.9) erkek ve 13'ü (%48.1) kadın olup ortalama yaş 57 (39-80) idi. ECOG performans skoru 20 (%77) hastada 0 veya 1 iken diğer hastalarda 2 olarak bulundu. Tanı anında 10 hasta uzak metastaza sahipken 17 hasta lokal ileri hastalığa sahipti. Hastalar medyan 4 kür kemoterapi aldı. Tüm yanıt oranı %44.4'tü. (8 hastada parsiyel yanıt, 4 hasta komplet yanıt) ve 7 (%25.9) hasta stabil hastalığa sahipti. Hastalık kontrol oranı %70.3'tü. Hastaların medyan progresyonsuz sağkalımı 6.2 (%95 CI: 5.13 7.28) ve medyan genel sağkalımı 11.1 (%95 CI: 7.77-14.5) aydı. Hastaların % 40.7'sinde grade 3-4 nötropeni ve % 11.1'inde grade 3-4 trombositopeni saptandı.

Sonuç: Sisplatin ve kısa süreli infüzyonel 5-florourasil (5-FU) kombinasyonu ilaç infüzyonu için kateter gerektiren infüzyonel rejime alternative bir tedavi olarak düşünülebilir.

Anahtar Kelimeler: Özefagus kanseri, lokal ileri, metastatic, sisplatin, 5-florourasil

ABSTRACT

Objective: Cytotoxic chemotherapy is the basic treatment for locally advanced and metastatic esophageal cancer. We evaluated the benefits and side effects of the first-line short-term infusional 5- Fluorouracil (5-FU) and cisplatin combination regimen in patients with locally advanced and metastatic esophageal squamous cell cancer.

Methods: We retrospectively reviewed the untreated locally advanced or metastatic squamous cell esophageal cancer patients treated with short-term infusional 5-FU and cisplatin combination between December 2006 and July 2013. Chemotherapy regimen was administered as; cisplatin 75 mg/m² on day 1 (1-3-h infusion), ca-leucovorin 60 mg/m² d1-2 and 5-FU 500 mg/m² d1-2 (15-min infusion) every 14 days.

Results: There were 14 (51.9%) male and 13 (48.1%) female patients. The median age was 57 (range, 39-80) years. Twenty patients had an Eastern Cooperative Oncology Group performance status of 0 to 1 (77%), while the rest had PS of 2 (23%). At first diagnosis, 10 patients had distant metastases and 17 patients had localized disease. In total, 27 patients were treated with a median of four cycles. The overall response rate was 44.4% (8 partial responses, 4 complete responses) and 7 patients (25.9%) had stable disease. The disease control rate was 70.3%. Median progression free survival was 6.2 (95% CI: 5.13 7.28) months and median overall survival was 11.1 (95% CI: 7.77-14.5) months. Among the patients, 40.7% of them had grade 3-4 neutropenia, 11.1% of those patients had grade 3-4 thrombocytopenia.

Conclusion: Short-term infusional 5-FU and cisplatin combination regimen can be considered as an alternative treatment to an infusion regimen in which a catheter is necessary for the drug infusion.

Key words: Esophageal cancer, locally advanced, metastasis; cisplatin; 5- Fluorouracil



Introduction

Esophageal cancer is among the main causes of cancer death worldwide because of its extremely aggressive nature and poor survival rate. Approximately half of the patients with localized esophageal cancer die within the first 2 years following tumor resection due to progression to metastatic disease. Cancer of the esophagus typically occurs in one of two forms; upper two-thirds is a squamous cell carcinoma (SCC) and lower one-third is an adenocarcinoma. It is assumed that there are complete differences between esophageal adenocarcinomas and squamous cell cancer, such as the treatment protocol and prognosis.(1,2,3)

Cytotoxic chemotherapy is the most effective treatment modality for esophageal cancer patients with metastatic disease.(4) Grunberger et al. have showed that palliative chemotherapy can prolong the survival of metastatic esophageal cancer patients, relieve their symptoms and improve their quality of life. Nevertheless, no optimizing chemotherapy regimen has been developed for either locally advanced or metastatic disease and especially for squamous cell cancer (SCC) histology.(5) Numerous single agents and combination chemotherapy regimens have been evaluated in patients with metastatic carcinoma of the esophagus and combination therapies have been shown to be superior to monotherapies. Cisplatin-based combinations are well reported to show high response rates (15%-53%) and median survival durations range from 3.2 to 9.8 months. Cisplatin in combination with various drugs like bleomycin, vinorelbine and etoposide were tested.(6,7,8,9) However, the combination of cisplatin plus 5-Fluorouracil (5-FU) has been one of the most commonly used regimens in both metastatic and localized esophageal cancer due to its activity and well-established toxicity profile. Currently, cisplatin and infusional 5-FU regimen is considered to be standard therapy for the first-line treatment of metastatic esophageal cancer patients in many centers.(10,11,12) Addition of taxanes or anthracyclins to combination regimens can provide a statistically significant improvement in esophagogastric adenocarcinoma subtype. But the efficacy of triplet regimens in squamous subtype is not clear.(13,14)

In particular, many studies regarding infusional 5-FU regimens in gastrointestinal

and head-neck cancers showed more frequent catheter-related complications (infection and venous thrombosis).(15,16) So, we aimed to investigate the efficiency of short-term infusion of 5-FU and cisplatin combination in previously untreated patients with metastatic esophageal squamous cell cancer.

Materials and Methods

Patients

The data of 27 patients diagnosed with locally advanced or metastatic esophageal squamous cell cancer and presenting at the Medical Oncology Outpatient Clinic of Izmir Katip Celebi University Ataturk Training and Research Hospital between December 2006 and July 2013 were evaluated retrospectively. We included the patients treated with short-term infusional 5-FU and cisplatin combination in previously untreated locally advanced or metastatic esophageal squamous cell cancer, because they could not be treated with the 5-day infusion due to catheter-associated problems and social issues. Other inclusion criteria were Eastern Cooperative Oncology Group (ECOG) performance score (PS) of 0 to 2 (17) and adequate hepatic, renal, and marrow function (leukocyte count $> 3000/\text{L}$, absolute neutrophil count $> 1500/\text{uL}$, platelet count $\geq 100,000/\text{L}$, total bilirubin ≤ 1.5 times the institutional upper limits of normal and creatinine $\leq 1.5 \text{ mg/dL}$).

Treatment Plan

Chemotherapy regimen was administered as; cisplatin 75 mg/m^2 on day 1 (1-3-h infusion), ca-leucovorin 60 mg/m^2 d1-d2 and 5-FU 500 mg/m^2 d1-d2 (15-min infusion). Cisplatin was given with pre- and post-hydration and furosemide-induced diuresis. The regimen was repeated every 14 days. Before chemotherapy, standard premedication procedures were performed. Dose modifications were made according to nadir count of previous cycles. Cisplatin dose was reduced by 25% and 5-FU by 50% in case of leukocyte count $< 1 \times 10^9/\text{L}$ or platelet nadir $< 5 \times 10^9/\text{L}$. Cisplatin was stopped if serum creatinine $> 3 \text{ mg/dL}$ or creatinine clearance $< 40 \text{ mL/min}$.

Response Evaluation and Toxicity

Baseline tumor assessment was performed in all patients via abdominopelvic computed tomography (CT) and magnetic resonance imaging, and chest CT to rule out



other metastases. Radiological assessment was repeated every 8-10 weeks or every four-six cycles of therapy until progressive disease (PD) or cessation of chemotherapy. If a patient's disease was in response or stable at the time of treatment withdrawal, the patient was observed every 6-8 weeks until PD.

Progression free survival (PFS) was the investigated primary endpoint, which was defined as the time from the start of first-line cisplatin plus 5-FU treatment to the first documentation of progression. First documentation of progressive disease was based on the definition of PD in the RECIST (Response Evaluation Criteria in Solid Tumors 1.1) guidelines (18) and death as a result of any cause in the absence of previously documented PD. We censored the last clinical visit data for patients that died without known progression. Response duration was measured from the day of its initial documentation until confirmed disease progression and overall survival (OS) was measured from the initiation of treatment to death or to the last follow-up assessment. Patients were evaluated for hematological and nonhematological toxicities and were graded according to the National Cancer Institute (NCI) Common Toxicity Criteria, version 3.0 (19).

Statistical Analysis

The primary objective was the activity evaluated as overall response rate (ORR) (complete + partial response). PFS and OS were calculated using the Kaplan-Meier method. The SPSS software (ver. 15.0) was used for statistical analysis. Quantitative data are presented as the means, standard errors, medians, minimums and maximums; the results of qualitative analyses are presented as frequencies and percentages.

Results

Patients

We retrospectively reviewed the data of 27 patients with a diagnosis of locally advanced or metastatic esophageal squamous cell cancer presenting. There were 14 (51.9%) male and 13 (48.1%) female patients. The median age was 57 (range, 39-80) years. Twenty patients had an ECOG PS of 0 to 1 (77%), while the rest had PS of 2 (23%). Nearly half of the patients (n:13, 48%) had moderate differantation, 2 patients had well differantation, 9 patients had poor

differantation and 3 patient could not be evaluated. At first diagnosis, 10 patients had distant metastases and 17 patients had localized disease. Primer tumor localizations were upper esophagus in 14 (51.9%) patients, middle esophagus in 9 (33.3%) patients and lower esophagus in 4 (14.8%) patients. Patient characteristics are shown in *Table 1*.

Table 1. Patient characteristics and treatment details

Clinical findings	No. of patients	%
<i>Age (years)</i>		
Median	57	
Range	39-80	
<i>ECOG Performance status</i>		
0	10	(38.5)
1	10	(38.5)
2	6	(23.0)
<i>Tumor Differantation</i>		
Well	2	(8.3)
Moderate	13	(54.2)
Poor	9	(37.5)
<i>Primary tumor location</i>		
Upper	14	(51.9)
Middle	9	(33.3)
Lower	4	(14.8)
<i>Stage at first diagnosis</i>		
Localised	17	(63.0)
Metastatic	10	(37.0)
<i>Metastatic sites</i>		
0 or 1	18	(66.0)
≥2	9	(33.0)
Treatment		
<i>Prior surgery</i>		
No surgery	13	(48.1)
R0	11	(40.8)
R1-2	3	(11.1)
<i>Prior radiotherapy</i>		
No radiotherapy	16	(59.3)
Neoadjuvant	5	(18.5)
Primary definitive	3	(11.1)
Adjuvant	3	(11.1)
<i>Time from surgery to metastasis</i>		
Median, month	14.7	
Range	2-70	

ECOG PS= Eastern Cooperative Oncology Group performance status

Treatment Modalities

The median number of chemotherapy courses for the entire group was four (range, 2



to 12). Fourteen patients had previous surgery while 11 patients had previous radiotherapy before metastatic disease. Only 3(11.1%) of 11 patients had adjuvant radiotherapy for R1-R2 resection after surgery while 5(18.5%) patients had radiotherapy as neoadjuvant treatment. None had received prior chemotherapy for metastatic disease.

Response Rates and Toxicity

The overall response rate (ORR) was 44.4% (8 partial responses, four complete responses). Seven patients (25.9%) had stable disease and the disease control rate was 70.3%. Response rates to treatment are shown in Table 2. The most common reason for treatment withdrawal was disease progression.. The most common grade 3-4 toxicities were neutropenia. While 40.7% of the patients had grade 3-4 neutropenia, 11.1% of those patients had grade 3-4 thrombocytopenia. The most common non-hematologic toxicities were nausea/vomiting and less commonly mucositis. There was no treatment-related death. Table 3 lists the common treatment-related toxicities.

Table 2. Objective response, clinical benefit and disease control rates

Response	No. of patients	%
Objective response	12	44.4
Complete response	4	14.8
Partial response	8	29.6
Stable disease for ≥ 3 months	7	25.9
Disease control rate	19	70.3

Table 3. Hematologic and non-hematologic toxicity profiles.

