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Türk Jinekolojik Onkoloji Dergisi, Türk Jinekolojik Onkoloji Derneğinin bilimsel yayın organı olup, kadın kanserleri alanındaki klinik ve deneysel çalışmalara dayalı orijinal araştırma yazıları, derlemeler, orijinal olgu sunumları ve editöre mektupları yayınlayan uluslararası bir dergidir.

Türk Jinekolojik Onkoloji Dergisi yılda üç kez yayınlanır. Derginin yazı dili Türkçe ve İngilizcedir. Jinekolojik onkolojik cerrahi, radyoterapi, kemoterapi, patoloji, sitoloji, endokrinoloji, genetik, moleküler biyoloji ve epidemiyoloji temelinde Jinekolojik onkoloji ile ilgili tüm branşlar tarafından hazırlanan çalışmalar kabul edilmektedir.

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AMAÇ ve KAPSAM

Türk Jinekolojik onkoloji dergisi; Jinekolojik Onkoloji alanında ülkemizde ve dünyada yapılan güncel çalışmaları yayınlayarak kadın kanserleri ile uğraşan ulusal ve uluslararası tüm hekimlerin bireysel gelişimine katkı sağlamayı amaçlamaktadır.Türk jinekolojik onkoloji dergisi'nin hedef okuyucu kitlesi, jinekolojik onkoloji uzmanı hekimler, yan dal uzmanlık eğitimi öğrencileri, jinekolojik onkolojiye ilgi duyan tüm Kadın hastalıkları ve doğum uzmanları ve uzmanlık eğitimi öğrencileridir. Aynı zamanda, medikal onkoloji, radyasyon onkolojisi, patoloji uzmanları, akademisyenler ve uzmanlık eğitimi öğrencilerini de hedeflemekte, bu anlamda dergimiz interdisipliner kapsamda mezuniyet sonrası eğitim, sürekli mesleki gelişim ve araştırma perspektifinin ulusal ve uluslararası düzeyde yaygınlaşmasına katkı sağlamayı amaçlamaktadır. Sadece yazılı makalelerle değil video makalelerle de okuyucuların cerrahi bilgi, görgü ve tecrübelerini artırabilmeleri hedeflenmiştir.

Türk Jinekolojik Onkoloji Dergisi, kadın kanserleri ile uğraşan tüm disiplinleri içine alan ve kendi alanları ile ilgili Türkçe ve İngilizce yayın yapan bir dergidir. Derginin kısa ismi Turk J Gynecol Oncol' dür. Türk jinekolojik onkoloji dergisi, bilimsel yayınlara açık erişim sağlar. Yazarlardan makalelerin yayımlanması için herhangi bir ücret talep edilmez. Uygun bir hipotezle, bilimsel yöntemler kullanılarak yapılan özgün araştırmaları yayınlar. İnterdisipliner özellik gösteren temel ve klinik araştırmalar, toplum tabanlı araştırmalara dergide yer verilmektedir. Güncel gelişmelerleri içeren konularla ilgili derlemeler, nadir rastlanan olgu sunumları, editör görüşleri, video makaleler, alanında uzmanlaşmış hekimlerin deneyim ve yorumlarını içeren editöre mektupları yayımlar. Dergipark online makale yükleme sistemi üzerinden makaleler kabul edilmektedir. Dergide yayımlanmak üzere gönderilen yazıların daha önce elektronik ya da basılı olarak, başka bir yerde yayımlanmamış olması ya da gönderim zamanında başka bir derginin incelemesi altında olmaması gerekmektedir. Dergi önyargısız-çift kör hakemlik ilkeleri çerçevesinde yayın yapmaktadır. Dergiye gönderilen makale biçimsel esaslara uygun ise editör ve en az iki hakemin incelemesinden geçtikten sonra; gerek görüldüğü takdirde, istenen değişiklikler yazarlarca yapıldıktan sonra yayımlanır.Yayınlanan makalelerde ifade edilen tüm görüşler, editörlerin, yayın kurulunun ve/veya yayıncının görüşlerini değil, yazar(lar)ın görüşlerini yansıtır. Editörler, yayın kurulu ve yayıncı ifade ve görüşler için herhangi bir sorumluluk veya yükümlülük kabul etmez.

AÇIK ERŞİM POLİTİKASI

Türk Jinekolojik Onkoloji Dergisi, açık erişimli bir dergi olup makalelere ücretsiz olarak erişilebildiği anlamına gelmektedir. Kullanıcılar, yayıncıdan veya yazardan izin almaksızın makalelerin tam metinlerini okuyabilir, indirebilir, kopyalayabilir, dağıtabilir, yazdırabilir, bağlantı verebilir.

ETIK İLKELER VE YAYIN POLITIKASI

Türk Jinekolojik Onkoloji Dergisi, yılda üç (3) kez yayımlanan hakemli bir dergidir. Türk Jinekolojik Onkoloji Dergisi hem yazarların hem de derginin haklarını korumak amacıyla etik ilkelerin sağlanmasına büyük önem vermektedir. Bu doğrultuda dergiye yazı gönderen yazarların aşağıdaki etik kurallara uymaları istenmektedir.

1. Yazarların Dikkat Etmesi Gereken Hususlar

· Dipnot ve Kaynakça'daki eserler listesi eksiksiz olmalıdır.
· İntihal ve sahte veriye yer verilmemelidir.
· Aynı araştırmayı birden fazla dergide yayımlamamalı ve bilimsel araştırma ve yayın etiğine uymalıdır.
· Araştırmaya önemli oranda katkıda bulunan tüm yazarların isimleri yayında yazılmalı
· Araştırmaya katkıda bulunmayan yazarların isimlerine yer verilmemeli.
· Araştırmaya önemli oranda katkıda bulunmayıp bir şekilde katkı sunanlar yazar olarak ismi verilmemeli ilgili araştırmaya sunduğu katkıdan dolayı teşekkür edilmeli.
· Tüm yazarlar editörün düzeltmelerini yapmakla yükümlüdür.

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· Hakemler değerlendirmelerinde tarafsız olmalıdır.
· Hakemler araştırmayla, yazarlarla ve/veya araştırma fon sağlayıcılar ile çıkar çatışması içerisinde olmamalıdır.
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3. Editör/Editörlerin Dikkat Etmesi Gereken Hususlar

· Editörler bir makaleyi kabul ya da reddetmek için tüm sorumluluğa ve yetkiye sahiptir.
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· Sadece alana katkı sağlayacak makaleler kabul edilmelidir.
· Hatalar bulunduğu zaman düzeltilmesini, yayımlanmasını ya da geri çekilmesini desteklemelidir.
· Hakemlerin ismini saklı tutmalıdır ve intihal/sahte veriye engel olmalıdır.

4. Bilimsel Araştırma ve Yayın Etiğine Aykırı Eylemler
a) İntihal: Başkalarının özgün fikirlerini, metotlarını, verilerini veya eserlerini bilimsel kurallara uygun biçimde atıf yapmadan kısmen veya tamamen kendi eseri gibi göstermek,
b) Sahtecilik: Bilimsel araştırmalarda gerçekte var olmayan veya tahrif edilmiş verileri kullanmak,
c) Çarpıtma: Araştırma kayıtları veya elde edilen verileri tahrif etmek, araştırmada kullanılmayan cihaz veya materyalleri kullanılmış gibi göstermek, destek alınan kişi ve kuruluşların çıkarları doğrultusunda araştırma sonuçlarını tahrif etmek veya şekillendirmek,
ç) Tekrar yayım: Mükerrer yayınlarını akademik atama ve yükselmelerde ayrı yayınlar olarak sunmak,
d) Dilimleme: Bir araştırmanın sonuçlarını, araştırmanın bütünlüğünü bozacak şekilde ve uygun olmayan biçimde parçalara ayırıp birden fazla sayıda yayımlayarak bu yayınları akademik atama ve yükselmelerde ayrı yayınlar olarak sunmak,
e) Haksız yazarlık: Aktif katkısı olmayan kişileri yazarlar arasına dâhil etmek veya olan kişileri dâhil etmemek, yazar sıralamasını gerekçesiz ve uygun olmayan bir biçimde değiştirmek, aktif katkısı olanların isimlerini sonraki baskılarda eserden çıkartmak, aktif katkısı olmadığı halde nüfuzunu kullanarak ismini yazarlar arasına dâhil ettirmek.

5. Makalelerde Yapılan İntihalleri Ortaya Çıkarma
Türk Jinekolojik Onkoloji Dergisi araştırmacıların mağdur olmasını engellemek için özel bir intihal programı vasıtasıyla değerlendirilmek için gönderilen makalelerin daha önceden yayımlanıp yayımlanmadığını ve makale içerisinde intihal olup olmadığını tespit etmeye çalışmaktadır.

YAYIN POLİTİKASI

1.Türk Jinekolojik Onkoloji Dergisi yazarlardan makale değerlendirme ve yayın süreci için herhangi bir ücret talep etmemektedir. Yayınlanan makaleler için telif ücreti ödenmez.
2. Dergiye yayımlanmak üzere gönderilen yazılar editörün ön incelemesinden sonra Yayın Kurulu tarafından belirlenen konunun uzmanı iki hakeme gönderilir.
Yazının gönderildiği her iki hakemden olumlu cevap gelmesi durumunda yazının yayımlanmasına karar verilir. İki hakemin olumsuz görüş bildirmesi durumunda yazı yayımlanmaz. Bir olumlu, bir olumsuz görüş bildirilmesi durumunda, Yayın Kurulu raporların içeriğini dikkate alarak ya üçüncü bir hakeme gönderme ya da reddetmeye karar verebilir.
Yayımlanmasına karar verilen yazıların hakem raporlarında belirtilen düzeltmelerin yapılması için makale yazarına iade edilir. Düzeltmelere yapıldıktan sonra hakem uyarılarının dikkate alınıp alınmadığı editör tarafından kontrol edilerek yazının yayımlanıp yayımlanmayacağına karar verilir. Ön incelemeden itibaren makalenin yayına hazır duruma gelebilmesi için gerekli olan azami süre 2 aydır.

3. Hakeme gönderilmiş makaleler yayın etiği ile ilgili geçerli bir neden olmadığı müddetçe yazar tarafından geri çekilemez.

ORİJİNAL MAKALE/ORIGINAL ARTICLE

DERLEME/REVİEW

OLGU SUNUMU/CASE REPORT

TÜRK JİNEKOLOJİK ONKOLOJİ DERGİSİ
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ORGINAL ARTICLE / ORJİNAL MAKALE

Epitelyal over kanserlerinde obezite ile asit ilişkisi ve sağkalıma etkisi

The relationship between obesity and ascites in ephitelial ovarian cancers and its effect on survival

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ÖZ

Amaç: Bu çalışmada amaç epitelyal over kanseri tanısı olan hastalarda obezitenin, asit ile ilişkisinin toplam ve hastalıksız sağkalım üzerine etkisini incelemektir.

Gereç ve yöntem: Çukurova Üniversitesi Balcalı Hastanesi Kadın Hastalıkları ve Doğum Anabilim Dalı Jinekolojik Onkoloji kliniğinde 1992 ile 2018 yılları arasında hastanemizde epitelyal over kanseri tanısı almış 1053 hastanın dosyaları geriye dönük incelendi. Antropometrik verilerine ulaşılabilen 939 hasta çalışmaya dahil edildi. Hastaların vücut kitle indeksi hesaplamaları yapılarak, Dünya Sağlık Örgütü'nün obezite sınıflamasına göre kategorize edildi. Hastaların analizinde vücut kitle indeksi, görüntüleme ile asit varlığı ve operasyon sırasında asit varlığı ve tümör evresi gibi parametreler incelendi.

Verilerin istatistiksel analizinde SPSS (Statistical Package for the Social Sciences) 23.0 paket programı kullanıldı.

Bulgular: Çalışmada yer alan hastaların yaş ortalamaları 53,9±12,9 yıl iken; hastalardan 347 (%37.0)'si 50 yaş altı, 436 (%34.7)'sı 50-65 yaş aralığında, 156 (%16.6)'sı ise 65 yaş üzerinde oldukları tespit edildi. Zayıf, normal, aşırı kilolu, obez ve morbid obez hasta grupları için ortalama toplam sağkalım bulguları sırasıyla 49.7, 77.1, 75.5, 56.8 ve 42.3 ay olarak saptandı. Bununla birlikte ortalama hastalıksız sağkalım süreleri sırasıyla 16.2, 23.5, 24.7, 18.7 ve 20.9 ay olarak hesaplandı.

Zayıf, obez ve morbid obez grubunda yer alanların toplam sağkalım sürelerinin, normal ve aşırı kilolu grupta yer alan hastalara göre daha düşük olduğu tespit edildi (p=0,001). Görüntüleme ve operasyon sırasında asit varlığı, morbid obez grubunda anlamlı olarak yüksek olduğu bulundu. Hastalıksız sağkalım açısından gruplar arasında anlamlı fark bulunmazken, görüntülemede ve operasyon sırasında asit varlığı olan hastalarda hastalıksız sağkalım süresi anlamlı olarak düşük saptandı.

Sonuç: Over kanseri, sahip olduğu kötü prognostik özellikler nedeniyle oldukça ölümcül seyreden malign bir hastalıktır. Sonuçlarımız, obez hastalarda, asit birikiminin daha geç fark edilmesi nedeniyle tanıda gecikmeye neden olabileceğini ve bu durumun hastalığın ilerlemesi ve toplam sağkalım üzerinde olumsuz etkisi olabileceğini göstermektedir.

Anahtar Kelimeler: Epitelyal Over Kanserleri, Obezite, Asit, Toplam Sağkalım, Hastalıksız Sağkalım

ABSTRACT

Aim: The aim of this study is to examine the effect of obesity and its association with ascites on overall and disease-free survival in patients diagnosed with epithelial ovarian cancer.

Materials and methods: The files of 1053 patients which were diagnosed with epithelial ovarian cancer between 1992 and 2018 in the Department of Gynecologic Oncology of Obstetrics and Gynecology of Çukurova University, Balcalı Hospital were retrospectively analyzed. Among these patients, 939 patients whose anthropometric data could be accesed were included in the study. The body mass index (BMI) of these patients included in the study were calculated and they were categorized according to the obesity classification of the World Health Organization. In the analysis; patients' BMI, amount of ascites on imaging and during operation, and tumor stage were evaluated.

SPSS (Statistical fort he Social Sciences) 23.0 package program was used for statistical analysis of the data.

Results: The mean age of the patients included in the study was 53,9±12,9 years, and it was determined that 347 of the patients were over the age of 65. The mean overall survival course for the underweight, normal, overweight, obese and morbid obese patient was 49.7, 77.1, 75.5, 56.8, and 42.3 months. However the mean disease-free survival time was calculated as 16.2, 23.5, 24.7, 18.7 and 20.9 months. It was determined that the overall survival times of the patients in obese, morbid obese and underweight BMI categories were lower than the normal or overweight BMI groups (p=0,001). The presence of ascites on imaging and during operation was found as significantly higher in the morbid obese group. While there was no significant difference between BMI groups in terms of disease-free survival, it was found as significantly lower in patients with ascites on imaging and during operation

Conclusion: Ovarian cancer is a malignant disease with a very fatal course due to its poor prognostic features. Our results Show that in obese patients, delayed regocnition of ascites may cause a delay in diagnosis, and this may have a negative impact on disease progression and overall survival.

Keywords: Epithelial Ovarian Cancers, Obesity, Ascite, Overall Survival, Disease-Free Survival

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GİRİŞ

Over kanseri, gelişmiş ülkelerde ikinci en sık jinekolojik malignite iken, gelişmekte olan ülkelerde üçüncü en sık jinekolojik malignitedir. Beş yıllık sağkalım oranları %45'in altındadır. Türkiye'de yaşayan kadınlar içerisinde endometrium kanserinin ardından ikinci en sık görülen jinekolojik malignitedir. (1) Over kanserlerinin yaklaşık %90'ı epitelyal hücrelerden kaynaklanmakta olup, en sık görülen alt tipi high grade seröz karsinomlardır. Germ hücreli over tümörleri ve seks kord stromal tümörler ise diğer görülen histolojik tipler olarak karşımıza çıkmaktadır. Başlıca risk faktörleri arasında ileri yaş, erken menarş ve/veya geç menopoz, nulliparite, infetilite, endometriozis, polikistik over sendromu, postmenopozal hormon kullanımı, BRCA 1/2 ve Lynch Sendromu gibi genetik faktörler, ailede meme kanseri öyküsü, sigara kullanımı, asbest, talk maruziyeti gösterilmiştir.(2)

Malignite ilişkili asit yumurtalık, meme, kolon, akciğer, pankreas ve karaciğer maligniteleri gibi birçok malign durumda görülebilir. Tipik olarak tekrarlayan veya ilerlemiş kanserlerde gelişmektedir. Epitelyal over tümörleri, lenfatik obstrüksiyon ve damar geçirgenliğinin artmasına bağlı olarak peritoneal karsinomatozise neden olma eğilimindedir.(3, 4)

Obezite, Dünya Sağlık Örgütü (DSÖ)'nün tanımına göre insan sağlığına zarar verecek düzeyde insan vücudunda aşırı miktarda yağ birikimidir. Bireyin kilogram cinsinden ağırlığının boyunun metre cinsinden karesine bölünerek elde edilen vücut kitle indeksi sınıflamasına göre vücut kitle indeksinin 30 kg/m^{2}'den fazla olması obezite olarak tanımlanmaktadır. DSÖ 2016 yılında Dünya'da 18 yaş üzeri nüfusun yaklaşık 650 milyondan fazlasının obez olduğunu bildirmiştir. Obezitenin, içlerinde endometrium, meme ve kolon kanserinin de bulunduğu birçok malignite için artmış risk faktörü olduğu gösterilmiştir.(5)

Yaptığımız çalışmada epitelyal over kanserli hastaların, vücut kitle indeksi (VKİ), evre, görüntülemede ve operasyon sırasında asit miktarı gibi özellikleri birlikte analiz ederek obezite ve asit arasındaki ilişki ile beraber sağkalıma etkisini ortaya koymayı amaçladık.

GEREÇ VE YÖNTEM

Çukurova Üniversitesi Tıp Fakültesi Balcalı Hastanesi Kadın Hastalıkları ve Doğum kliniğinde 1992 ile 2018 yılları arasında hastanemizde epitelyal over kanseri tanısı almış 1053 hastanın dosyaları geriye dönük incelendi. Bu hastalar içerisinde antropometrik verilerine ulaşılabilen 939 hasta çalışmaya dahil edildi. Çalışmaya alınan hastaların VKİ hesaplamaları yapılarak, Dünya Sağlık Örgütü'nün obezite sınıflamasına göre kategorize edildi. Çalışmaya alınan hastalar kategorize edilirken VKİ 18,5'in altında olan hastalar zayıf, 18,5 – 24,9 arasında olan hastalar normal kilolu, 25 – 29,9 arasında olan hastalar fazla kilolu, 30 – 39,9 arasında olan hastalar obez, 40 ve üzerinde olan hastalar ise morbid obez olarak tanımlandı. Hastaların analizinde vücut kitle indeksi, tanı anındaki evre, preop asit varlığı, operasyon sırasında asit varlığı, gibi parametreler geriye dönük hasta dosyaları taranarak incelendi. Hastaların tanı tarihinden itibaren ölüme kadar geçen süre toplam sağkalım, tanı aldıkları tarihten itibaren, takipler sırasında hastalığın radyolojik ve/veya patolojik olarak nüks ettiği tarihe kadar geçen süre hastalıksız sağkalım olarak değerlendirildi. Tüm VKİ gruplarında toplam ve hastalıksız sağkalım verileri geçmişe dönük dosyalar taranarak ve hastane otomasyon sistemi aracılığıyla nüfus kayıt bilgilerine ulaşılarak incelendi.