Toxicity	Grade 1-2		Grade 3-4	
	No. of patients	(%)	No. of patients	(%)
<i>Hematological</i>				
Anemia	20	(74.1)	1	(3.7)
Nötropenia	10	(37)	11	(40.7)
Thrombocytopenia	4	(14.8)	3	(11.1)
<i>Non-hematological</i>				
Mukocyt mucositis	9	(33.3)	2	(7.4)
Nause/vomiting	14	(51.9)	3	(11.1)
Diarrhea	3	(11.1)	0	(0)

Survival Analysis

Median follow-up was 15.0 months (range, 3-95 months). Median time from operation to the first development of metastases was 14.7 months (range, 2-70 months). Median PFS was 6.2 months (95% CI: 5.13-7.28) and median OS was 11.1 months (95% CI: 7.77-14.5). The PFS curve is shown in Figure 1 and the OS curve in Figure 2. By the time the data were reviewed, 22 patients (81.5%) had died and 23 patients (85.2%) had progressed.

Figure 1. Progression-free survival curve of the metastatic esophagus cancer patients treated with first-line cisplatin plus 5-FU

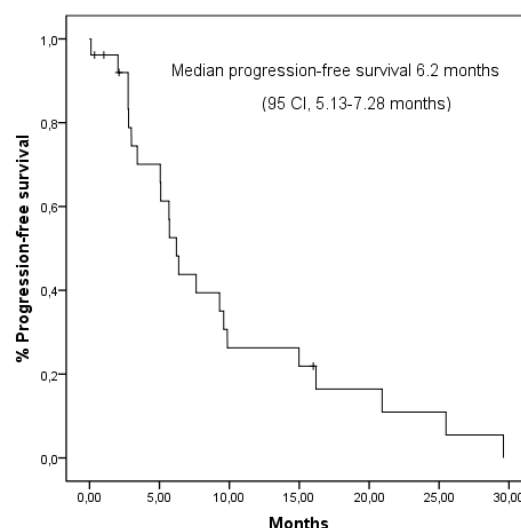
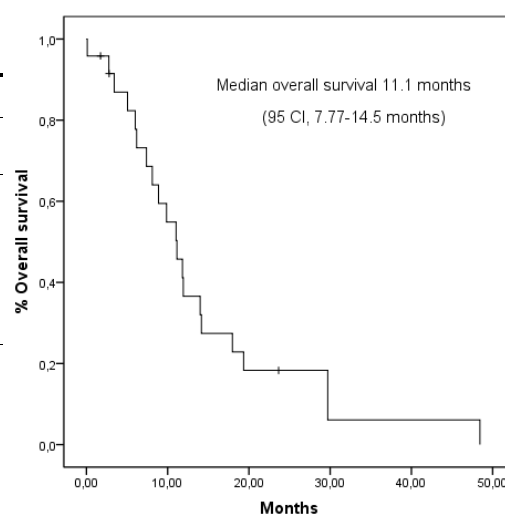


Figure 2. Overall survival curve of the metastatic esophagus cancer patients treated with first-line cisplatin plus 5-FU



Discussion

The role of chemotherapy has been poorly investigated in patients with advanced esophageal cancer. When we reviewed the literature, we found that trials relevant to chemotherapy have poor quality. Because they included small number of patients and the histologic types of esophageal cancer was not (adenocarcinoma and SCC) taken into account. (20,21) Although combination chemotherapies seem superior to monotherapies, the gain in response might be counterbalanced by a decreased tolerability or an increased toxicity. Therefore, even now, the benefit of chemotherapy in patients with disseminated disease is far from being proven and the prognosis of patients with advanced esophageal carcinoma is still poor. (22)

Currently, cisplatin and 5-FU combination is considered the standart regimen for patients with esophageal carcinoma. In a phase 2 study, H.Bleiberg et al. investigated 88 patients with locally advanced or metastatic squamous cell carcinoma of the oesophagus and treated them with cisplatin 100 mg/m² combined with 5-FU at a dose of 1000 mg/m² as a continuous infusion from days 1-5 (Arm A) or with cisplatin alone (Arm B) every 3 weeks. The response rate was 35% in Arm A and 19% in Arm B. The median duration of survival was 33 weeks and 28 weeks for Arm A and Arm B, respectively. Haematological and non-haematological toxicities were more frequent and more severe in Arm A. Grade 3-4 neutropenia was observed in 14% of patients and vascular trombotic events occurred in 9% patients. (22) Kies et al. and Ajani et al. have both reported high response rates of about 60% for resectable or localized tumors with cisplatin and 5-FU combination. However, Iizuka et al reported a response rate of only 35.9% with the same combination for patients with metastatic, recurrent, or bulky unresectable esophageal cancer. (23,24)

Jacqueline et al. in a phase 3 randomized study, compared the efficacy and toxicity of cisplatin plus bolus 5-FU versus infusional 5-FU as a first-line treatment in 232 patients with advanced esophageal, gastric and pancreatic cancer. Among the patients, only 38 of them were esophageal cancer while 19 had squamous cell histology. Most of the patients were gastric and pancreatic cancer. In this study, at first cycle these patients received

either FP (arm A: 5-FU 800 mg/m²/d in continuous infusion 5 days and cisplatin 100 mg/m² on day 1 or 2), or FLP (arm B: LV, 100 mg/m²/d in bolus 5 days, followed by 5-FU 350 mg/m²/d in 1 h infusion 5 days and cisplatin 100 mg/m² on day 1 or 2). Efficacy in terms of tumor response and survival was similar in two arms, showing an objective response rate of 18.6% in arm A vs. 15% in arm B, an overall median survival of 24 weeks in arm A vs. 24.7 in arm B ($p = 0.83$) and a median progression-free survival of 12.4 weeks vs. 12.1 in arms A and B ($p = 0.91$), respectively. Grade 3-4 neutropenia was observed %35.1 in arm B vs. %33.1 in arm A (12).

In another phase II study, 30 patients with unresectable, locally advanced or metastatic squamous cell or adenocarcinoma of the esophagus used folinic acid 200 mg/m²/d, 5-FU 300 mg/m²/d, and cisplatin 20 mg/m²/d intravenously for 5 days every 4 weeks. Two of 13 patients with squamous cell carcinoma had a complete response. Six other patients (3 SCC) had a partial response with a median duration of 9 months for an overall response rate of 27%. Further 6 patients (20%) had stable disease. Grade 4 neutropenia occurred in 6 patients (20%), with 5 requiring antibiotics for associated fever. Other grade 4 toxicities were nausea and vomiting, anemia, and thrombocytopenia occurred in one each (20).

In our study, the overall response rate was 44.4% (8 partial responses, 4 complete responses). Seven patients (25.9%) had stable disease. The disease control rate was 70.3%. Median PFS was 6.2 (95% CI: 5.13-7.28) months and median OS was 11.1 (95% CI: 7.77-14.5) months. Among the patients, 40.7% of them had grade 3-4 neutropenia, 11.1% of those patients had grade 3-4 thrombocytopenia. According to our results and the previous reports, short-term infusional 5-FU and cisplatin combination in previously untreated locally advanced or metastatic esophageal squamous cell cancer were seem to be similar with continuous infusional 5-FU in terms of median OS and PFS. However, grade 3-4 toxicity rates were more frequent than infusional 5-FU except for grade 3-4 non-hematological adverse effects. When treatment-related toxicities of infusional and



bolus 5-FU-containing regimens were compared in advanced-stage gastrointestinal and head-neck cancer, bolus 5-FU regimens appear to have a higher rate of hematologic toxicities, while gastrointestinal toxicities (diarrhea, vomiting, etc.) were seen less frequently.(15,25,26) As a result, this combination appears to be an active and convenient regimen for advanced esophageal cancer, resulting in prolonged remission and survival in some patients.

Despite the consideration of infusional chemotherapy as standard regimen for the treatment of esophageal cancer, there is a main problem with these regimens. This is the necessity for a central venous catheter and ambulatory infusion pump. Many studies regarding infusional 5-FU regimens in gastrointestinal and head-neck cancers showed more frequent catheter-related complications (infection and venous thrombosis).(15,16) So, thrombosis and catheter infections are major problems with infusion regimens. Deaths due to thrombosis around the central catheter have been reported. For example, a major drawback to the ECF (Epirubicin, cisplatin, 5-FU) regimen used in advanced esophagogastric adenocarcinoma is the need for a central venous line. In this randomized trial, central venous line complications occurred in 15 percent of those receiving ECF.(13)

Since this regimen carries a high risk for febrile neutropenia, it can be managed with primary prophylactic granulocyte colony-stimulating factor. Nevertheless, short-term infusional 5-FU and cisplatin combination regimen can be considered an alternative treatment to an infusion regimen due to similar survival outcome of the patients.

Conflict of Interest: None

References

1. Jemal A, Siegel R, Xu J, Ward E: Cancer statistics, 2010. *CA Cancer J Clin*, 60: 277–300, 2010.
2. Thorban S, Roder JD, Nekarda H, Funk A, Siewert JR, Pantel K: Immunocytochemical detection of disseminated tumor cells in the bone marrow of patients with esophageal carcinoma, 88: 1222-1227, 1996.
3. Thrift AP, Pandeya N, Whiteman DC: Current status and future perspectives on the etiology of esophageal adenocarcinoma. *Front Oncol*, 2: 11, 2012.
4. Leichman L, Berry BT: Experience with cisplatin in treatment regimens for esophageal cancer. 18: 64-72, 1991.
5. Grünberger B, Raderer M, Schmidinger M, Hejna M: Palliative chemotherapy for recurrent and metastatic esophageal cancer. *Anticancer Res*, 27: 2705-2714, 2007.
6. Kelsen D, Hilaris B, Coonley C, Chapman R, Lesser M, Dukeman M, Heelan R, Bains M: Cisplatin, vindesine, and bleomycin chemotherapy of local-regional and advanced esophageal carcinoma. *Am J Med*, 75: 645-652, 1983.
7. Dinwoodie WR, Bartolucci AA, Lyman GH, Velez-Garcia E, Martelo OJ, Sarma PR: Phase II evaluation of cisplatin, bleomycin, and vindesine in advanced squamous cell carcinoma of the esophagus. a Southeastern Cancer Study Group Trial. *Cancer Treat Rep*, 70: 267-270, 1986.
8. Spiridonidis CH, Laufman LR, Jones JJ, Gray DJ, Cho CC, Young DC: A phase II evaluation of high dose cisplatin and etoposide in patients with advanced esophageal adenocarcinoma. *Cancer*, 78: 2070-2077, 1996.
9. Conroy T, Etienne PL, Adenis A, Ducreux M, Paillot B, Oliveira J, Seitz JF, Francois E, Van Cutsem E, Wagener DJ, Kohser F, Daamen S, Praet M, Gorlia T, Baron B, Wils J: European Organisation for Research and Treatment of Cancer Gastrointestinal Tract Cancer Cooperative Group. Vinorelbine and cisplatin in metastatic squamous cell carcinoma of the oesophagus: response, toxicity, quality of life and survival. *Ann Oncol*, 13: 721, 2002.
10. Etienne MC, Bernard S, Fischel JL, Formento P, Gioanni J, Santini J, Demard F, Schneider M and Milano G: Dose reduction without loss of efficacy for 5-fluorouracil and cisplatin combined with folinic acid. In vitro study on human head and neck carcinoma cell lines. *Br J Cancer*, 63: 372-377, 1991.
11. Lacave AJ, Baron FJ, Anton LM, Estrada E, De Sande LM, Palacio I, Esteban E, Gracia JM, Buesa JM, Fernandez OA: Combination chemotherapy with cisplatin and 5-fluorouracil 5-day infusion in the therapy of



advanced gastric cancer: a phase II trial. *Ann Oncol*, 2: 751-754, 1991.

12. Duffour J, Bouché O, Rougier P, Milan C, Bedenne L, Seitz JF, Buecher B, Legoux JL, Ducreux M, Vetter D, Raoul JL, François E, Ychou M: Safety of cisplatin combined with continuous 5-FU versus bolus 5-FU and leucovorin, in metastatic gastrointestinal cancer. *Anticancer Res*, 26: 3877-3883, 2006.

13. Webb A, Cunningham D, Scarffe JH, Harper P, Norman A, Joffe JK, Hughes M, Mansi J, Findlay M, Hill A, Oates J, Nicolson M, Hickish T, O'Brien M, Iveson T, Watson M, Underhill C, Wardley A, Meehan M: Randomized trial comparing epirubicin, cisplatin, and fluorouracil versus fluorouracil, doxorubicin, and methotrexate in advanced esophagogastric cancer. *J Clin Oncol*, 15: 261, 1997.