İstatistiksel Değerlendirme: Verilerin istatistiksel analizinde SPSS (Statistical Package for the Social Sciences) 23.0 paket programı kullanıldı. Kategorik ölçümler sayı ve yüzde olarak, sürekli ölçümler ortalama ve standart sapma (gerekli yerlerde ortanca ve minimum -maksimum) olarak özetlendi. Kategorik parametrelerin karşılaştırılmalarında ki-kare ve

Fisher exact keskinlik tanı testlerine başvuruldu. Çalışmada yer alan parametrelerin normal dağılım gösterip göstermediğini belirlemede Shapiro-Wilk testi kullanıldı. Normal dağılım göstermeyen parametrelerde Kruskall wallis testi kullanıldı. Gruplar arasındaki farklılığın kaynağını incelemede Post Hoc Bonferroni testine başvuruldu. Sağkalım analizlerinde kaplan meier testi ile log rank testlerine başvuruldu. Hastaların mortalite etkilerini incelemesinde çoklu lojistik regresyon testi kullanıldı. Tüm testlerde istatistiksel önemlilik düzeyi 0.05 olarak alındı.

BULGULAR

Epitelyal over kanseri tanılı 939 hasta çalışmaya dahil edildi. Çalışmada yer alan hastaların yaş ortalamaları 53.9±12.9 yıl iken; hastalardan 347 (% 37.0)'si 50 yaş altı, 436 (% 46.4)'sı 50-65 yaş aralığında, 156 (% 16.6)'sı ise 65 yaş üzerinde oldukları tespit edildi. Çalışmaya alınan hastalar VKİ gruplarına göre değerlendirildiğinde 24 hasta zayıf, 253 hasta normal kilolu, 417 hasta aşırı kilolu, 222 hasta obez ve 23 hasta morbid obez olarak sınıflandırıldı.

Yaş aralığı 50-65 aralığında olanların VKİ bulguları aşırı kilolu, obez ve morbid obez görülme sıklığı, VKİ bulguları zayıf ve normal olan hastaların oranına göre anlamlı daha yüksek idi (p<0.001). Normal ve aşırı kilolu grupta yer alan hastalarda karın şişliğinin daha az, karın ağrısı şikayetinin ise diğer gruplarda yer alan hastalara göre daha sık gözlendiği belirlendi (p<0.001) (Tablo 1).

Tablo 1. Hasta karakteristikleri ile gruplar arasındaki karşılaştırmalar

	<18.5 Zayıf (n=24)		18.5-24.9 Normal (n=253)		25-29.9 Aşırı Kilolu (n=417)		30-39.9 Obez (n=222)		>40 Morbid Obez (n=23)		p[c]
	n	%	n	%	n	%	n	%	n	%	
Yaş Aralığı											
<50	14	58.3	114	45.1	145	34.8	69	31.1	5	21.7	**<0.001****
50-65	5	20.8	96	37.9	206	49.4	111	50.0	18	78.3	
>65	5	20.8	43	17.0	66	15.8	42	18.9	-	-	
Evre											
Evre 1	7	29.2	89	35.2	114	27.4	59	27.1	3	13.0	0.154
Evre 2	-	-	16	6.3	27	6.5	18	8.3	3	13.0	
Evre 3	16	66.7	128	50.6	247	59.4	130	59.6	17	73.9	
Evre 4	1	4.2	20	7.9	28	6.7	11	5.0	-	-	
Semptom											
Asemptomatik	1	4.3	-	-	4	1.0	5	2.3	1	4.3	**<0.001****
Karın şişliği	10	41.7	35	13.8	58	13.9	73	32.9	8	34.8	
Karın ağrısı	10	41.7	204	80.6	324	77.7	122	55.0	9	39.1	
Vajinal kanama	1	4.2	11	4.3	25	6.0	17	7.7	3	13.0	
Diğer	2	8.3	3	1.2	6	1.4	5	2.3	2	8.7	

* p<0.05, **p<0.001, +: p=0.011, ++: p=0.002, b: Kruskal Wallis test, Post Hoc Bonferroni, c: ki-kare ve fisher exact test

Morbid obez grubunda olan hastaların görüntülemede asit varlığı diğer VKİ gruplarında yer alan hastalara göre daha sık gözlendiği tespit edildi (p=0.002). Operasyon sırasında asit varlığı 1 L üzerinde görülme sıklığı morbid obez grubunda yer alan hastalarda, diğer VKİ gruplarında yer alan hastalara göre daha yüksek idi (p=0.003) (Tablo 2).

Tablo 2. Asit varlığı bulguları ile VKİ grupları arasındaki karşılaştırmalar

	<18.5 Zayıf (n=24)		18.5-24.9 Normal (n=253)		25-29.9 Aşırı Kilolu (n=417)		30-39.9 Obez (n=222)		>40 Morbid Obez (n=23)		p
	n	%	n	%	n	%	n	%	n	%	
Görüntülemede Asit Varlığı											
Yok	7	36.8	71	29.5	112	28.2	81	38.0	3	15.0	
Minimal	4	21.1	70	29.0	82	20.7	30	14.1	3	15,0	**0.002**
Var	8	42.1	100	41.5	203	51.1	102	47.9	14	70.0	
Operasyon Sırasında Asit Varlığı											
Yok	9	42.9	76	30.4	127	31.3	96	44.2	5	22.7	**0.003**
< 1 L	5	23.8	73	29.2	92	22.7	36	16.6	3	13.6	
> 1 L	7	33.3	101	40.4	187	46.1	85	39.2	14	63.6	

* p<0,05, **p<0,001, b: Kruskal Wallis test, Post Hoc Bonferroni, c: ki-kare ve fisher exact test

Debulking cerrahide interval sitoredüktif cerrahi oranının morbid obez grubunda yer alan hastalarda, diğer VKİ gruplarında yer alan hastaların oranlarına göre anlamlı daha yüksek olduğu saptandı (p<0.001). Cerrahi zorluk skoru (SCS) 3 ve altında görülme sıklığı morbid obez grubunda yer alan hastalarda daha yüksek idi (p=0.011).

Primer operasyon süresi morbid obez grubunda yer alan hastalarda, diğer gruplarda yer alan hastalara göre anlamlı daha düşük idi (p<0.001) (Tablo 3).

Tablo 3. Operasyon bulguları ile gruplar arasındaki karşılaştırmalar

	<18.5 Zayıf (n=24)		18.5-24.9 Normal (n=253)		25-29.9 Aşırı Kilolu (n=417)		30-39.9 Obez (n=222)		>40 Morbid Obez (n=23)		p^c
	n	%	n	%	n	%	n	%	n	%	
Debulking Cerrahi											
Yapılmadı	-	-	26	10.3	30	7.2	6	2.7	2	8.7	
Primer	21	87.5	218	86.2	366	87.8	184	82.9	16	69.6	**<0.001****
İnterval	3	12.5	9	3.6	21	5.0	32	14.4	5	21.7	
Sitoredüksiyon Optimizasyonu											
R0	18	81.8	198	81.1	314	76.8	164	75.9	16	72.7	
R1	4	18.2	19	7.8	52	12.7	35	16.2	4	18.2	0.147
Nonoptimal	-	-	27	11.1	43	10.5	17	7.9	2	9.1	
Cerrahi Zorluk Skoru (SCS)											
≤3 düşük	8	34.8	134	54.5	227	55.0	89	40.5	15	65.2	
4-7 orta	14	60.9	105	42.7	180	43.6	124	56.4	8	34.8	**0.011***
≥8 yüksek	1	4.3	7	2.8	6	1.5	7	3.2	-	-	

	<18.5 Zayıf (n=24)	18.5-24.9 Normal (n=253)	25-29.9 Aşırı Kilolu (n=417)	30-39.9 Obez (n=222)	>40 Morbid Obez (n=23)	p^b
	Ort±ss	Ort±ss	Ort±ss	Ort±ss	Ort±ss	
PCILT	11.4±7.7	10.9±4.9	11.1±4.9	10.6±6.2	11.9±8.9	0.347
Primer Operasyon Süresi	125.2±46.7	136.7±35.7	134.2±37.4	128.7±44.1	117.6±44.3	<0.001**

* p<0.05, **p<0.001, b: Kruskal Wallis test, Post Hoc Bonferroni, c: ki-kare ve fisher exact test

Görüntülemede asit varlığı bulgusu var ve minimal olan hastaların toplam sağkalım süresi, görüntülemede asit varlığı tespit edilmeyen hastalara göre daha düşük idi (p<0.001;). Operasyon sırasında asit varlığı bulgusu 1 L ve üzeri olanların toplam sağkalım süreleri, diğer gruplara göre daha düşük olduğu saptandı (p<0.001 Tablo 4).

Tablo 4. Toplam sağkalım bulguları ile ilgili parametreler incelenmesi

	Ortalama	SE	95% Güven Aralığı		p
			En Düşük Değeri	En Yüksek Değeri	
Evre					
Evre 1	114.6	4.8	105.2	123.9	**<0.001****
Evre 2	94.7	8.7	77.6	111.9	
Evre 3	56.2	2.0	52.2	60.2	
Evre 4	48.4	4.4	39.8	56.9	
VKİ					
<18.5 zayıf	49.7	6.2	37.5	61.9	**0.001****
18.5-24.9 normal	77.1	4.0	69.1	84.9	
25-29.9 aşırı kilolu	75.5	3.0	69.6	81.5	
30-39.9 obez	58.8	3.2	52.4	65.1	
40> morbid obez	42.3	3.3	35.8	48.9	
Görüntülemede asit varlığı					
Yok	114.3	5.3	103.8	124.7	**<0.001****
Minimal	69.6	3.4	62.9	76.2	
Var	53.6	2.2	49.2	57.9	
Operasyon sırasında asit varlığı					
Yok	106.8	4.8	97.3	116.2	**<0.001****
<1 L	71.3	3.7	64.0	78.5	
>1 L	51.8	2.0	47.7	55.8	

* p<0.05, **p<0.001, Log rank test

Görüntülemede asit bulguları var olan hastaların, diğer gruplara göre hastalıksız sağkalım süresi daha düşük idi (p<0.001). Operasyon sırasında asit 1 L üzerinde olanlarda, olmayan ile 1 L altında olanlara göre daha düşük hastalıksız sağkalım süresine sahip oldukları tespit edildi (p=0.001 Tablo 5)

Tablo 5. Hastalıksız sağkalım bulguları ile ilgili parametreler incelenmesi

	Ortalama	SE	95% Güven Aralığı		p
			En Düşük Değeri	En Yüksek Değeri	
Evre					
Evre 1	33.4	5.6	22.4	44.3	**0.001**
Evre 2	29.7	4.5	20.9	38.5	
Evre 3	19.2	1.1	16.9	21.4	
Evre 4	16.9	4.0	8.9	24.7	
VKİ					
<18.5 zayıf	16.2	2.4	11.4	20.9	0.225
18.5-24.9 normal	23.5	2.9	17.8	29.2	
25-29.9 aşırı kilolu	24.7	2.7	19.5	29.9	
30-39.9 obez	18.7	1.4	15.9	21.5	
40> morbid obez	20.9	2.8	15.5	26.3	

Görüntülemede asit varlığı					
Yok	26.4	3.4	19.8	32,9	
Minimal	29.7	3.6	22.7	36,8	**<0,001****
Var	17.7	1.2	15.3	20,1	
Operasyon sırasında asit varlığı					
Yok	23.7	2.9	18.0	29,5	
<1 L	29.3	3.1	23.3	35,3	**0,001****
>1 L	18.7	1.5	15.8	21,7	

* p<0.05, **p<0.001, Log rank test

TARTIŞMA

Over kanseri, sahip olduğu kötü prognostik özellikler nedeniyle oldukça ölümcül seyreden malign bir hastalıktır. 5 yıllık sağkalım oranları % 50'nin altında, 10 yıllık sağkalım oranları ise % 35'in altındadır.(6) Sağkalımı etkileyen önemli faktörlerden bir tanesi tanı anındaki evredir. Tanı anındaki ileri evre olduğu saptanan hastaların sağkalım süreleri daha önce yapılmış bir çok çalışma tarafından gösterilmiştir.(7) Öte yandan, geçmiş dönemde yapılan bazı çalışmalarda obezitenin, jinekolojik kanserler üzerinde kötü prognostik etkisi olduğu gösterilmiştir.(8) Epitelyal over kanserinde batın içi asit miktarı önemli bir prognostik belirteçtir. Batında biriken asit miktarı arttıkça, hastalığın prognozu kötüleşmektedir.(9)

Over kanseri ele alındığında, obezitenin sağkalıma etkisi tam olarak aydınlatılamamıştır. Bu konu üzerinde yapılan çalışmalar çok farklı sonuçlar ortaya koymuştur. Barret ve arkadaşlarının yaptığı çalışmada artmış VKİ'nin, over kanseri prognozuna anlamlı bir etkisi saptanmamıştır.(10) Skirnisdottir ve arkadaşlarının yaptığı çalışmada VKİ <18.5 olan hasta grubunda sağkalım oranının, diğer VKİ gruplarına göre kıyaslandığında anlamlı olarak daha kısa olduğu sonucu gösterildi. Yine aynı çalışmada hastalıksız sağkalım oranları karşılaştırıldığında VKİ grupları arasında anlamlı fark bulunmadığı gösterilmiştir.(11) Bizim yaptığımız çalışmada ise VKİ değeri zayıf, obez ve morbid obez grubunda yer alanların toplam sağkalım sürelerinin, VKİ değeri normal ve aşırı kilolu grupta yer alan hastalara göre daha düşük olduğu tespit edildi. Bu sonuçlardan ideal vücut ağırlığının altında ya da üstünde olmanın, over kanserinde toplam sağkalıma olumsuz etkisi bulunduğu yargısına varılabilir.

Yaptığımız çalışmada operasyon öncesi görüntülemelerde ve operasyon sırasında asit varlığı ve miktarının, obez ve morbid obez hastalarda anlamlı olarak yüksek olduğu gösterilmiş olup çalışmamızın önemli bulgularından biridir. Yakın zamanda yapılan bir hayvan çalışmasında epitelyal over kanserli obez farelerin, zayıf fareler ile karşılaştırıldığında tümör yükünün daha fazla olduğu izlendi. Bununla birlikte obez farelerin sağkalım sürelerinin daha kısa olduğu gözlenmiştir.(12) Bu durumun, özellikle obez ve morbid obez olan hastalarda artmış adipoz doku yoğunluğunun, çeşitli biyokimyasal süreçler ile tümör yayılımını arttırması, asit oluşumunu ve miktarını arttırması ve tümör yükünün artmasına sebep olabileceğini düşündürmektedir. Bunun yanı sıra, özellikle obez hastalarda, asit birikiminin daha geç fark edilip göz ardı edilmesi nedeniyle tanıda gecikmeye neden olduğunu düşündürmektedir. Aynı zamanda bu durumun hastalığın ilerlemesi ve toplam sağkalım üzerinde olumsuz etkisi olduğu yargısına varılmaktadır.

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ORGINAL ARTICLE / ORJİNAL MAKALE

Clinicopathological characteristics and prognosis in ovarian metastatic tumors from non-gynecologic primary sites

Jinekolojik olmayan primer bölgelerden kaynaklanan overin metastatik tümörlerinde klinikopatolojik özellikler ve prognoz

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ABSTRACT

Aim: To investigate clinicopathological characteristics and prognosis in ovarian metastatic tumors from non-gynecologic primary sites.

Materials and methods: This study was a retrospective trial enrolling consecutive patients with ovarian metastasis from non-gynecologic primary sites, either diagnosed synchronous or metachronously, who underwent surgery at a single institution between January 2015 and December 2021. Clinicopathological characteristics of patients were extracted from patients' charts and electronic database; and analyzed using Cox proportional hazard models.

Results: Of the 291 malignant ovarian tumors that underwent surgery, 33 (11.3%) had a diagnosis of ovarian metastasis from non-gynecologic primary sites. The most common primary tumor sites were colorectum (45.5%), stomach (15.2%), and breast (12.1%). Most of the patients exhibited elevated preoperative serum Ca-125 levels (71.4%); roughly half of the patients had syncronous ovarian metastases (48.5%); and approximately one third had peritoneal involvement (36.4%) and/or ascites (30.3%). A complete resection (R0) was achieved in 72.0% of the patients. The median follow-up time was 15.5 months, ranging from 2 to 85 months. The median overall survival (OS) was 41 months with estimated 18-, 24- and 36-month OS rates of 60.1%, 56.1% and 50.5%, respectively. Age (>45 years; hazard ratio (HR): 3.199; 95% confidence interval (CI): 0.899 – 11.380) and presence of ascites (HR: 4.109, 95% CI: 1.436 – 11.757) were independent predictors of OS.

Conclusion: In ovarian metastatic tumors from non-gynecologic primary sites, age and the presence of ascites are the main determinants of prognosis, while no survival benefit of cytoreductive surgery was demonstrated.

Keywords: Ovarian, Metastasis, Prognosis, Survival

ÖZ

Amaç: Jinekolojik olmayan primer bölgelerden kaynaklanan overin metastatik tümörlerinde klinikopatolojik özellikler ve prognozun araştırılması.

Gereç ve yöntem: Bu çalışma, Ocak 2015 ile Aralık 2021 tarihleri arasında tek bir merkezde ameliyat edilen, senkron veya metakron tanı konmuş, jinekolojik olmayan primer bölgelerden over metastazı olan ardışık hastaları içeren retrospektif bir çalışmadır. Hastaların klinikopatolojik özellikleri hasta dosyalarından ve elektronik veri tabanından elde edilmiş ve Cox orantılı hazard modelleri kullanılarak analiz edilmiştir.

Bulgular: Cerrahi uygulanan 291 malign over tümöründen 33'ünde (%11.3) jinekolojik olmayan primer bölgelerden overe metastaz tanısı saptandı. En sık primer tümör bölgeleri sırası ile kolorektum (%45.5), mide (%15.2) ve meme (%12.1) idi. Hastaların çoğunda ameliyat öncesi serum Ca-125 düzeyleri yüksekti (%71.4); yaklaşık yarısında senkron over metastazı (%48.5); yaklaşık üçte birinde peritoneal tutulum (%36.4) ve/veya asit (%30.3) mevcuttu. Hastaların %72.0'sinde tam rezeksiyon (R0) elde edildi. Ortanca takip süresi 15.5 ay olup, 2 ila 85 ay arasında değişmektedir. Ortanca genel sağkalım 41 ay iken tahmini 18, 24 ve 36 aylık sağkalım oranları sırasıyla %60,1, %56,1 ve %50,5 idi. Yaş (>45 yıl; hazard oranı (HR): 3.199; %95 güven aralığı (CI): 0.899 - 11.380) ve asit varlığı (HR: 4.109, %95 CI: 1.436 - 11.757) sağkalımın bağımsız belirleyicileri olarak saptandı.

Sonuç: Jinekolojik olmayan primer bölgelerden kaynaklanan overin metastatik tümörlerinde, yaş ve asit varlığı prognozun ana belirleyicileri iken sitoredüktif cerrahinin sağkalım yararı gösterilememiştir.

Anahtar Kelimeler: Over, Metastaz, Prognoz, Sağkalım

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INTRODUCTION

When a malignancy is diagnosed or suspected, patients often expect to be informed about the prognosis and treatment options. However, answering this basic request is not always easy for many reasons. The histopathological type and extent of the disease are the most important among the many parameters needed to answer these vital questions. As physicians dealing with gynecologic oncology, we have the chance to clearly inform our patients when the diagnosis of malignancy is of direct gynecologic origin. On the other hand, metastatic tumors of the ovary which is reported to be found in 15 to 20% of all malignant ovarian tumors (1,2), may pose a challenge for the physicians in adequately informing patients preoperatively since they may be the presenting finding in a significant proportion of cases. (3) Moreover, in some cases, the correct diagnosis may not be made even with extensive histopathological and immunohistochemical examinations.

Histopathologically, ovarian metastases containing a significant amount of mucin-filled signet-ring cells (more than 10% of tumor size) are called Krukenberg tumors. (4) The most common primary site of Krukenberg tumors is the stomach (~40%), followed by the colorectum (~25%), breast (~10%) and appendix (5%). (4) The metastases to the ovaries from other sites that do not fullfill the diagnostic criteria of Krukenberg tumors may arise from colon, breast, small intestine, pancreas, and skin. (1-3)

In the current study, we aimed to investigate the clinicopathological characteristics, prognosis, and factors associated with overall survival (OS) in patients with ovarian metastasis from non-gynecologic primary sites.