14. Ajani JA, Fodor MB, Tjulandin SA, Moiseyenko VM, Chao Y, Cabral Filho S, Majlis A, Assadourian S, Van Cutsem E: Phase II multi-institutional randomized trial of docetaxel plus cisplatin with or without fluorouracil in patients with untreated, advanced gastric, or gastroesophageal adenocarcinoma. *J Clin Oncol*, 23: 5660-5667, 2005.

15. Hitt R, Paz-Ares L, Brandáriz A, Castellano D, Peña C, Millán JM, Calvo F, Ortiz de Urbina D, López E, Alvarez-Vicent JJ, Cortés-Funes H: Induction chemotherapy with paclitaxel, cisplatin and 5-fluorouracil for squamous cell carcinoma of the head and neck: long-term results of a phase II trial. *Ann Oncol*, 13: 1665-1673, 2002.

16. Hansen RM, Ryan L, Anderson T, Krzywda B, Quebbeman E, Benson A 3rd, Haller DG, Tormey DC: Phase III study of bolus versus infusion fluorouracil with or without cisplatin in advanced colorectal cancer. *J Natl Cancer Inst*, 15: 88: 668-674, 1996.

17. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP: Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol*, 6: 649-655, 1982.

18. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J: New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*, 45: 228-247, 2009.

19. Trotti A, Colevas AD, Setser A, Rusch V, Jaques D, Budach V, Langer C, Murphy B, Cumberlin R, Coleman CN, Rubin P: CTCAE v3.0: development of a comprehensive grading system for the adverse effects of cancer treatment. *Semin Radiat Oncol*, 13: 176-181, 2003.

20. Warner E, Jensen JL, Cripps C, Khoo KE, Goel R, Kerr IA, Bjarnason GA, Fields AL, Hrinco A: Outpatient 5-fluorouracil, folinic acid and cisplatin in patients with advanced esophageal carcinoma. *Acta Oncol*, 38: 255-259, 1999.

21. Ajani JA: Contribution of chemotherapy in the treatment of carcinoma of the esophagus: Results and commentary. *Semin Oncol*, 21, 474-482, 1994.

22. Bleiberg H, Conroy T, Paillot B, Lacave AJ, Blijham G, Jacob JH, Bedenne L, Namer M, De Besi P, Gay F, Collette L, Sahmoud T: Randomised phase II study of cisplatin and 5-fluorouracil (5-FU) versus cisplatin alone in advanced squamous cell oesophageal cancer. *Eur J Cancer*, 33: 1216-1220, 1997.

23. Kies MS, Rosen ST, Tsang TK, Shetty R, Schneider PA, Wallemark CB, Shields TW: Cisplatin and 5-fluorouracil in the primary management of squamous esophageal cancer. *Cancer*, 60: 2156-2160, 1987.

24. Ajani JA, Ryan B, Rich TA, McMurtrey M, Roth JA, DeCaro L, Levin B, Mountain C: Prolonged chemotherapy for localised squamous carcinoma of the oesophagus. *Eur J Cancer*, 28: 880-884, 1992.

25. Jeong J, Jeung HC, Rha SY, Im CK, Shin SJ, Ahn JB, Noh SH, Roh JK, Chung HC: Phase II study of combination chemotherapy of 5-fluorouracil, low-dose leucovorin, and oxaliplatin (FLOX regimen) in pretreated advanced gastric cancer. *Ann Oncol*, 19: 1135-1140, 2008.

26. Pfister DG, Bajorin D, Motzger R, et al: Cisplatin, fluorouracil, and leucovorin. Increased toxicity without improved response in squamous cell head and neck cancer. *Arch Otolaryngol Head Neck Surg*, 120: 89-95, 1994.



Colon Cancer and Glioblastoma Multiforme Co-occurrence at an Early Age; A Case Report

Erken Yaşta Kolon Kanseri ve Glioblastome Multiforme Birlikteliği; Olgu Sunumu

Fatma Buğdaycı Başal¹, Umut Demirci¹, Ahmet Şiyar Ekinci², Muzaffer Altundağ³, Levent Gürses¹, Ferit Aslan¹, Ayşe Demirci¹, Necati Alkış¹

¹Dr. A. Y. Ankara Onkoloji Eğitim Araştırma Hastanesi, Tıbbi Onkoloji Kliniği, Ankara, Türkiye

²Dr. A. Y. Ankara Onkoloji Eğitim Araştırma Hastanesi, Radyasyon Onkolojisi Kliniği, Ankara, Türkiye

³Dışkapı Yıldırım Beyazıt Eğitim Araştırma Hastanesi, Beyin Cerrahi Kliniği, Ankara, Türkiye

Dergiye Ulaşma Tarihi: 26/12/2014 Dergiye Kabul Tarihi: 13/01/2015 Doi: [10.5505/aot.2015.36349](https://doi.org/10.5505/aot.2015.36349)

ÖZET

Kolon kanseri ve beyin tümörü birlikteliği klinikte karşımıza Muir-Torre Sendromu, Turcot Sendromu, Cowden Sendromu ya da Gardner Sendromu olarak çıkabilir. Turcot Sendromu multiple adenomatöz kolon polipleri ile santral sinir sisteminin (SSS) primer tümörünün birlikte görüldüğü DNA tamir genlerinde mutasyonlarla seyreden nadir bir hastalıktır. Biz bu olguda polipozis zemininde gelişen kolon kanseri tanısından üç yıl sonra glioblastome multiforme (GBM) tanısı alan fakat genetik çalışmada Turcot Sendromu desteklenemeyen genç bir kadın hastayı sunduk.

Anahtar Kelimeler: Kolon kanseri, Glioblastome multiforme; Turcot Sendromu

ABSTRACT

The co-occurrence of colon cancer and brain tumor can be observed as Muir-Torre syndrome, Turcot syndrome, Cowden syndrome or Gardner's syndrome, in clinical practice. Turcot syndrome is an uncommon disease with mutations in DNA repair genes that consist of multiple adenomatous colon polyps and central nervous system (CNS) tumor. We report a case of a young woman presents with polyposis related colon cancer who develops glioblastoma multiforme (GBM) three years after the diagnosis which cannot be explained with Turcot Syndrome by genetic studies.

Key words: Colon cancer, Glioblastoma multiforme; Turcot's Syndrome

Giriş

Kolon kanseri ve beyin tümörü birlikteliği klinikte karşımıza bazı sendromlarla çıkar. Muir-Torre Sendromu (sebasöz neoplazm, keratoakantom, viseral malignite, beyin tümörü), Turcot Sendromu (polipozis koli, beyin tümörü), Cowden Sendromu (serebellumda displastik gangliositom ve kolonda hamartomatöz polipler) ya da Gardner Sendromu (polipozis koli, osteom, mezenkimal tümör, kraniofarenjiom) bu iki kliniğin birlikte görüldüğü sendromlardır (1-4). Literatürde Muir-Torre Sendromu ile Turcot Sendromu'nun çakıştığı olgular bildirilmiştir (1,5).

Turcot Sendromu multiple adenomatöz kolon polipleri ile santral sinir sisteminin (SSS) primer tümörünün birlikte görüldüğü

nadir bir hastalıktır (6). İlk olarak 1949'da Crail tarafından tanımlanmış ve 1959'da J. Turcot ve ark. tarafından beyin tümörü ve polipozis coli birlikteliği olan iki kardeşte 'Turcot's Sendromu' şeklinde rapor edilmiştir (7). Tanı alan hastalar genellikle 10-20 yaş aralığındadır (7,8). Turcot sendromunun genetik temeli karmaşık olup klinik ve genetik olarak çeşitli tiplerde kliniğe yansıyabilir. Literatürde yaklaşık 150 vaka bulunmaktadır (9-11). Biz bu olguda polipozis zemininde gelişen kolon kanseri tanısından üç yıl sonra glioblastome multiforme (GBM) tanısı alan genç bir kadın hastayı sunduk.

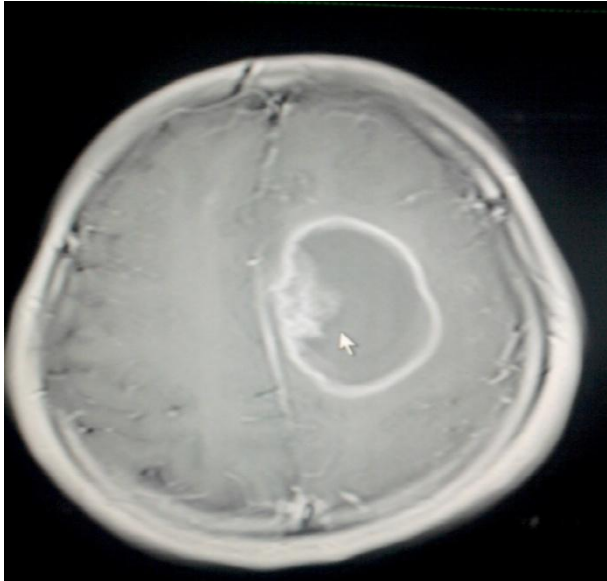
Olgu Sunumu

Yirmi iki yaşında kadın hasta Haziran 2011 yılında karın ağrısı nedeni ile yapılan

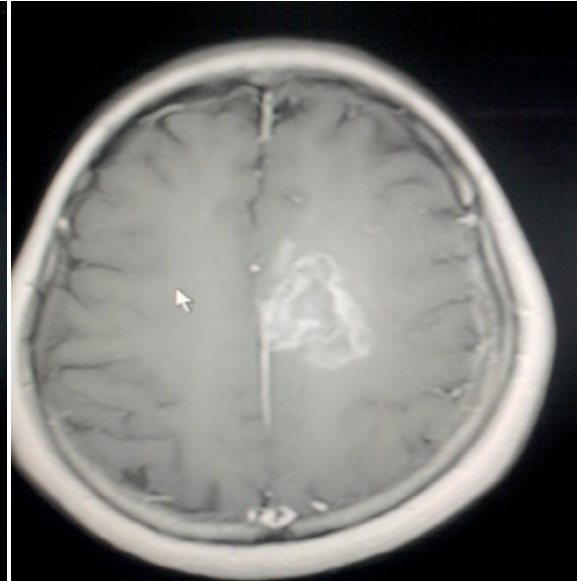
kolonoskopisinde çekumda, transvers, inen, sigmoid kolonlarda ve rektosigmoid bölgede multipl sayıda polip saptanmıştı. Total kolektomi sonrasında multipl odakta iyi diferansiye adenokarsinom, çok sayıda tübülovillöz adenom ve 10 adet reaktif lenf nodu saptanmış ve adjuvan FUFA (5FU+ Folinik asit) tedavisi uygulanmıştı. Remisyonda izlenen hasta Aralık 2013'te sağ üst extremitede kuvvet kaybı gelişmesi üzerine dış merkezde çekilen beyin manyetik rezonans görüntülemesinde (MRG) sol frontal lobda 5.5 cm'lik kitle saptanmış (Resim 1) ve biyopsi yapılmış. Tanısal olmayan biyopsi sonrası fokal epileptik nöbet geçiren hasta başka bir merkeze başvurmuş. Gros total olarak çıkartılan kitle (Resim 2) patolojisi GBM olarak raporlanan hasta idame tedavisi için hastanemize başvurdu. Özgeçmişinde kolon kanseri olan hastanın bir kız kardeşinin de beyin tümörü nedeniyle kaybedildiği öğrenildi.

Hastanın fizik muayenesinde sırtında akne benzeri lezyonları ve gövdede ve kollarda maküler kahverengi olmayan koyu renkli alanları vardı. Hastanın radyoterapi eş zamanlı temozolamid tedavisi sonrası idame temozolamid tedavisi tamamlandı. Hasta radyolojik ve klinik olarak progresyonsuz izlenmektedir.

Hastanın polipozis koli ve GBM tanıları birlikte ele alındığında Turcot Sendromu akla gelmekteydi. Bu nedenle hastanın kolon operasyonuna ait patoloji preparatları mikrosatellit instabilite (MSI) açısından immunohistokimyasal olarak değerlendirildi. Çalışmada neoplastik hücreler MLH1, PMS2, MSH6 ile pozitif olup MSH2 ile belirgin boyanma saptanmadı. Kontrolünde de boyanma saptanmadığından MSH2 kayıp olarak değerlendirilmedi. Bu nedenle hastada DNA tamir genlerinin kaybına rastlanmadı.