METHODS

Study design and endpoints

The study was a retrospective trial enrolling consecutive patients with ovarian metastasis from non-gynecologic primary sites, either diagnosed synchronous or metachronously, who underwent surgery at a single institution between January 2015 and December 2021. The study was approved by the local ethics committee. Due to the retrospective nature of the study, the need for informed consent was waived by the ethics committee. The study was performed in accordance with the ethical standards described in an appropriate version of the 1975 Declaration of Helsinki, as revised in 2013.

Data regarding age, preoperative levels of serum tumor markers and albumin, primary tumor site, time of ovarian metastasis (synchronous vs. metachronous), site of ovarian metastasis (unilateral vs. bilateral), the largest size of ovarian metastasis, presence of extraovarian disease, ascites and peritoneal carcinomatosis, surgical resections, operative time, 30-day postoperative mortality, length of follow-up time, and survival status were extracted from the patient charts and institutional electronic database following the ethics committee approval. The timing of ovarian metastasis was defined as metachronous if the metastasis was detected more than three months after the initial diagnosis of the primary tumor, or synchronous if the metastasis was detected at the initial diagnosis or within the first three months. (5) Ascites was defined as determination of free-fluid in the peritoneal cavity exceeded 100 ml at the beginning of the surgical exploration.

The primary endpoint of the study was determination of clinicopathological characteristics and prognosis of patients; and the secondary endpoint was determination of factors associated with OS. The duration in months between the date of surgery and the date of death from any cause or the date of last contact was defined as OS.

Statistical analysis

Statistical analyses were performed using SPSS Statistics 20.0 (SPSS Inc, Chicago, IL, USA) software. The binary variables were reported as

counts and percentages, while the continuous variables were reported as median and range. Univariate analyses were performed to determine factors associated with OS. Variables with a p-value <0.05 in univariate analyses were included in the Cox proportional hazard models for multivariate analyses. The model results were presented as hazard ratios (HR) with 95% confidence intervals (CI). Survival curves were generated with the Kaplan–Meier method, and compared using the log-rank test. Patients alive at the last known follow-up were censored in OS analyses.

RESULTS

During the study period, a total of 291 histologically confirmed malignant ovarian tumors were treated at our clinic. Of those, 33 (11.3%) had a diagnosis of ovarian metastasis from non-gynecologic primary sites.

Table 1 displays the clinicopathological characteristics of patients. The median age was 51 years (range, 30 – 90 years). Preoperative serum Ca-125 levels were measured in 28 of 33 patients and found to be increased (>35 U/ml) in 71.4% of these patients. The median Ca-125 level was 66.9 U/ml (range, 10.8 – 1064 U/ml). The most common primary tumor site was the colorectum (15/33, 45.5%), followed by stomach (5/33, 15.2%), breast (4/33, 12.1%), lung (2/33, 6.1%), pancreas (2/33, 6.1%), appendix (2/33, 6.1%), small intestine (1/33, 3.0%), mesothelioma (1/33, 3.0%), and unknown site (1/33, 3.0%). Sixteen patients (48.5%) presented with synchronous ovarian metastasis, while 17 (51.5%) developed metachronous ovarian metastasis after the initial diagnosis of primary tumor. In metachronous metastases, the median time interval was 18 months. Roughly half of the patients (51.5%) had bilateral ovarian metastasis. Extraovarian disease was evident in most of the patients (72.7%), whereas only 36.4% had peritoneal involvement and 30.3% had ascites.

Table 1. Clinicopathologic chararacteristics of patients

Variables	Values	
	n	%
Age, years, median (range)	51 (30 – 90)	
Preoperative tumor markers, median (range)		
Ca-125, U/mL (n=28)	66.90 (10.8 – 1064)	
> 35 U/mL, n (%)	20/28	71.4
CEA, µg/L (n=23)	6.08 (1.22 – 205.05)	
Ca-19.9, U/mL (n=21)	42.40 (2- 4836)	
Ca-15.3, U/mL (n=16)	12.75 (4.40 – 77)	
Preoperative serum albumin level, g/dL, median (range), (n=12)	4.05 (3.20 – 4.50)	
Primary tumor site, n (%)		
Colorectal	15	45.5
Stomach	5	15.2
Breast	4	12.1
Lung	2	6.1
Pancreas	2	6.1
Appendix	2	6.1
Small intestine	1	3.0
Mesothelioma	1	3.0
Unknown primary	1	3.0
Time of ovarian metastasis, n (%)		
Synchronous	16	48.5
Metachronous	17	51.5
Time interval, months, median (range)	18 (3–30)	
Site of ovarian metastasis, n (%)		
Unilateral	16	48.5
Bilateral	17	51.5
Largest size of ovarian metastasis, cm, median (range)	8.5 (0.30 – 32)	
Extraovarian disease, n (%)	24	72.7
Ascites, n (%)	10	30.3
Peritoneal carcinomatosis, n (%)	12	36.4
Localized	4	12.1
Diffuse, miliary	8	24.2

Surgical and postoperative chararacteristics of patients are presented in Table 2. Almost all (96.9%) patients underwent salpingo-oophorectomy, 23 (69.6%) received total hysterectomy, 22 (66.6%) received omentectomy, 9 (27.2%) received large bowel resection, 8 (24.2%) received appendectomy, 5 (15.1%) received systematic pelvic-paraaortic lymph node dissection, 4 (12.1%) received liver resection, 4 (12.1%) received pelvic periton excision, 4 (12.1%) received paracolic periton

excision, 4 (12.1%) received diaphragmatic periton stripping, 3 (9.1%) received small bowel resection, 2 (6.0%) received pancreatectomy, 1 (3.0%) received splenectomy, and 1 (3.0%) received total gastrectomy with esophagojejunostomy. The median operative time was 225 minutes. A complete resection (R0) was achieved in 72.0% of the patients.

Postoperative 30-day mortality was observed in 2 (6.0%) patients. One of those patients had pancreatic primary tumor origin. She developed deep and uncontrolled metabolic acidosis postoperatively, and died of disease on postoperative day-7. The other one had an advanced and unserectable gastric cancer. An attemp to replace a jejunostomy tube was failed, and she died of disease on postoperative day-28. The median follow-up time was 15.5 months, with a range of 2 to 85 months. At the time of analysis, 6 patients (18.2%) were alive with no evidience of disease, 9 patients (27.3%) were alive with disease, 16 patients (48.5%) were dead of disease, and 2 (6.1%) were lost to follow-up (Table 2).

The median OS was 41 months, with a 95% CI ranging from 12.7 to 69.2 months. The estimated 18-, 24-, 36-, and 60-months OS rates were 60.1%, 56.1%, 50.5%, and 42.1%, respectively (Figure 1).

Analysis of factors associated with OS is presented in Table 3. In univariate analysis, two variables were significantly associated with death: age and ascites. In multivariate analysis, both age (HR: 1.056, 95% CI: 1.012 - 1.103) and presence of ascites (HR: 4.109, 95% CI: 1.436 – 11.757) remained independent factors associated with death. Optimal cutoff value of age for predicting death was found to be 45 years (HR: 3.199; 95% CI: 0.899 – 11.380), with a sensitivity of 81.3% and specificity of 66.7% (Figure 2). Kaplan-Meier analyses revealed that patients with an age greater than 45 years had a significantly poorer OS than those with an age younger than 45 years, (18 months OS, 49.4% vs. 75.0%, p=0.033), (Figure 3A). Similarly, patients wih ascites had significantly poorer OS than those without ascites (18 months OS, 34.3% vs. 71.1%, p=0.014), (Figure 3B).

Table 2. Surgical and postoperative chararacteristics of patients

Variables	Values	
	n	%
Salpingo-oophorectomy, n (%)	32	96.9
Unilateral	4	12.1
Bilateral	28	84.8
Hysterectomy, n (%)	23	69.6
Omentectomy, n (%)	22	66.6
Bowel resection, n (%)		
Large bowel	9	27.2
Colorectal resection	5	15.1
Right hemicolectomy	2	6.0
Transverse colon resection	2	6.0
Small bowel	3	9.1
Peritonectomy (partial and/or total), n (%)		
Pelvic	4	12.1
Paracolic	4	12.1
Diaphragm	4	12.1
Appendectomy, n (%)	8	24.2
Total gastrectomy with esophagojejunostomy, n (%)	1	3.0
Liver resection, n (%)	4	12.1
Splenectomy, n (%)	1	3.0
Pancreatectomy, n (%)	2	6.0
Systematic pelvic-paraaortic LN dissection, n (%)	5	15.1
Residual disease after surgery, n (%)		
No residual	24	72.0
<1 cm in maximum size	3	9.1
≥1 cm in maximum size	6	18.2
Operative time, minutes, median (range)	225 (45 – 630)	
Postoperative 30-day mortality, n (%)	2/33	6.0
Follow-up time, months, median (range)	15.5 (2 – 85)	
Survival status, n (%)		
Alive with no evidience of disease	6	18.2
Alive with disease	9	27.3
Dead of disease	16	48.5
Lost to follow-up	2	6.1
Overall survival, months, median (95% CI)	41 (12.71 – 69.28)	
18 months, %	60.1	
24 months, %	56.1	
36 months, %	50.5	
60 months, %	42.1	

LN; lymph node, CI; confidence interval.