Resim- 1; Tanı anında çekilen T1 transvers kesit



Resim- 2; Operasyon sonrası T1 transvers kesit

Tartışma

Olgumuz genç yaşta kolonda multipl polipler nedeniyle opere edilmesinin ardından iyi diferansiye adenokarsinom tanısı almış ve adjuvan tedavi sonrası remisyonda izlenirken GBM tanısı almıştır. Bu iki tümörün birlikteliği hastada Turcot Sendromu varlığını akla getirmektedir.

Hereditör nonpolipozis koli (HNPCC) DNA tamir genlerinin (Mismatch Repair

Genes; MMR) mutasyonundan kaynaklanır. HNPCC sıklıkla MSH2, MLH1 ve PMS2 genlerindeki mutasyondan kaynaklanır (9,12). Olguların %90'ında MSI görülür (9,13). MSH2 mutasyonu sıklıkla multipl tümör gelişimi ile ilişkilidir (14). Turcot sendromu modern literatürde beyin tümörü polipozis sendromu olarak bilinmektedir (9,11). Nadir bir hereditör hastalık olup HNPCC ve familiyal adenomatozis polipozisin (FAP) varyantları olarak görülür (12). Tip 1 ve tip 2 olmak üzere

iki farklı klinikte karşımıza çıkar. Tip 1 otozomal resesif geçişli olup, HNPC ve sıklıkla GBM olmak üzere beyin tümörleri birlikteliği ile görülür. Tip 2 ise otozomal dominant geçişli olup FAP ve medulloblastom birlikteliği ile görülür. Bu iki tip sendrom arasında kesin bir ayırım yoktur. Tip 1'de kolon poliplerinin sayısı 100'den azdır ve beyin tümörleri gliomlar şeklinde görülür. Tip 2 Turcot Sendromu'nda kolonda polipler yüzler hatta binlere ulaşmakta ve %20 vakada kolorektal kansere rastlanmaktadır. Beyinde medulloblastom %60 vakada görülür (9-11,15). Bu anlamda bizim olgumuz tip 1 Turcot Sendromu'nu akla getirmektedir fakat yapılan incelemede MMR genlerinde mutasyona rastlanmamıştır.

Kolonik ve serebral semptomlar aynı anda ortaya çıkabileceği gibi birbirini de takip edebilir. İlk semptom ortaya çıktıktan sonra beş yıl içinde diğer semptomlar kendini gösterir (7). Genellikle barsak lezyonları beyin tümörü tanısından bir yıl sonra başgösterir yada postmortem saptanır (6). Ayrıca kolon rezeksiyonundan 2-8 yıl sonra da SSS malignitesi ortaya çıkabilir (6,15). Bizim olgumuzda da kolon kanseri tanısı aldıktan üç yıl sonra serebral semptomlar ortaya çıkmıştır. Cinsiyet ve ırk eğilimi bilinmemektedir fakat 10-30 yaşları arasında görülür (6). Kliniğe yansımaları spesifik değildir. Pigmente nevüs, kafeola, bazal hücreli karsinoma gibi deri bulguları görülür (9,11). Bizim olgumuzda da sırtta akne benzeri lezyonlar, gövde ve kollarda kahverengi olmayan koyu renkli maküler lezyonları mevcuttu.

Olgumuz tip 1 Turcot Sendromu kliniğine uyması ve aile hikayesinin olması itibarıyla genetik incelemeyi hak etmiş ilginç bir hastadır. Fakat Türkiye'den literatürde varolan herhangi bir Turcot olgusu olmadığı gibi bizim olgumuzda da Turcot Sendromu'nu destekleyecek MMR genlerine rastlanmamıştır. Yine de bu hasta grubu eşlik edebilen multipl tümörler nedeni ile yakın izlenmelidir.

Çıkar Çatışması: Yok

Kaynaklar

1. Grandhi R, Deibert CP, Pirris SM, Lembersky B, Mintz AH. Simultaneous Muir-Torre and Turcot's syndrome: A case report and review of the literature. *Surg Neurol Int* 2013; 4: 52
2. Park MD, Yeane GA, Hamilton RL, Mabold J, Urban N. Identifying Muir-Torre syndrome in a patient with glioblastoma multiforme. *Neuro Oncol* (August 2009) 11 (4): 452-455
3. Yuasa H, Motokishita T, Tokito S, Tokunaga M, Goto M. Lhermitte-Duclos disease associated with Cowden's disease-case report. *Neurol Med Chir (Tokyo)* 1997 Sep;37(9):697-700
4. Bozbuga M, Suslu HT, Hicdonmez T, Bayindir Ç. Primary cerebellopontine angle craniopharyngioma in a patient with Gardner syndrome. *Journal of Clinical Neuroscience* Volume 18, Issue 2, February 2011, Pages 300-301
5. Kleinerman R, Marino J, Loucas E. Muir-Torre Syndrome / Turcot Syndrome overlap? A patient with sebaceous carcinoma, colon cancer, and a malignant astrocytoma. *Dermatology Online Journal* 18 (5): 3
6. Radin DR, Fortgang KC, Zee CS, Mikity VG, Halls JM. Turcot syndrome: a case with spinal cord and colonic neoplasms. *AJR Am J Roentgenol* 1984 Mar;142(3):475-6
7. Ma S, Hu Y, Yang J, Zhou X. Turcot's syndrome associated with intestinal non-Hodgkin's lymphoma: case report and review of literature. *Clin Neurol Neurosurg* 2013 Feb;115(2):117-20
8. McLaughlin MR¹, Gollin SM, Lese CM, Albright AL. Medulloblastoma and glioblastoma multiforme in a patient with Turcot syndrome: a case report. *Surg Neurol* 1998 Mar;49(3):295-301
9. Ozerov SS, Zakharov IV, Talypov SR, Konovalov DM, Kisliakov AN. Turcot syndrome: Rare observation and literature review. *Zh Vopr Neirokhir Im N N Burdenko* 2013;77(3):49-53
10. Hamilton SR, Liu B, Parsons RE, Papadopoulos N, Jen J, et al. The molecular basis of Turcot's syndrome. *N Engl J Med* 1995 Mar 30;332(13):839-47
11. Paraf F, Jothy S, Van Meir EG. Brain tumor-polyposis syndrome: two genetic diseases? *JCO* Jul 1, 1997;2744-58
12. Lebrun C, Olschwang S, Jeannin S, Vandenbos F, Sobol H. Turcot syndrome confirmed with molecular analysis. *Eur J Neurol* 2007 Apr;14(4):470-2
13. De Vos M, Hayward BE, Picton S, Sheridan E, Bonthron DT. Novel PMS2 pseudogenes can conceal recessive mutations causing a distinctive childhood cancer syndrome. *Am J Hum Genet* 2004 May;74(5):954-64
14. Balaguer F, Cervantes A, Arnold D. Familial risk-colorectal cancer: ESMO Clinical Practice Guidelines. Balmaña J, ESMO Guidelines Working Group. *Ann Oncol* 2013 Oct;24 Suppl 6:vi73-80
15. Itoh H, Ohsato K, Yao T, Iida M, Watanabe H. Turcot's syndrome and its mode of inheritance. *Gut* 1979 May;20(5):414-9

Castleman Disease Localized On The Right And Left Buccal Mucosa

Sağ Ve Sol Bukkal Mukoza Yerleşimli Castleman Hastalığı

Caner Kılıç¹, Metin Kaya², Ela Cömert¹, Ümit Tunçel¹, Nazan Bozdoğan³

¹Ankara Onkoloji Eğitim Araştırma Hastanesi, Kulak Burun Boğaz Kliniği, Ankara, Türkiye

²Batman Devlet Hastanesi

³Ankara Onkoloji Eğitim Araştırma Hastanesi, Patoloji Kliniği, Ankara, Türkiye

Dergiye ulaşma tarihi: 15/11/2014, Dergiye kabul tarihi: 30/04/2015, Doi: [10.5505/aot.2015.72693](https://doi.org/10.5505/aot.2015.72693)

ÖZET

Castleman hastalığı (CH), en sık mediastende asemptomatik kitle olarak görülen lenfoproliferatif bir hastalıktır. Baş boyun bölgesinde ise en sık boyun da görülür. Oral kavite de yerleşimi nadirdir. Tedavisinde cerrahi eksizyon uygulanır. Bu makalede sağ ve sol yanak mukozasında, giderek büyüyen şişlik şikayeti ile tarafımıza başvuran ve histopatolojik tanısı castleman hastalığı- plazma hücreli tip olarak raporlanan, non hodgkin lenfoma (NHL) öyküsü olan hasta, literatür eşliğinde sunulmuştur.

Anahtar Kelimeler: Bukkal Mukoza, Castleman Hastalığı, Non hodgkin lenfoma

ABSTRACT

Castleman disease (CD) is a lymphoproliferative disorder that is most frequently seen as an asymptomatic mass in the mediastinum. Among the head and neck region, the neck is the most frequent localization. It is seldom localized in the oral cavity. Surgical excision is the primary choice of treatment. The current study presents a patient with previous non-Hodgkin Lymphoma (NHL) history, who was complaining of a mass gradually increasing in size beneath the right and left buccal mucosa and a histopathological diagnosis of Castleman disease – plasma cell type. The related literature is also reviewed.

Key words: Buccal Mucosa, Castleman Disease, Non Hodgkin Lymphoma

Introduction

Castleman disease (CD) is a lymphoproliferative disorder characterized by lymphoid tissue hyperplasia. It is also called angiomatous lymphoid hamartoma. Histopathologically, the disease is classified as hyalinic vascular, plasma cell, and mixed variants. The most frequent subtype is the hyalinic variant, which has a low recurrence rate. The plasma cell subtype is more aggressive and is concomitant with systemic diseases (1). It is most commonly localized in the mediastinum as an asymptomatic mass. Among the head and neck region, the neck is the most frequent localization (2). Chronic inflammation and immune insufficiency are responsible for the etiology and it is seen concomitantly with autoimmune diseases like pemphigus.³ Clinically, isolated or multicentric subtypes can be seen. Isolated subtypes generally are seen in younger patients and multicentric types in older patients. In the treatment, total or near total surgical excision can be performed according the localization (4). Radiotherapy may be used as an adjuvant or a mass reductive modality (5). We herein

report a patient with previous NHL history, who had CD lesions localized beneath right and left buccal mucosa. We present the treatment of this patient who shows a rare localization of the disease and a review of the literature as well.

Case Report

A 64-year-old male patient who had gradually growing masses in the oral cavity (beneath both sides the buccal mucosa) was admitted to the Ankara Oncology Teaching and Research Hospital Ear Nose Throat Department. The physical exam revealed rigid masses with smooth surfaces, and reduced mobility was observed under the right and left buccal mucosa (Figure 1). No other abnormalities were found.

Systemic signs such as fever and sweating were absent. Laboratory tests and viral markers were normal. Systemic physical exams were normal, as well. According to the patient's medical history,



he had received chemotherapy almost nine years before due to diffuse B cell NHL. He underwent lymph node excision in his neck 4.5 years prior and the specimen revealed plasma cell type CD. Radiological examination was natural.

Horizontal incisions were made on the mucosa transorally above the masses to diagnose and treat the patient. Minor salivary glands under the mucosa were lateralized and masses with smooth surfaces adhered to the surrounding tissue were observed.

The mass under the left buccal mucosa and near total excision of the mass under the right buccal mucosa were totally excised. The histopathological examination of both specimens revealed Castleman disease with plasma cell subtype (Figure 2). Neither adjuvant radio nor chemotherapy was recommended by oncology departments. During the three-year follow up, no recurrence was occurred.