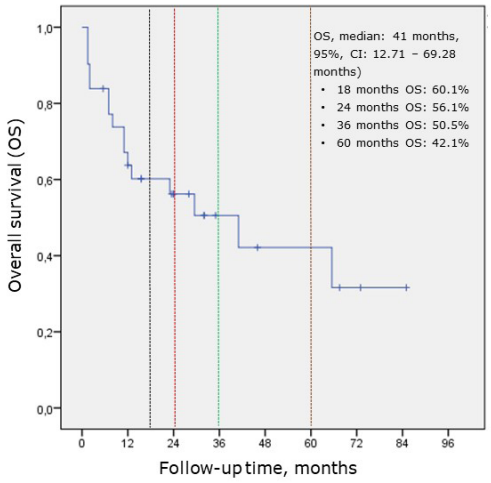

Figure 1. Overall survival analysis of whole cohort

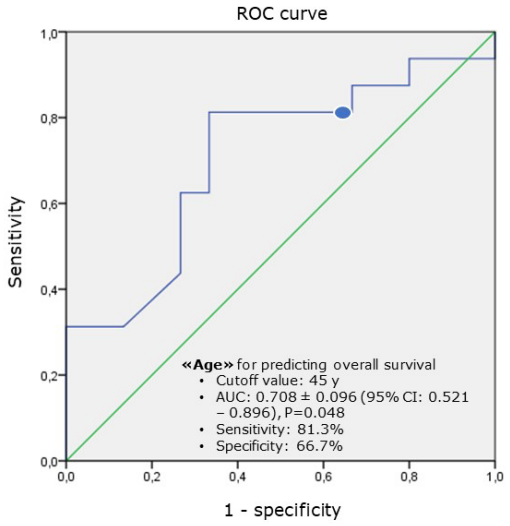

Figure 2. Receiver operating characteristic (ROC) analysis to calculate optimal cutoff value of age for predicting death

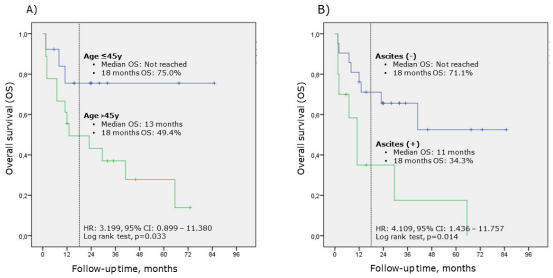

Figure 3. Impact of age (A) and presence of ascites (B) on overall survival

Table 3. Factors associated with overall survival

Variables	Unadjusted			Adjusted		
	HR	95% CI	p	HR	95% CI	p
Age, years	1.043	1.005- 1.083	**0.028**	1.056	1.012- 1.103	**0.013**
Preoperative serum Ca-125 level, U/mL	1.000	0.998 – 1.002	0.897	–	–	–
Preoperative serum albumin level, g/dL	1.133	0.170 – 7.528	0.897	–	–	–
Primary tumor site						
Colorectal vs. Non-colorectal	1.078	0.400 – 2.907	0.881	–	–	–
Largest size of ovarian metastasis, cm	1.006	0.918 – 1.104	0.892	–	–	–
Site of ovarian metastasis						
Unilateral vs. Bilateral	1.799	0.665 – 4.865	0.248	–	–	–
Time of ovarian metastasis						
Synchronous vs. Metachronous	0.897	0.336 – 2.391	0.828	–	–	–
Ascites						
No vs. Yes	3.219	1.192 – 8.695	**0.021**	4.109	1.436 – 11.757	**0.008**
Diffuse peritoneal carcinomatosis						
No vs. Yes	2.757	0.992 – 7.663	0.052	–	–	–
Residual disease after surgery						
No vs. Yes	2.019	0.729 – 5.597	0.177	–	–	–
<1 cm vs. ≥1 cm	2.254	0.779 – 6.521	0.134	–	–	–

HR, Hazard ratio; CI, confidence interval Note: Bold values denote statistical significance at the P <0.05 level

DISCUSSION

This study investigated the clinicopathological characteristics, prognosis, and factors associated with OS in patients with ovarian metastasis from non-gynecologic primary sites. The study revealed that 11.3% of the malignant ovarian tumors were the metastases to the ovaries from non-gynecologic primary sites, and the most common primary tumor site was the colorectum (45.5%). Most patients exhibited elevated preoperative serum Ca-125 levels (71.4%); roughly half of the patients developed syncronous ovarian metastases (48.5%), and had bilateral disease (51.5%); and approximately one third of the patients had peritoneal involvement (36.4%) and/or ascites (30.3%). Age and presence of ascites were independent predictors of OS. Patients who had an age >45 years were 3 times more likely to experience death as compared to those with an age younger than 45 years; while patients wih ascites were 4 times more likely to experience death as compared to those without ascites.

The rate of non-gynaecologic ovarian metastasis in our study (11.3%) is slightly lower than the average rates of 15-20% reported in the literature. (1,2) The reason for this disparity might be due to that our institution is a tertiary-care center and the indications for surgeries are determined in a multidisciplinary manner, thus some of the patients may have been operated on by other disciplines such as general/gastrointestinal surgery. Other clinicopathological data in our study regarding the median age of the patients, laterality of the ovarian mass, timing of metastasis, and the primary sites of tumors were found to be in accordance with the literature as to reflect-population based prevalances of each cancer type. (1-3,6,7)

A meticulous preoperative effort to diagnose an adnexal metastatic tumor of non-gynecologic origin is invaluable because the surgical management of ovarian metastases from non-gynecologic sites differs from that of primary ovarian cancers. For example, a systematic lymph node dissection is not indicated for non-gynecologic metastatic ovarian tumors, an intervention that will only lead to increased morbidity and operative time. (8) Furthermore, in contrast to the clear evidence provided for primary ovarian cancers, there are no randomized controlled trials evaluating the potential benefits of cytoreductive surgery for metastatic tumors of the ovary, although some retrospective series have reported that cytoreductive surgery may be beneficial in a selected group of patients with ovarian metastases from colorectal cancers confined to the pelvis. (3, 8-10)

Ayhan et al. (8) investigated the prognostic factors and role of cytoreductive surgery in 154 patients with nongenital cancers metastatic to the ovaries. The authors reported that age, menopausal status, primary tumor site, diffuse peritoneal involvement and optimal cytoreductive surgery were prognostic factors for OS. The median OS of patients that underwent optimal (R<10 mm) cytoreductive surgery was 48 months, compared with 26 months for patients with suboptimal (R≥10 mm) cytoreduction (P=0.003). The authors concluded that cytoreductive surgery seems to have a beneficial effect on survival of selected patients, especially for patients with colorectal cancer metastatic to the ovary. (8) Sal et al. (9) investigated the prognostic factors in 131 patients with metastatic ovarian tumors from extragenital primary sites, and reported that residual disease, preoperative serum CA 19-9 level, and primary cancer site were the independent prognostic factors for OS. The authors noted that the survival benefit of cytoreductive surgery was significant especially if the residual disease was less than 5 mm. They also stated that the presence of concurrent ovarian and extraovarian metastases exhibited a significantly worse prognosis and that an optimal cytoreduction was less frequently possible in this group of patients. (9) Zhang et al. (3) studied the clinicopathologic features

of 177 patients with ovarian metastases from non-gynecologic primary sites operated on over a 13-year period. The authors reported that while optimal cytoreduction (defined as largest residual lesion <2 cm), primary tumor site, tumor differentiation, and postoperative adjuvant treatment were prognostic indicators, age, menopausal status, presence of ascites, CA-125 level, bilaterality of ovarian metastasis, extraovarian disease, and time of diagnosis (synchronous vs. metachronous) were not associated with OS. The median OS was 25 months in patients with optimal cytoreduction whereas it was 14 months in patients with suboptimal cytoreduction ($p = 0.001$). On the other hand, the authors noted that an optimal cytoreduction could be achieved in only half of the patients.

In our study, a complete resection was achieved in 72% of patients. However, neither optimal cytroreduction nor primary tumor site (colorectal vs. non-colorectal) was found to be associted with OS. The small sample size of our study might have precluded us from achieving a statistically significant relationship. Similarly, in a recent study analyzing outcomes of 70 patients with metastatic tumors to the ovary, Ramesan et al. (11) reported no statistically significant difference in OS between patients with peritoneal carcinomatosis and patients with metastases confined to the ovary. While OS rates were comparable between different primary tumor sites, the sole factor associated with better OS was performance status. Thus, the authors concluded that the evidence for the benefit of cytoreductive surgery is lacking, so the focus of the treatment should be on improving the quality of life.

The main limitation of the current study is its retrospective design, which potentially could lead to a selection bias. Single-center nature of the study, small sample size and relatively short follow-up period are other limitations that may hamper the generalizability of our findings. Additionally, data from small samples or with short follow-up periods can lead to inaccuracies in survival estimates. However, studies with time-to-event endpoints may not always meet the accurate sample size requirement owing to main reasons including the rarity of the disease and the nature of the study design, as was the case in our study. Despite the limitations, this study is valuable in terms of demonstrating the significance of the presence of ascites, which is an easily detectable finding preoperatively that helps to inform patients about the prognosis.

CONCLUSION

In conclusion, ovarian metastases from non-gynecologic primary sites should be kept in mind in the preoperative differential diagnosis of suspicious adnexal masses as the treatment algorithms and prognoses may significantly differ from that of primary ovarian malignancies. Based on our results, age and the presence of ascites are independent risk factors for poor disease outcomes, but there is no survival benefit of cytoreductive surgery in patients with ovarian metastases from non-gynecologic primary sites. Further trials with larger sample sizes are needed to clarify the role of cytoreductive surgery in this group of patients.

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Conflict of interest

Authors have no conflicts of interest relevant to this article.

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Ethical Decleration

Ethical permission was obtained from the Local Ethics Committee of the Antalya Training and Research Hospital for this study with date March 27, 2023 and number 013 and Helsinki Declaration rules were followed to conduct this study.

Authorship Contributions

Concept: TT, IU and MCK, Design: TT and IU, Supervising: IU, SK and MG, Data acquisition and curation: AK, MG, AA, NY, and MCK, Analysis and interpretation: TT and MCK, Literature search: AK, MG, AA, NY and SK, Writing: MCK and TT, Critical review: MG and IU

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ORGINAL ARTICLE / ORJİNAL MAKALE

The clinical and reproductive outcomes of endometrial intraepithelial neoplasia: experience of 117 cases

Endometrial intraepitelyal neoplazinin klinik ve repordüktif sonuçları: 117 vakanın deneyimi

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ABSTRACT

Aim: Hysterectomy is the suggested treatment for endometrial intraepithelial neoplasia since there is a high risk of coexisting endometrial adenocarcinoma in this subset of patients. However, fertility sparing treatment modalities can also be an option for patients with endometrial intraepithelial neoplasia who desire to preserve their fertility. In this study our aim was to evaluate the clinical and reproductive outcomes of endometrial intraepithelial neoplasia.

Materials and methods: We retrospectively analyzed the records of 117 patients with atypical hyperplasia (AH)/endometrial intraepithelial neoplasia (EIN) in a tertiary gynecological cancer center. The median follow-up time was 54 (7-96) months.