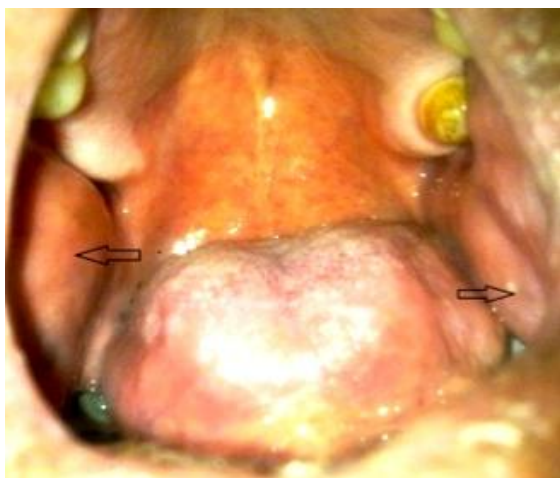


Figure 1: Masses under the right and left buccal mucosa.

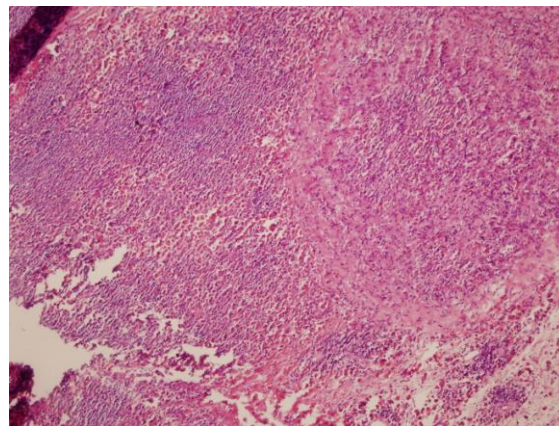


Figure 2: Castleman disease with plasma cell subtype

Discussion

Castleman disease was first described in a patient as an isolated mediastinal mass. It is also called angiofollicular lymph node hyperplasia, giant lymph node hyperplasia, lymph node hamartoma, and benign giant lymphoma. It is seen equally among the genders and more frequently in young adults (1). The etiology is not clearly identified. However, it may be seen concomitantly with other disorders such as NHL, multiple myeloma, B cell lymphoma, Kaposi's sarcoma (6). It was reported that viral infections such as HHV-8, HIV, EBV.⁷ The patient presented herein received treatment for NHL nine years prior, and he is still in remission.

Depending on clinical presentation, the disease can also be divided into isolated or multicentric subtypes. The multicentric type is generally seen with other systemic diseases and shows progress more aggressively (5). Histopathologically, CD is also classified into three different subtypes as vascular, plasma cell, and mixed (1). The plasma cell type accounts for almost 10% of the cases, is generally multicentric, and is associated with systemic symptoms such as fever, sweating, elevated sedimentation rate, anemia, and thrombocytopenia. Although the current patient's lesions were multicentric, and histopathologically of the plasma cell type, he did not present systemic signs.

Castleman disease that occurs in the head and neck region, is most frequently seen in the neck, and it was reported to be rarely seen in the parotis, mouth floor, and oral cavity, as well (2). One study in the literature



reported a study of 14 patients with CD in the neck, in which the mass was found unilaterally and at level II all the patients (8). Karakoc et al. reported that in a patient with dysphagia, a postoperative pathological specimen revealed CD, which was thought to be parapharyngeal schwannoma preoperatively (9). In a patient who had been followed-up for cervical mass and treated with preoperative embolization due to enhanced peripheral vascularization in the MRI, the postoperative specimen showed CD (10). Deshmukh et al. reported that a patient who had been diagnosed with squamous cell carcinoma of the tongue with stage T1N3M0 had undergone cervical dissection. After the dissection, the specimen revealed CD, so the authors accepted the stage of the disease as T1N0M0 (11). These studies suggest that CD in the neck localized laterally may mimic many different disorders (2). Three years ago, the current patient underwent cervical node biopsy at level II and the specimen showed CD plasma cell subtype.

CD localized in the oral cavity is rarely described. There is only one case of a well-defined submucosal mass unilaterally beneath the buccal mucosa in literature (12). The current case was admitted to our department with asymptomatic masses localized under the right and left buccal mucosa. A case with masses with such localization is presented for the first time in the literature.

Histopathological confirmation is needed for the definitive diagnosis. Fine needle aspiration biopsy has no diagnostic value, and the diagnosis is made by incisional or excisional biopsy. Total or near total excision should be performed for the treatment (4). Corticosteroids should be added in the therapy of patients with systemic symptoms. Due to autoimmunity being blamed for the etiology, cytotoxic drugs or immunomodulators such as interferon and intravenous immunoglobulin are used (13). The recurrence rate is high in the plasma subtype, and thus, chemotherapy and radiotherapy (RT) can be added. It was reported that a partial or complete response can be obtained in the treatment of CD with 40-50 Gy. doses of radiotherapy. In the same study, the authors claimed that response rate of the RT in patients with the plasma cell type was better than the other types due to higher tumoral activity of the plasma cell type (14).

Although Castleman disease has good prognosis with surgery, long term recurrences

are reported in literature. Total excision was performed in the treatment of a patient with CD plasma cell variant, and recurrence occurred 11 months later. Re-excision and chemotherapy was given for the recurrence (15). We performed total excision for the left and near total excision for the right buccal masses in the treatment. During the three-year follow-up, neither recurrence nor additional systemic symptoms occurred.

Early diagnosis is very important in Castleman disease, especially in the multicentric and plasma cell subtypes, due to accompanying systemic disorders with high mortality, potential of malignant transformation and high recurrence rates. CD, localized under buccal mucosa like in the current case, should be remembered in the differential diagnosis of asymptomatic masses in the oral cavity and the physician should be aware of concomitant disorders.

References

1. Gangopadhyay K, Mahasin ZZ, Kfoury H. Castleman disease (giant lymph node hyperplasia). Arch Otolaryngol Head Neck Surg 1997;123(10):1137-9.
2. Markou KD, Goudakos JK, Psillas G, Antoniadis A, Karasmanis I, Vital V, Nicolaou A. Castleman's disease of the neck: report of a case and review of the literature. B-ENT.2009;5(3):189-93.
3. Uskul B, Ertugrul M, Selvi A, Mihmanli A, Zindanci I, Turker H. A rare association: Castleman's disease and pemphigus vulgaris .Tuberk Toraks. 2005;53(2):172-6
4. Bowne WB, Lewis JJ, Filippa DA, Niesvizky R, Brooks AD, Burt ME, et al. The management of unicentric and multicentric Castleman's disease. Cancer 1999;85(3):706-17.
5. Vries I, MS van Acht M, BJ Demeyere T, LM Lybeert M, Zoete J.P, Nieuwenhuijzen G. Neoadjuvant radiotherapy of primary irresectable unicentric Castleman's disease: a case report and review of the literature. Radiation Oncology 2010;5:7
6. Maslovsky I, Uriev L, Lugassy G. The heterogeneity of Castleman disease: report of five cases and review of the literature. Am J Med Sci 2000;320(4):292-5.
7. Gomes H, Huyett P, Laver N, Wein RO. A unique presentation of Epstein-Barr virus-associated Castleman's disease. Am J Otolaryngol 2013;34(3):262-4.
8. Chen YF, Zhang WD, Sun CZ, Ouyang D, Chen WK, Luo RZ, Wu MW. Clinical features and outcomes of head and neck castleman's disease. J Oral Maxillofac Surg 2012;70(10):2466-79.
9. Zawawi F, Varshney R, Haegert DG, Daniel SJ. Castleman's Disease: a rare finding in a pediatric neck. Int J Pediatr Otorhinolaryngol 2014;78(2):370-2



10. Karakoc O, Kilic E, Ilica T, Tosun F, Hidir Y. Castleman disease as a giant parapharyngeal mass presenting with dysphagia. *J Craniofac Surg* 2011;22(6):54-7.
11. Sanchez-Ros-Sanchez A, Infante-Cossio P, Gonzalez-Garcia A, Borrero-Martin JJ. Preoperative embolization for the treatment of cervical Castleman disease. *J Craniofac Surg* 2012;23(3):257-9.
12. Deshmukh M, Bal M, Deshpande P, Jambhekar NA. Synchronous squamous cell carcinoma of tongue and unicentric cervical Castleman's disease clinically mimicking a stage IV disease: a rare association or coincidence? *Head Neck Pathol* 2011;5(2):180-3.
13. Maruyama S, Hao N, Cheng J, Horino K, Ohnishi M, Fukushi M, Fujii M, Saku T. Castleman's disease of the buccal mucosa: report of a case and review of the literature of head and neck cases. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2002;93(3):305-10.
14. Bowne WB, Lewis JJ, Filippa DA, Niesvizky R, Brooks AD, Burt ME, et al. The management of unicentric and multicentric Castleman's disease: a report of 16 cases and a review of the literature. *Cancer* 1999; 85(3):706-17.
15. de Vries IA, Van Acht MM, Demeyere T, Lybeert ML, de Zoete JP, Nieuwenhuijzen GA. Neoadjuvant radiotherapy of primary irresectable unicentric Castleman's disease: a case report and review of the literature. *Radiat Oncol* 2010;2:5-7.



İris nevi and melanomas: Distinguishing parameters

İris nevüsleri ve melanomları: Ayırt edici parametreler

Reşat Duman¹, Nilay Duman², Rahmi Duman³, Mustafa Doğan¹

¹Afyon Kocatepe Üniversitesi, Tıp Fakültesi, Göz Hastalıkları Ana Bilim Dalı, Afyonkarahisar

²Afyon Kocatepe Üniversitesi, Tıp Fakültesi, Dermatoloji Ana Bilim Dalı, Afyonkarahisar

³Bursa Şevket Yılmaz Eğitim Ve Araştırma Hastanesi, Göz Hastalıkları Ana Bilim Dalı, Bursa

Dergiye Ulaşma Tarihi: 18/03/2015 Dergiye Kabul Tarihi:30/05/2015 Doi: 10.5505/aot.2015.77487

ÖZET

İris melanomlarının çoğu daha önce var olan iris nevüsleri üzerinden gelişmektedir. İris melanomlarının enükleasyon, metastaz ve fonksiyonel kayba neden olma riskleri nedeniyle erken tanılar oldukça önemlidir. İris nevüsünden melanom gelişimini kestirecek klinik parametrelerin farkında olunması melanom gelişimi açısından riskli nevüs grubunun belirlenmesini ve iris melanomların erken tespitini kolaylaştıracaktır. Bu derlemede iris nevüslerinin ve melanomlarının klinik özellikleri ve ayırt edici klinik parametreler sunuldu. Böylelikle bu hastalara klinik yaklaşımda yardımcı olunması amaçlandı.

Anahtar Kelimeler: iris, nevüs, melanom.

ABSTRACT

Most of the iris melanomas arise from pre-existing iris nevi. Early diagnosis of iris melanomas is quite important because of potential risk of enucleation, metastasis and functional loss. Being aware of the clinical parameters predicting the development of melanoma from pre-existing nevus will help determining the hazardous nevus group and early diagnosis of iris melanomas. In this review, clinical features of iris nevi and melanomas and distinguishing clinical parameters were presented. Thus, helping in the clinical management of such patients were aimed.

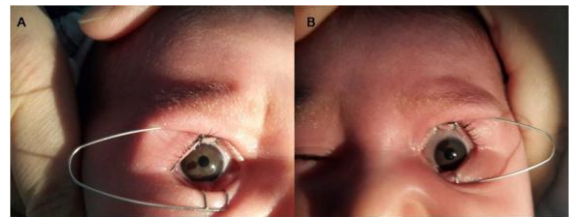
Key words: iris, nevus, melanoma.