Results: One hundred and one women underwent hysterectomy. The rate of coexistent endometrial carcinoma in women with AH/EIN was 33.7%. Sixteen women were treated conservatively. The complete response rate was 75% in patients after a treatment period of 12 months. Four of the patients in the infertile group had a successful live birth, 2 spontaneously and 2 with in vitro fertilization. Two patients in the fertile group had a successful live birth, 2 spontaneously.

Conclusion: Fertility sparing management is a feasible option for patients with atypical hyperplasia. However, it is crucial that there are high rates of coexisting endometrial cancer in these patients. Patients with AH/EIN should be followed up carefully for endometrial adenocarcinoma with regular endometrial samplings.

Keywords: Endometrial Hyperplasia, Endometrial Intraepithelial Neoplasia, Endometrial Cancer, Fertility-Sparing Treatment

ÖZ

Amaç: Histerektomi, endometrial intraepitelyal neoplazi için önerilen tedavidir, çünkü bu hasta alt grubunda endometrial adenokarsinom ile birliktelik riski yüksektir. Bununla birlikte, fertilitesini korumak isteyen endometrial intraepitelyal neoplazili hastalar için fertilite koruyucu tedavi modaliteleri de bir seçenek olabilir. Bu çalışmada amacımız endometriyal intraepitelyal neoplazinin klinik ve reprodüktif sonuçlarını değerlendirmektir.

Gereç ve yöntem: Üçüncül bir jinekolojik kanser merkezinde atipik hiperplazi (AH)/endometrial intraepitelyal neoplazi (EIN) olan 117 hastanın kayıtlarını retrospektif olarak incelendi. Median takip süresi 54 (7-96) aydır.

Bulgular: Yüz bir kadına histerektomi yapıldı. AH/EIN'li kadınlarda eşlik eden endometriyal karsinom oranı %33,7 idi. On altı kadın konservatif olarak tedavi edildi. 12 aylık tedavi süresinden sonra hastalarda tam yanıt oranı %75 idi. İnfertil gruptaki hastaların 2'si spontan, 2'si tüp bebek ile olmak üzere 4'ü başarılı bir canlı doğum gerçekleştirdi. Fertil grupdaki 2 hasta spontan olarak başarılı 2 canlı doğum gerçekleştirdi.

Sonuç: Atipik hiperplazisi olan hastalar için fertilite koruyucu tedavi uygulanabilir bir seçenektir. Bununla birlikte, bu hastalarda yüksek oranda birliktelik gösteren endometrial kanser oranları çok önemlidir. AH/EIN'li hastalar, düzenli endometrial örneklemeler ile endometriyal adenokarsinom açısından dikkatle izlenmelidir.

Anahtar Kelimeler: Endometriyal Hiperplazi, Endometriyal İntraepitelyal Neoplazi, Endometriyal Kanser, Fertilite Koruyucu Tedavi

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INTRODUCTION

Endometrial cancer (EC) is the second most common female genital tract cancer in the world. The precursor lesions of endometrioid adenocarcinoma are endometrial atypical hyperplasia (AH) and endometrioid intraepithelial neoplasia (EIN). The new classification, WHO 2014, accepted by the International Society of Gynaecological Pathologists, divided hyperplasia into two groups: benign hyperplasia and atypical hyperplasia (AH)/endometrial intraepithelial neoplasia (EIN) (1). The WHO 2014 schema is more likely to successfully identify precancerous lesions than the WHO 94 classification. Atypical hyperplasia is the least common type; however, it is the most strongly associated type with endometrial cancer (2). The probability of AH to progress to type 1 endometrial carcinoma was reported to be 29% previously (3). Also, in numerous series the coexistence of endometrial carcinoma in the hysterectomy specimens of the women with a diagnosis of AH was reported as %17 to %64 (4). According to these data the recommended treatment for AH/EIN is hysterectomy with or without bilateral salpingo-oopherectomy. Additionally, sentinel lymph node mapping should be performed for detecting sentinel lymph node, because of the possibility of coexisting endometrial cancer (5). However up to 5% of women with AH and endometrial carcinoma diagnosed before 40 years of age (6). Subfertility is a common problem of this group of patients since subfertility and endometrial neoplasia share some common risk factors such as polycystic ovarian syndrome, chronic anovulation, obesity, hyperinsulinemia and insulin resistance (3). Additionally, there is a subgroup of patients who may choose to be treated conservatively regardless of reproductive concerns and some of the patients are not fit enough for surgical treatment (7). In these patients who wish to be treated conservatively the most commonly studied treatment modality is oral progestins. In the literature there are several studies showing that these patients can be treated safely with oral progestins even though five deaths reported previously due to progression of the disease or a synchronous malignancy failed to be diagnosed (3). The type and the dosage of the progestin is unclear as well as the duration of the treatment but most commonly studied oral progestins were megestrol acetate (MA) and medroxyprogesterone acetate (MPA).

In this retrospective cohort study our aim was to report clinical and reproductive outcomes of patients diagnosed to have AH/EIN at our institution and treated either with hysterectomy or conservatively by oral progestins.

METHODS

Women with a diagnosis of AH/EIN were detected from clinical database. Diagnosis and the response to treatment were based on either endometrial dilatation and curettage (D&C) or hysteroscopy. All of the pathological specimens were evaluated by the same gynecologic pathologists at our institution according to WHO criteria (8). The final pathology report of the women who proceeded to hysterectomy as initial treatment are evaluated. A management plan was programmed for all of the women who desired to be managed conservatively and all of the women were followed by our gynecologic oncology department. The selected progestin regimen was MA for all of the women with a daily dose of 160 mg. After 3 months and 6 months of treatment the women underwent endometrial sampling. Additionally, women underwent multiple biopsies at variable intervals after the complete remission achieved. Complete response was defined as absence of any endometrial hyperplastic or neoplastic pathology. The stable disease was defined as the persistence of AH/EIN after 6 months of treatment, and progression was defined as the endometrial carcinoma detected during follow up. In cases of stable disease and progression surgical treatment recommended to the patients. Assisted reproductive technologies

were offered to patients who desired to conceive but could not get spontaneously pregnant within six months. The pregnant women were followed up in perinatology department. Women underwent multiple biopsies at variable intervals after the delivery. Routine hysterectomy was not performed after pregnancy. For the conservatively treated group the primary outcome was the response rate in the first 12 months. Secondary outcome of interest was the fertility outcomes of patients who desired to conceive. All of the women were informed about the potential risks of conservative management of the AH/EIN. A written informed consent was obtained from the patients who wanted to be treated conservatively.

All statistical analyses were performed using Statistical Package for the Social Science (IBM SPSS, Version 25.0. Armonk, NY: IBM Corp.) for Windows software. Continuous data were described using medians and ranges; categorical variables were described using frequencies and proportions.

RESULTS

Records of 117 patients with AH/EIN were analyzed. The flow diagram is shown in Figure 1.

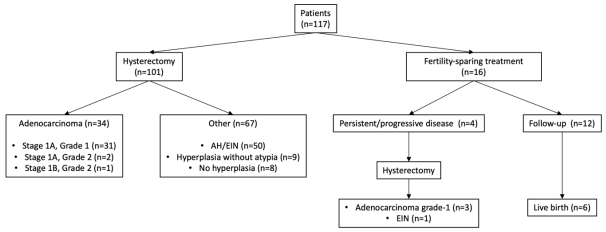

Figure 1. Flow-chart of the study participants (AH, atypical hyperplasia; EIN, endometrial intraepithelial neoplasia).

One hundred and one women underwent hysterectomy. The final pathology was stage 1A, grade 1, endometrioid adenocarcinoma in 31 patients; stage 1A, grade 2, endometrioid adenocarcinoma in 2 patients; stage 1B, grade 2, endometrioid adenocarcinoma in 1 patient; AH/EIN in 50 patients; hyperplasia without atypia in 9 patients; and no hyperplasia in 8 patients. The rate of coexistence of endometrial carcinoma in women with AH/EIN was 33.7%. The median follow-up time was 54 (7-96) months. No adjuvant therapy was given.

Sixteen women were treated with oral progestins. Baseline characteristics of the patients with AH/EIN who underwent fertility-sparing treatment were shown in Table 1. The median age of the patients who underwent fertility-sparing treatment was 34 (24-39) years, and the median follow up time was 30 (7-86) months. The complete response rate was 75% in patients after a treatment period of 12 months. Eleven (68.8%) of the patients were infertile. Five patients who have at least one live birth did choose to be managed conservatively. Four of the patients underwent a hysterectomy in their first year of follow up; 3 from the fertile group for endometrial adenocarcinoma and 1 from the infertile group for persistence of the disease and patients desired for operation. Four (40%) of the patients from the remaining 10 patients in the infertile group had a successful live birth, 2 spontaneously and 2 with in vitro fertilization. Two patients in the fertile group had a successful live birth, 2 spontaneously.

Table 1. Baseline characteristics of the patients with AH/EIN who underwent fertility-sparing treatment (n=16).

	n	%
Age (years)	34 (24-39)	
Gravida	0 (0-1)	
Parity	0 (0-1)	
BMI (kg/m²)	30.66 ± 2.64	
Initial symptoms		
Irregular genital bleeding	3	18.8%
Menstrual abnormality	2	12.5%
Infertility	11	68.8%
Live birth	6	

Data are expressed as number (%), mean± SD or median (range).
AH, atypical hyperplasia; BMI, body mass index; EIN, endometrioid intraepithelial neoplasia.

DISCUSSION

Premenopausal women diagnosed with AH/EIN often seek fertility-sparing treatment for their disease. Our study suggests that fertility-sparing treatment using oral progestins is a feasible option for these patients. On the other hand, it is crucial that there are high rates of coexisting endometrial cancer in these patients. The Society of Gynecologic Oncology recommends that exclusion of a concurrent carcinoma is necessary in all patients with a new diagnosis of atypical endometrial hyperplasia or endometrial intraepithelial neoplasia (9, 10). In this cohort, 101 women underwent hysterectomy. The rate of coexistence of endometrial carcinoma in women with AH/EIN was 33.7%. Erturk et al. reported that endometrial cancer rate in patients with AH was 32.6% in their study including 189 patients (11). A retrospective evaluation of 169 endometrial intraepithelial neoplasia patients by Vetter et al. showed that of these patients, 87 (51.5%) had a final diagnosis of endometrial intraepithelial neoplasia/other benign disease, whereas 82 (48.5%) were ultimately diagnosed with endometrial cancer (12). Similar findings were found by Robbe et al. They reported that a coexisting endometrial carcinoma was present in 25 of 39 patients (64.1%) (4).