İris nevüsleri

Normal nüfusta göz içi lezyonları değerlendirildiğinde iris nevüsleri sık görülen tanılardan birisidir. İris nevüsleri toplumun %4-6' sında görülür.¹ Çocukluktaki iris lezyonlarının %25'ini, genç erişkinlerde % 36'sını ve orta ve ileri yaş erişkinlerdeki iris lezyonlarının %47'sini oluşturur.² İris nevüsleri nadiren doğuştan mevcut iken sıklıkla ergenlik sonrası belirginleşerek tanı alır (Resim 1). Çoğunlukla beyaz ırkta ve mavi-gözlü bireylerde, sıklıkla 5.dekatta tespit edilir. Her iki cinsiyette de ortaya çıkabilse de son serilerde kadınlarda biraz daha yüksek oranda bildirilmiştir.³

İris nevüsleri irisin herhangi bir kısmını tutabilse de sıklıkla alt kadranda ortaya çıkar. Şekilleri, boyutları ve pigmentlenme özellikleri olgudan olguya değişiklik gösterir. Tekil ya da çoklu; yassı veya nodüler lezyonlar şeklinde ortaya çıkabilirler, küçük ve iyi sınırlı

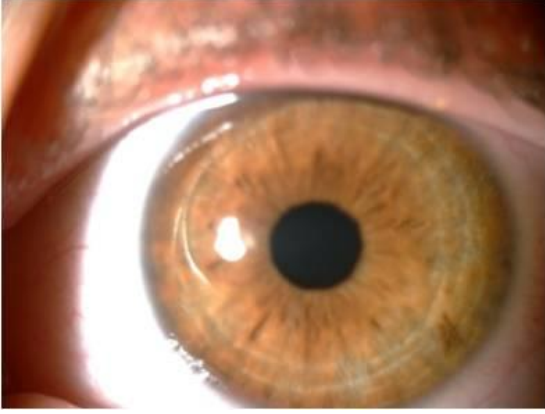
olabilecekleri gibi, büyük ve yaygın olabilirler (Resim 2).



Resim 1. Bebek olguda doğuştan mevcut çift taraflı iris nevüsü.

İris nevüsleri sıklıkla pigmentlidirler, nadiren amelanotik olabilirler.¹ Yaygın lezyonlar tüm sektörü ya da tüm irisi tutabilir, genellikle doğumsal oküler melanositozlu hastalarda ortaya çıkar, heterokromiye neden olabilir, iris nevüs sendromunda izlenebilir.





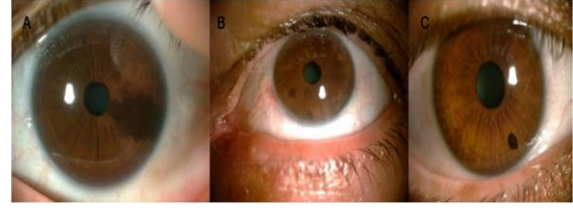
Resim 2. İris kenarında yer alan küçük tekil nevüs.

İris nevüs sendromu (Cogan-Reese sendromu); iridokorneal endotelial sendrom spektrumu içinde yer alırken, yaygın nevüs ve buna eşlik eden diğer iris anomalileri (çoklu nodüller, ektropiyon uvea, vb) ve tek taraflı glokom ile karakterizedir.⁴ Bir diğer iris nevüs tipi tapioca nevüstür. Bu tip nevüslerde, yüzey çoklu nodüler görünümündedir, tapioca bitkisinin köklerine benzediği için bu isimlendirme kullanılmıştır.⁵ Bir diğer iris nevüs tipi melanositomdur. Melanositomer, klinik olarak daha yoğun ve daha derin pigment içerir, çoğunlukla koyu kahve-siyah granüler yüzeye sahip nodüler lezyonlar olarak ortaya çıkar, belirgin bir damarlanma artışı göstermez. Melanositomer kendiliğinden nekroze olabilir, bunun sonucunda çevreye pigment ekimi olabilir ve trabeküler ağda tıkanma sonucu ikincil glokom gelişebilir. Melanositomer zamanla malign dönüşüm gösterebilir.⁶

Genel olarak, iris nevüslerinin çapı 3 mm'den, kalınlığı 1 mm'den küçüktür.¹ Yakın zamanlı bir seride pupile yakın lezyonların daha büyük olduğu ve daha uzamış ve üçgen şekilli olduğu, pupile uzak lezyonların ise daha küçük ve yuvarlak olduğu bildirilmiştir (Resim 3).⁷ İris nevüslerinin histopatolojisinde yüzeysel iris stromasında melanosit çoğalması izlenir, hücreler sıklıkla iğsi tiptedir. Epiteloid hücrelerin baskın olduğu olgularda melanomla karışabilir.⁸

İris nevüslerinde belirgin bir damar artışı izlenmez.¹ Sıklıkla pupil tepkilerinde bozukluk oluşmaz.¹ İris nevüslerinde sektör katarakt, iridokorneal aç tutulumu, pupile yakın yerleşimli lezyonlarda pupiller kenarda hafif bozulma ve ektropiyon uvea gelişimi ve zamanla yavaş büyüme izlenebilir, bunlar

eskiden düşünüldüğünün aksine her zaman malign dönüşümü düşündürmez.¹



Resim 3. A: Pupile yakın yerleşimli, büyük ve uzamış nevüs, B, C: Pupile uzak yerleşimli küçük ve yuvarlak hatlı nevüs.

İris nevüslerinin üzerinden melanom gelişme riski kesin olarak bilinmemektedir. Farklı çalışmalarda oranlar %2-5 olarak bildirilmiştir.^{3,9} 1611 iris nevüsü içeren yakın zamanlı bir seride olguların 27'sinde (%2) melanom gelişmiştir ve bu ortalama 69 ayda (aralık 4-214 ay, ortanca 46 ay) izlenmiştir.³ Ayrıca bu seride, Kaplan-Meier analizi ile iris nevüsünden melanom gelişme riskinin 10 yılda %4, 15 yılda %8 ve 20 yılda %11 olduğu gösterilmiştir.³ Genel olarak bazal çapın 3 mm'den fazla olması, damarlanmanın artışı, tümörün hızla büyümesi, göz dışına yayılım, siliyer cisim tutulumu ve eşlik eden ilaç tedavilerine dirençli glokomun varlığı melanom gelişimini akla getirmelidir.¹ Yakın zamanda Shields ve ark.³ iris nevüsünden melanom gelişimini öngörücü faktörler olarak ABCDEF kuralını önermiştir. Bu kural;
A: Age young (40 yaşından küçük olma),
B: Blood (hyphema) (hifemanın varlığı),
C: Clock hour inferior (saat 4-9 arası altta yerleşim),
D: Diffuse (yaygın lezyon varlığı),
E: Ectropion uvea (ektropiyon uvea varlığı) ve
F: Feathery margins (tüylü sınır varlığı) olarak belirlenmiştir. Bu kriterleri taşıyan nevüsleri olan hastalarda melanom riski daha yüksek olduğu için, tümör büyümesini değerlendirmek için daha yakın klinik takip önerilmektedir.

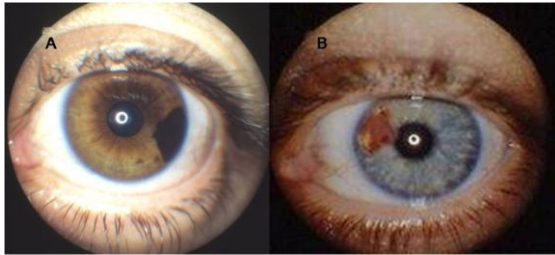
İris melanomları

İris melanomları oldukça nadir görülen tümörlerdir, tüm üveal melanomların %2-10'unu oluşturur.^{10,11} Çalışmalardaki tahmin edilen yıllık sıklığı milyonda 0.4-0.9'dur.¹² İris melanomlarının sıklığı son yıllarda artış



göstermiştir.^{12,13} Bu artışın güneş ışınlarına bağlı olduğu düşünülmektedir.¹⁴

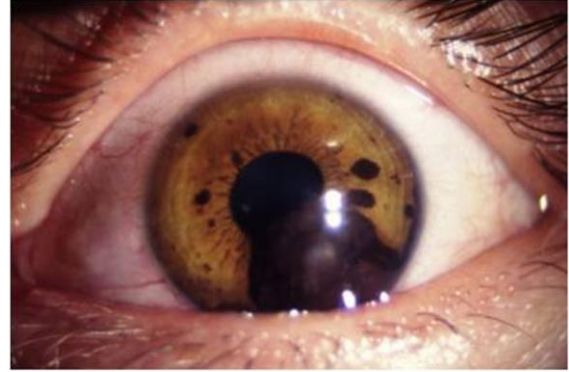
İris melanomları de novo ortaya çıkabileceği gibi, çoğunlukla daha önce var olan iris nevüsleri üzerinden gelişir.¹⁵ Cinsiyet ayrımı yapmaz, her yaşta ortaya çıkabilse de sıklıkla 40-50 yaşlarda tanı alır.¹⁶ Çoğunlukla beyaz ırkta ve açık renkli irislerde ortaya çıkar.¹⁶ Her iki gözde benzer oranlarda izlenir.¹² İris melanomları, sınırlı veya yaygın lezyonlar olarak ortaya çıkabilir.⁸ Zamanla büyüme gösterir, iris stromasının yerini değiştirir ve ikincil glokoma, katarakta, belirgin damar artışına veya ektropion uveaya neden olabilir.¹⁷ Sınırlı lezyonlar sıklıkla alt kadranda pigmentli nodüler lezyonlar şeklinde ortaya çıkar.¹² Yaygın lezyonlar ise edinilmiş heterokromi şeklinde tek taraflı koyu iris görünümüne neden olur.⁸ İris melanomları sıklıkla kahverengidir ancak pigmentasyon özellikleri olgudan olguya değişiklik gösterebilir, lezyonlar çok renkli veya amelanotik de olabilir (Resim 4).^{10,12}



Resim 4. A: Pigmente iris melanomu. B: Pigmentsiz iris melanomu (Resimler Dr. İlhan Günalp'a ait olup, onun izniyle kullanılmıştır).

Lezyonlarda sıklıkla damar artışı izlenir.¹⁰ Ortalama tümör çapı 6.2 mm, ortalama kalınlık 2.3 mm'dir.¹² İris melanomları pupil sınırında, orta zonda yerleşebilir, ya da pupilden çevre irise kadar uzanabilir, uydu lezyonlar şeklinde yayılım gösterebilir (Resim 5).¹⁰ Önde ön kamaraya doğru arkada ise arka kamaraya doğru büyüyebilir, silier cismi lokal ya da yaygın olarak tutabilir, arkada bu büyüme lens tarafından sınırlandırılır ve bu USG'de aslan pençesi görünümüne sebep olur.¹⁸ İris melanomlarının histopatolojik incelemesinde iğsi, epitelooid veya hem epitelooid hem de iğsi melanom hücreleri izlenebilir. Literatür olgularının yarısından fazlasında iğsi hücreler bildirilmiştir.¹⁰ Epitelooid hücre tipi veya karışık hücreli tip daha saldırgan biçimlerle

ilişkilendirilmiştir.^{12,15,18} Yaygın melanomlar, genellikle epitelooid tiptedir ve sınırlı lezyonlara kıyasla daha saldırgan klinik seyre sahiptir ve metastaz riski daha yüksektir.^{15,18}



Resim 5. Saat 4 ile 6 arasında yerleşim gösteren iris melanomu ve uydu lezyonları (Resim Dr. İlhan Günalp'a ait olup, onun izniyle kullanılmıştır).

İris melanomlarının çeşitli klinik tipleri mevcuttur. Tapioca melanomların yüzeyi çoklu nodüler görünüme sahiptir. Bir diğer iris melanom tipi trabeküler ağ melanomudur (halka melanom). Bu melanom sadece trabeküler ağı tutar, kütle oluşumundan ön kamara açısı etrafında yaygın yayılım gösterir ve tek taraflı glokomla ortaya çıkar.⁸

İris melanomlarının olası komplikasyonları arasında hifema, glokom, katarakt, metastaz ve ölüm yer alır.^{6,8,10} Glokom tümör ekimine, açılı kapanmasına veya yeni damar oluşumuna bağlı gelişebilir. Yaygın ve halka melanomlarda ikincil glokom riski daha yüksektir.^{8,15,18} Bu glokom sıklıkla ilaç tedavilerine dirençlidir ve optik diskte ağır derecede çukurlaşma ve fonksiyonel kayba neden olabilir.^{18,19}

İris melanomlarının metastaz oranları farklı çalışmalarda 5 yılda %3-11, 10 yılda %5-9 ve 20 yılda %10-11 arasında bildirilmiştir.^{10,12,20,21} Yaygın melanom varlığında, tümör kalınlığı fazla ise, eşlik eden glokom varlığında, arka tümör sınırı açı veya iris köküne ulaşmışsa, tümör göz dışına uzanım gösteriyorsa ve lezyona daha önce bir cerrahi işlem uygulanmışsa metastaz riski artmıştır.^{18,19,21} İris melanomlarının koroid ve siliyer cisim kaynaklı diğer uveal melanomlara göre daha iyi seyirli olduğu bilinmektedir.¹² Daha iyi klinik seyrin daha düşük biyolojik aktiviteye veya tümör çapına bağlı olduğu düşünülmektedir.¹² Shields ve ark.²⁰ 8033 uveal melanomu dahil ettikleri çalışmalarında iris melanomlarının ortalama çapının ve



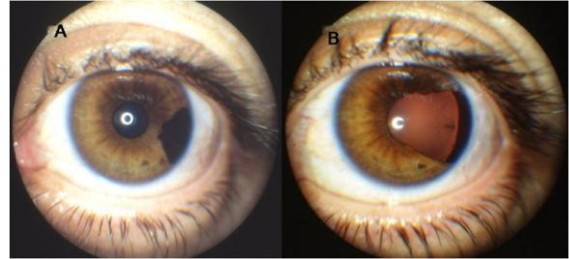
kalınlığının(5.5 mm/2.1 mm) koroidal melanoma (11.0 mm/4.5 mm) ($P<0.01$) ve siliyer cisim melanomuna (11.0 mm/6.0 mm) ($P<0.001$) kıyasla anlamlı olarak daha az olduğunu ve artan kalınlığın artmış metastaz riski ile uyumlu olduğunu göstermişlerdir. İris melanomlarında mortalite oranları melanom hücre tipi, melanom evresi, metastaz varlığı ve siliyer cisim tutulumu olup olmasına göre %0-11 arasında değişir.²² Metastaz varlığında, evre ileri ise, hücre tipi epitelioid hücre/epitelioid+iğsi hücre karakterinde ise ve siliyer cisim tutulmuşsa mortalite artış göstermektedir.²² Yaşın prognoz üzerine etkisi tartışmalıdır.¹² Bazı serilerde çocuklardaki uveal melanomların daha iyi prognoza sahip olduğu gösterilmiştir.²⁰ Shields ve ark.¹² 317 olguluk serilerinde çocuklardaki iris melanomlarında tümör boyutunun, aç tutulumunun ve ikincil glokom gelişiminin erişkinlere kıyasla anlamlı olarak daha az olduğunu gösterdiler de metastaz ve mortalite açısından yaşa göre bir farklılık tespit etmemişlerdir.

İris melanomlarında evrelendirme için 2009 Amerika Birleşik Kanser Komitesi evrelendirme sistemi kullanılmaktadır.²³ Buna göre irise sınırlı tümör T1, siliyer cisim veya koroide uzanan tümör T2, ek olarak skleraya uzanım gösteren tümör T3, ve sklera dışı uzanım gösteren tümör T4 olarak kabul edilmektedir. Metastazsız sağkalım T1 tümörler için 100%, T2 tümörlerde %90, T3 ve T4 tümörlerde %50'dir.^{6,10}

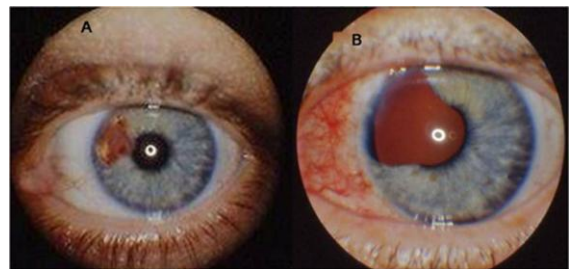
İris nevüslerinin ve melanomlarının tanısı genellikle klinikle konur. Bu lezyonlar gonyoskopi ile ayrıntılı olarak incelenmeli ve belli zaman aralıklarında fotoğraflanarak boyutları takip edilmelidir. Tümörün arka sınırlarını değerlendirmede transluminasyon testi de kullanılabilir. Karanlıkta ışık kaynağı ile transkonjonktival veya transkorneal olarak gözün aydınlatılmasıyla tümör sınırları görülebilmektedir. Şüpheli vakalarda malign-benign ayrımı için, iris floresan anjiyografi, ultrason biyomikroskopi (UBM), transluminasyon testi, ön segment optik koherens tomografi ve ince iğne aspirasyon biyopsisi kullanılabilir.¹ Ayırıcı tanıda; iris kistleri, yabancı cisimler, medülloepitelyoma ve leiomyoma gibi tümörlerin yanısıra metastatik kitleler de akılda tutulmalıdır.¹⁶

İris melanomunda tedavi yaklaşımı eğer tümör küçükse, saat 3-4 arasında

yerleşimli ise ve çevreye ekilmediyse cerrahi rezeksiyondur (iridektomi). Açıya yayılan tümörlerde iridosiklektomi tercih edilir (Resim 6, 7).²⁴ Cerrahideki amaç tümörü tamamen çıkarmak ve nükse ya da metastaza neden olabilecek tümör hücrelerini geride bırakmamaktır. Cerraha veya cerrahi tekniğe bağlı olarak kalıntı tümör, yerel nüks ve metastaz oranları sırasıyla %3-7, %2-14 ve %0-9 arasında değişir.¹⁶ Cerrahi sonrası nüks ortalama 45 ayda gelişir.¹⁶ Tümör büyükse ve çevreye ekilmişse, cerrahi sonrası histopatolojik olarak cerrahi sınırlar tutulmuşsa, klinik olarak kalıntı tümör mevcutsa veya takipte yerel nüks izlenmişse radyoterapi uygulanabilir.^{16,24} Radyoterapi radyoaktif bir plakla (plak brakiterapisi) veya dışsal ışın (proton radyoterapisi) şeklinde uygulanabilir.^{24,25} Kontrol edilemeyen glokom varlığında veya hızlı büyüme gösteren tümör varsa ve radyoterapi uygulanamıyorsa enükleasyon önerilmektedir.²⁴ Yaşam beklentisinin çok düşük olduğu ve komorbiteleri yüksek hastalarda sadece gözlem de uygun tedavi yaklaşımı olabilmektedir.¹⁶



Resim 6. İridosiklektomi ile tedavi edilen iris melanomu (Resimler Dr. İlhan Günalp'a ait olup, onun izniyle kullanılmıştır).



Resim 7. İridosiklektomi ile tedavi edilen iris melanomu (Resimler Dr. İlhan Günalp'a ait olup, onun izniyle kullanılmıştır).

Sonuçta iris melanomlarının sağkalım açısından prognozu iyi olsa da enükleasyon, metastaz ve fonksiyonel kayba neden olma riskleri nedeniyle erken tanılar önemlidir. İris melanomlarının çoğu daha önce var olan iris nevüsleri üzerinden gelişmektedir. Klinik



takipte yukarıda ele aldığımız kriterlerin kullanılması riskli nevüslerin belirlenmesi ve melanomların erken tespitini kolaylaştıracaktır.

Çıkar Çatışması: Yok

Teşekkür

Bilgilerini ve melanom hasta resimlerini bizimle paylaşan, bu derlemenin yazılma sürecinde bizden desteğini esirgemeyen sayın hocamız Prof. Dr. İlhan Günalp'a teşekkürlerimizi sunarız.

Kaynaklar

1. Kiratli H. Head and Neck: Iris Hamartomas. Atlas Genet Cytogenet Oncol Haematol. 2010; 14: 83-6.
2. Shields CL, Kancherla S, Patel J, et al. Clinical survey of 3680 iris tumors based on age at presentation. Ophthalmology. 2012; 119: 407-14.
3. Shields CL, Kaliki S, Hutchinson A, et al. Iris nevus growth into melanoma: analysis of 1611 consecutive eyes: the ABCDEF guide. Ophthalmology. 2013; 120: 766-72.
4. Ozdemir Y, Onder F, Coşar CB, Usubütün A, Kural G. Clinical and histopathologic findings of iris nevus (Cogan-Reese) syndrome. Acta Ophthalmol Scand. 1999; 77: 234-7.
5. Hassenstein A, Bialasiewicz AA, von Domarus D, Schäfer H, Richard G. Tapioca melanomas of the iris: immunohistology and report on two cases. Graefes Arch Clin Exp Ophthalmol. 1999; 237: 424-8.
6. Shields CL, Shields PW, Manalac J, Jumroendarasame C, Shields JA. Review of cystic and solid tumors of the iris. Oman J Ophthalmol. 2013; 6: 159-64.
7. Schwab C, Zalaudek I, Mayer C, et al. New insights into oculodermal nevogenesis and proposal for a new iris nevus classification. Br J Ophthalmol. 2014 Oct 30 [Epub ahead of print].
8. Jerry A, Shields JA, Shield CL. Intraocular Tumors: An Atlas and Textbook (2nd ed). Philadelphia; Lippincott Williams & Wilkins; 2008: 2; 14.
9. van Klink F, de Keizer RJ, Jager MJ, Kakebeeke-Kemme HM. Iris nevi and melanomas: a clinical follow-up study. Doc Ophthalmol. 1992; 82: 49-55.
10. Khan S, Finger PT, Yu GP, et al. Clinical and pathologic characteristics of biopsy-proven iris melanoma: a multicenter international study. Arch Ophthalmol. 2012; 130: 57-64.
11. Krohn J, Dahl O. Incidence of iris melanoma in western Norway. Acta Ophthalmologica. 2008; 86: 116-7.
12. Shields CL, Kaliki S, Shah SU, Luo W, Furuta M, Shields JA. Iris melanoma: features and prognosis in 317 children and adults. J AAPOS. 2012; 16: 10-6.
13. Jensen OA. Malignant melanoma of the iris. A 25-year analysis of Danish cases. Eur J Ophthalmol. 1993; 3: 181-8.
14. Michalova K, Clemett R, Dempster A, Evans J, Allardyce RA. Iris melanomas: are they more frequent in New Zealand? Br J Ophthalmol. 2001; 85: 4-5.

15. Millodot M, Hendler K, Pe'er J. Iris melanoma: a case report and review. Ophthalmic Physiol Opt. 2006; 26: 120-6.
16. McLaughlin JP, Fung AT, Shields JA, Shields CL. Iris melanoma in children: Current approach to management. Oman J Ophthalmol. 2013; 6: 53-5.
17. Shields JA, Sanborn GE, Augsburger JJ. The differential diagnosis of malignant melanoma of the iris. A clinical study of 200 patients. Ophthalmology. 1983; 90: 716-20.
18. Singh AD, Damato BE. Iris melanoma. In: Singh AD, Damato BE, eds. Clinical Ophthalmic Oncology (2nd ed). London; Springer; 2014: 137-158.
19. Demirci H, Shields CL, Shields JA, Eagle RC Jr, Honavar SG. Diffuse iris melanoma: a report of 25 cases. Ophthalmology. 2002; 109: 1553-60.
20. Shields CL, Furuta M, Thangappan A, et al. Metastasis of uveal melanoma millimeter-by-millimeter in 8033 consecutive eyes. Arch Ophthalmol. 2009; 127: 989-98.
21. Shields CL, Shields JA, Materin M, Gershenbaum E, Singh AD, Smith A. Iris melanoma: riskfactors for metastasis in 169 consecutive patients. Ophthalmology. 2001; 108: 172-8.
22. Geisse LH, Robertson DM. Iris melanoma. Am J Ophthalmol. 1985; 99: 638-48.
23. Edge SB, Byrd DR, Compton CC, et al. AJCC Cancer Staging Manual (7th ed). New York; Springer; 2009: 547-59.
24. Kanski JJ, Bowling B. Clinical Ophthalmology a systematic approach (7th ed). Philadelphia; Elsevier Saunders; 2011: 487-8.
25. Shields CL, Shah SU, Bianciotto CG, Emrich J, Komarnicky L, Shields JA. Iris melanoma management with iodine-125 plaque radiotherapy in 144 patients: impact of melanoma-related glaucoma on outcomes. Ophthalmology. 2013; 120: 55-61.



Primary Cardiac Angiosarcoma: A Case Report

Primer Kardiyak Anjiosarkoma: Bir Olgu Sunumu

Ayşe Gök Durnalı¹, Ayşe Yüksel², Muzaffer Bedri Altundağ³, Murat Vural⁴, Berna Öksüzöğlü¹, Necati Alkış¹

¹Dr.A. Y. Ankara Onkoloji Eğitim ve Araştırma Hastanesi, Tıbbi Onkoloji Kliniği, Ankara, Türkiye

²Ankara Onkoloji Eğitim ve Araştırma Hastanesi, Kardiyoloji Kliniği, Ankara, Türkiye

³Ankara Onkoloji Eğitim ve Araştırma Hastanesi, Radyasyon Onkolojisi Kliniği, Ankara, Türkiye

⁴Ankara Numune Eğitim ve Araştırma Hastanesi, Radyoloji Kliniği, Ankara, Türkiye

Dergiye Ulaşma Tarihi:26/02/2015 Dergiye Kabul Tarihi:28/05/2015 Doi: 10.5505/aot.2015.92400

ÖZET

Primer kardiyak anjiosarkoma, kötü prognozlu nadir bir hastalıktır. Açık kardiyak cerrahi operasyon olan ve sağ atriumda kardiyak anjiosarkoma tanısı alan 34 yaşında erkek hasta tıbbi onkoloji bölümüne başvurdu. Tümörün tam küratif rezeksiyonu mümkün olmamıştı ve hastaya postoperatif dönemde 6 siklus kombinasyon kemoterapi rejimi (doksorubisin ve mesna korumasıyla ifosfamid) verildi. Hastada 8 ay boyunca stabil hastalık mevcuttu ve progresyon sonrasında ikinci sıra kemoterapi (paklitaksel) başlandı, ancak hasta tanıdan 15 ay sonra kaybedildi. Kardiyak anjiosarkoma olgularının çoğunda küratif rezeksiyonlar mümkün olmadığından daha ileri tedavi seçeneklerine son derece ihtiyaç vardır.

Anahtar Kelimeler: Kardiyak anjiosarkoma, Kemoterapi

ABSTRACT

Primary cardiac angiosarcoma is a rare disease with poor prognosis. A 34-year-old male patient who underwent an open cardiac surgery and diagnosed as cardiac angiosarcoma on the right atrium was admitted to the medical oncology department. Complete curative resection of the tumor was not possible and postoperatively 6 cycles of combination chemotherapy regimen (ifosfamide with mesna protection and doxorubicin) was given. Patient had stable disease for 8 months, and after progression a second-line chemotherapy (paclitaxel) was started but he died after 15 months of diagnosis. Since curative resections are not possible in most of the cardiac angiosarcoma cases, further treatment options are desperately needed.

Key words: cardiac angiosarcoma, chemotherapy

Introduction:

Most of the malignant neoplasms located in the heart are metastatic tumors. Primary cardiac tumors are quite rare, and only 25% of them are malignant (1, 2). One of the malignant primary neoplasm of the heart, namely cardiac angiosarcoma originates from the mesenchymal tissue and endothelial subepicardium. It occurs more frequently in young middle-aged patients and its prognosis is very poor (3, 4). We have reported a patient with this disease and our treatment outcomes.

Case Report:

A 34-year-old man was admitted to the medical oncology department with the diagnosis of cardiac angiosarcoma. In his past

history, approximately one month ago, he was admitted to emergency department with chest pain, massive pleural effusion was detected on chest X-ray, and chest computerized tomography (CT) showed a mass in the right atrium. The chest tube was inserted and he underwent an open cardiac surgery. On exploration, pericardium was sticky and enclosed by vascular structures, there was a mass with irregular borders on the right atrium extending to the right ventricle, and invasion to the right pleura. Since complete curative resection was not possible, partial resection was undertaken. Pathological examination of resected material was reported as well-differentiated angiosarcoma with vascular invasion, 4x3 cm in size, and there was 9 mitosis per 10 high power field (HPF) and

eventually surgical margins were tumor-positive.

Cardiac magnetic resonance imaging (MRI), taken after admission to medical oncology department, revealed a mass, 81x55 mm in size, invading the anterior wall of right ventricle, protruding into the cavity of right ventricle with the suspicion of invasion to tricuspid valve and right atrium and aorta (Figure 1).

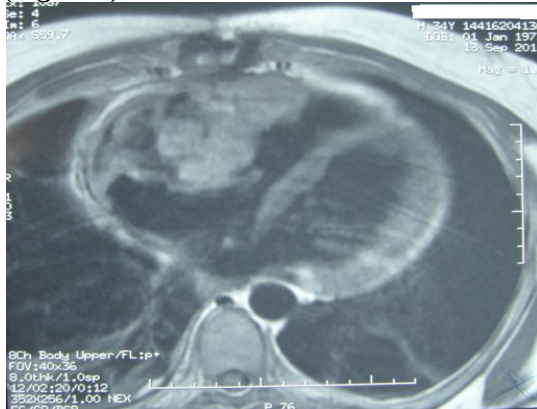


Figure 1: Magnetic resonance imaging taken after cardiac surgery revealed a mass, 81x55mm in size, invading the anterior wall of right ventricle.

Transthoracic echocardiography confirmed a semi mobile mass 50x40mm in size in the right atrium (Figure 2).



Figure 2: Transthoracic echocardiography showed a semi mobile mass 50x40mm in size in the right atrium

Abdominal ultrasonography was normal. A combination chemotherapy regimen used for other soft tissue sarcomas (ifosfamide 1800mg/m²/day on 1-5 days, with mesna protection, doxorubicin 60mg/m²/day on day 1, every 3 weeks), was started, and after the 1st cycle, febrile neutropenia developed and chemotherapy doses were reduced by 20% at the following cycles. After 3 cycles of

chemotherapy, there was a minimal regression on MRI findings and 3 more cycles were given. After 6 cycles, MRI and echocardiography revealed stable disease. Positron Emission Tomography (PET-CT) showed increased uptake of fluorodeoxyglucose only on right ventricular region. He was consulted to the heart surgery clinics for a second operation, however no more curative operation was considered to be possible. He was consulted with the radiotherapy clinics and radiotherapy was not indicated. About 5 months later, there was progression on cardiac MRI findings and chest CT showed metastatic nodules, 2 cm in diameter. With these findings second line chemotherapy (paclitaxel 175mg/m²/day on day 1, every 21 days) was started. After 3 cycles of paclitaxel chemotherapy, minimal regression was achieved, but after 6 cycles, clinical findings and imaging findings showed progression. Due to cardiac and respiratory failure, the patient died 45 days after the last chemotherapy cycle and 15 months after the initial diagnosis.

Discussion:

Primary cardiac angiosarcoma is seen infrequently, accounting for less than 10% of all primary cardiac tumors (5). It is seen mostly in right side of the heart and in young to middle-aged patients (3,4). Symptoms vary according to the size and site of the tumor: chest pain, cough, syncope, dyspnea, lung edema, arrhythmia, peripheral edema, dizziness are the most common symptoms (3,4,6,7,8). Transthoracic echocardiography and computed tomography (CT) are the useful tools for initial evaluation and suggestion of diagnosis, and MRI is helpful in preoperative differential diagnosis (8,9). Diagnosis of cardiac angiosarcoma is often confirmed by the resection of the tumor. Because of the fragility of the tumor, myocardial biopsy is not recommended. In the presented case, CT was used for the initial evaluation; and cardiac MRI and echocardiography for the evaluation of residual tumor and chemotherapy responses. Because of the rarity of this disease, there has been no standard treatment guideline. If possible, extensive surgical resection of tumor is considered as the best curative management (10,11). In some cases, radiotherapy after surgery was reported to improve outcomes

(2,10). There are insufficient data about the role of adjuvant chemotherapy. Chemotherapy regimens containing doxorubicin, ifosfamide, cisplatin and paclitaxel have been tried (6,12,13, 14). For advanced disease doxorubicin and weekly paclitaxel seem to provide some improvement in progression free survival (14). Several phase II trials have been published investigating vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitors such as sorafenib, imatinib, pazopanib, sunitinib and anti-vascular endothelial growth factor (VEGF) antibody, bevacizumab, demonstrated that some angiosarcoma patients had response or durable disease stabilization on these agents (14, 15, 16). One of these phase II studies, sorafenib showed limited antitumor activity in pretreated patients only, for both visceral and superficial angiosarcoma, with short duration of tumor control (16). Further studies are needed to confirm these findings and to identify which patients will benefit from these agents.

Whatever the chosen treatment modality, the prognosis of cardiac angiosarcoma is poor and the median survival is between 3 to 12 months. Surgical excision of the tumor may be associated with better survival increasing up to 21 months (10). If surgical resection is not possible, median survival is approximately 6 months (7,17). In one case report of a metastatic patient, multimodality palliative treatment with neoadjuvant and adjuvant chemotherapy and surgery improved survival (18). The patient presented herein had minimal symptomatic disease for about 8 months with multimodality treatment including incomplete resection and chemotherapy.

In conclusion, primary cardiac angiosarcoma is a rare and aggressive tumor with poor prognosis. For treatment options; surgical resection should be considered first and chemotherapy and radiotherapy may be indicated for palliative purposes.

Conflict of interest: None

References:

1. Reynen K: Frequency of primary tumors of the heart. *Am J Cardiol.* 1996; 77: 107
2. Moggio RA, Pucillo AL, Schechter AG, Pooley RW, Sarabu MR, Reed GE: Primary cardiac tumors: diagnosis and management in 14 cases. *NY State Med J Med.* 1992; 92: 48-52
3. Naka N, Ohsawa M, Tomita Y, Kanno H, Uchida A, Aozasa KI: Angiosarcoma in Japan: a review of 99 cases. *Cancer.* 1995;75: 989-996
4. Ge Y, Ro JY, Kim D, et al. Clinicopathologic and immunohistochemical characteristics of adult primary cardiac angiosarcomas: analysis of 10 cases. *Ann Diagn Pathol.* 2011;15(4): 262-7
5. Dennig K, Lehmann G, Richter T: An angiosarcoma in the left atrium. *N Engl J Med.* 2000;342:443-444.
6. Pezzuto A, Gencarelli G, Martone L, Bruno P, Mariotta S: Primary cardiac angiosarcoma in a young woman. *Case Rep Oncol.* 2010;3:24-29
7. Gong Y, Hong T, Chen M, Huo Y: A right heart angiosarcoma with rapidly progressing hemorrhagic pericardial effusion. *Intern Med.* 2011;50: 455-458
8. Castilla-Cabanes E, Pascual-Calleja I, Roncales-Garcia Blanco F, del Rio-Ligorit A: Clinical variations of cardiac sarcoma. *Rev Esp Cardiol.* 2009;62: 823-824
9. Di Bela G, Gaeta M, Patane L, Lentini S: Tissue characterization of a primary cardiac angiosarcoma using magnetic resonance imaging. Letter to editor. *Rev Esp Cardiol.* 2010; 63(11): 1382-3
10. Poole GV, Meredith JW, Brejer R: Surgical implications in malignant cardiac disease. *Ann Thor Surg.* 1983;36: 484-491
11. Erpolat OP, Icli F, Doğan OV, et al. Primary cardiac angiosarcoma: a case report. *Tumori.* 2008;94: 892-897
12. Sarrejeant JM, Butany J, Cusimano RJ: Cancer of the heart: epidemiology and management of primary tumors and metastasis. *Am J Cardiovasc Drugs.* 2003;3: 407-421
13. Ram Prabu MP, Thulker S, Ray R, Bakhshi S. Primary cardiac angiosarcoma with good response to paclitaxel. Letter to editor. *J Thorac Oncol.* 2011;6(10): 1778-1779
14. Penel N, Maréchal S, Robin YM, Hohenberger P. Angiosarcoma: state of the art and perspectives. *Crit Rev Oncol Hematol.* 2011 Nov;80(2):257-63
15. Park MS, Ravi V, Araujo DM. Inhibiting the VEGF-VEGFR pathway in angiosarcoma, epithelioid hemangioendothelioma and hemangiopericytoma / solitary fibrous tumor. *Curr Opin Oncol.* 2010 Jul;22(4):351-5
16. Ray-Coquard I, Italiano A, Bompas E, et al. Sorafenib for patients with advanced angiosarcoma: a phase II Trial from the French Sarcoma Group (GSF/GETO). *Oncologist* 2012;17(2):260-6
17. Simpson L, Kumar SK, Okuno SH, et al Malignant primary cardiac tumors: review of a single institution experience. *Cancer.* 2008;112: 2440-2446.
18. Pigott C, Welker M, Khosla P, Higgins RS: Improved outcome with multimodality therapy in primary cardiac angiosarcoma. *Nat Clin Pract Oncol.* 2008;5: 112-115