Fertility-sparing treatment should be considered because patients with AH/EIN are candidates for a conservative approach. Comprehensive evaluation prior to fertility-sparing treatment is the key to success. All patients should undergo detailed evaluation to exclude myometrial invasion and to confirm the diagnosis. Although there is no established standard for treatment, most patients will benefit from progestins. The current literature reported that remission rates ranged from 42% to 100% (13-17). However, these studies are inhomogeneous in terms of many factors such as the type, dose, the duration of treatment time and follow-up time, type of progestin used, progestin therapy indications, pathologic distributions, demographic characteristics, and response definitions. In 2018 Guillon et al conducted a systematic review and meta-analysis including 1604 patients and they observed that the remission rate was 0.75 (95% CI, 0.73–0.77), and also operative hysteroscopy for endometrial sampling was associated with higher remission rates (OR 2.31; 95% CI, 1.10–4.84; P=0.03) (17). In our study, complete response rate was 75% at one year. In a meta-analysis, Fan et al. reported the complete remission rate was 95.3% in patients with grade 1 stage IA endometrial cancer who underwent hysteroscopic resection followed by progestin therapy (18). In a series of 110 patients, He et al. reported that a complete response of 84% was noted after fertility-preserving retreatment in patients with recurrence of atypical endometrial hyperplasia and endometrial cancer (19). The relapse rate was 38% after fertility-preserving retreatment. They also reported that among the 21 patients who achieved complete response, 12 patients had a desire for fertility, among whom 8 patients had a successful pregnancy (66.7%, 8/12) and 6 patients experienced term birth (1 patient with natural pregnancy, and 5 patients with assisted reproductive technology). In our study, 4 patients in the infertile group had a successful live birth (2 spontaneously and 2 with in vitro fertilization), and 2 patients in the fertile group had a successful live birth (2 spontaneously). Ohyagi-Hara et al. published a retrospective study on 27 patients with endometrioid adenocarcinoma/complex atypical hyperplasia and showed that complete response was achieved in 81.8 % (9/11) of complex atypical hyperplasia cases and 68.8 % (11/16) of grade 1 endometrioid adenocarcinoma, and 5 patients (4 complex atypical hyperplasia and 1 grade 1 endometrioid adenocarcinoma) became pregnant and had 9 live births (20). The importance of fertility-sparing treatment in patients with AH/endometrial cancer has been denoted by Tamauchi et al in 2017. They reported a high rate of complete response using high-dose Medroxyprogesterone acetate. Complete response rates for the initial treatment were

89% for grade 1 endometrial cancer and 93% for AH. During their study period, a total of 14 pregnancies were recorded with 10 live births.

The possibility of recurrence cannot be excluded. In our cohort, no recurrence occurred. Ayhan et al. reported that the recurrence rate of the EIN patients was 7.4% (21). Therefore, after live birth or giving up future fertility, hysterectomy could be recommended to patients with AH/EIN or EC even if they have a complete response. Additionally, careful preoperative assessment of the adnexa is mandatory in young women with AH/EIN or EC. Among all synchronous cases of EC and ovarian cancer, approximately 15% may have normal-appearing ovaries (22, 23). There was no adnexal pathology in our patients who underwent hysterectomy. In a population-based study including endometrial cancer patients, synchronous ovarian malignancies were found in 14% of women who are younger than 45 years of age, compared with in 2% of women aged over 45 years (24).

Limitations of the presented study are the retrospective design. Due to the retrospective nature of the study, we could not reach the data concerning additional medication (metformin etc.) history, adverse effects of drugs used, or patients' weight gain, which may influence the study results. On the other hand, the strength of our study is that patient follow-up was up to 96 months.

CONCLUSION

Uterine preservation is a feasible option in women with precursor lesions of endometrial carcinoma who want to preserve their fertility within close follow-up. Assisted reproductive technology could help patients to become pregnant after fertility-sparing treatment. It is recommended for clinicians to evaluate patients with a multidisciplinary team.

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Conflict of interest

Authors have no conflicts of interest relevant to this article.

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Ethical Decleration

Ethical permission was obtained from Istanbul University, Istanbul Medical Faculty Ethical Committee for this study. Helsinki Declaration rules were followed to conduct this study.

Authorship Contributions

Concept: BG, HS, YS, MA, ÇT, Design: BG, EED, FK, ST, Supervising: YS, ST, MA, ÇT, Financing and equipment: BG, EED, DV, Data collection and entry: BG, EED, DV, FK, HS, Analysis and interpretation: BG, HS, DV, Literature search: FK, YS, ST, MA, Writing: BG, EED, YS, HS, DV, ÇT, Critical review: MA, ÇT

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ORGINAL ARTICLE / ORJİNAL MAKALE

Endometrium kanserinde lenfovasküler saha invazyonu ile kötü prognostik faktörlerinin ilişkisinin incelenmesi

The investigation of poor prognostic factors related to lymphovascular space invasion in endometrium cancer

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ÖZ

Amaç: Bu çalışmada endometrium kanserinde (EK) lenfovasküler saha invazyonu varlığının (LVSİ) tümör differansiasyon düzeyi (grade), miyometrial invazyon, lenf nodu metastazı ve tümör evresi gibi kötü prognostik faktörler ile ilişkisinin incelenmesi amaçlanmıştır.

Gereç ve yöntem: Kliniğimizde EK nedeniyle total histerektomi + bilateral salpingooferektomi ± pelvik ve/veya paraaortik lenfadenektomi + omentektomi yapılmış 44 hasta retrospektif olarak incelenmiştir. Patoloji sonuçlarına göre hastalar LVSİ pozitif ve negatif olmak üzere 2 gruba ayrılmıştır. LVSİ olmayan 29 hasta ile kontrol grubu ve LVSİ pozitif olan 15 hasta ile çalışma grubu oluşturulmuştur.

Bulgular: Çalışma grubunda istatistiksel olarak kontrol grubuna göre ana materyal nükleer grade daha yüksek bulunmuştur (p=0.001 ve p<0.05). Miyometrial invazyon varlığı açısından her iki grup arasında istatistiksel olarak anlamlı farklılık bulunamamış (p=0.999 ve p<0.05) olmasına rağmen LVSİ pozitif olan çalışma grubunda miyometrial invazyon derinliğinin istatistiksel olarak anlamlı şekilde daha fazla olduğu tespit edilmiştir (p=0.001 ve p<0.05). LVSİ pozitif olan grupta istatistiksel olarak anlamlı olacak şekilde pelvik lenf nodu tutulumu daha fazladır (sağ pelvik lenf nodu için p=0,003 ve p<0,005; sol pelvik lenf nodu için p=0.001 ve p<0.05). LVSİ pozitif olan grupta istatistiksel olarak anlamlı şekilde daha ileri evre hastalık bulunmuştur (p=0.009 ve p<0.05).

Sonuç: EK'de LVSİ varlığında yüksek gradeli tümör, derin myometrial invazyon, artmış lenf nodu tutulumu ve daha ileri evre hastalık tespit edilmektedir.

Anahtar Kelimeler: Endometrial Kanser, Lenfovasküler Saha Invazyonu, Prognostik Faktörler

ABSTRACT

Aim: It was aimed to investigate the relationship between the presence of lymphovascular space invasion (LVSI) in endometrial cancer (EC) and poor prognostic factors such as tumoral grade, myometrial invasion, lymph node metastasis and stage of the disease in this study.

Materials and methods: Forty-four patients who underwent total hysterectomy + bilateral salpingoophorectomy ± pelvic and/or paraaortic lymphadenectomy + omentectomy for EC in our clinic were retrospectively analyzed. According to the pathology results, the patients were divided into 2 groups as LVSI positive and negative. A control group with 29 patients without LVSI and a study group with 15 patients with positive LVSI were conducted.

Results: A statistically significant difference was found between two groups in terms of nuclear grade (p=0.001 and p<0.05). Although there was no statistically significant difference between the two groups in terms of the presence of myometrial invasion (p=0.999 and p<0.05), the depth of myometrial invasion was found to be significantly deeper in the study group (p=0.001 and p<0.05). Statistically significant differences were found in the group with positive LVSI in terms of right (p=0.003 and p<0.005) and left (p=0.001 and p<0.05) pelvic lymph node involvement. When both groups were compared in terms of main material surgical staging, we found that the LVSI positive group had more advanced stage disease (p=0.009 and p<0.05).

Conclusion: High-grade tumor, deep myometrial invasion, increased lymph node involvement and more advanced disease are detected in the presence of LVSI in EC.

Keywords: Endometrial Cancer, Lymphovascular Site Invasion, Prognostic Factors

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GİRİŞ

Endometrium kanseri (EK) gelişmiş ülkelerde en sık görülen jinekolojik malignitedir (1). Kadınlarda meme, akciğer ve kolon-rektum kanseri sonrası en sık görülen 4. kanserdir (1). Gelişmekte olan ülkelerde serviks kanserinden sonra en sık görülen jinekolojik kanserdir (2). Türkiye Kanser İstatistik 2017 yılı verilerine göre EK kadınlarda görülen tüm maligniteler içinde 5. ve jinekolojik kanserler içinde 1. sıradadır (3).

EK genellikle prognozun olumlu olduğu erken evrede tespit edilir (4). Bunun nedeni de EK'nın en sık anormal uterin kanamayla belirti vermesidir (4). Cerrahi ve adjuvan tedavi alan erken evre hastalarda 5 yıllık sağ kalım %80-90'dır (5). Uzak metastaz varlığında 5 yıllık sağkalım ise %25'in altındadır (6). EK'de evreleme ve hastalığın cerrahi sonrasındaki yönetiminde bize fikir verecek olan en önemli prognostik faktörler; tümörün histolojik tipi, derecesi, myometrial invazyon derinliği, alt uterin segment tutulumu, servikal tutulum ve lenf nodu metastazıdır (7).

Lenfovasküler saha invazyonu (LVSİ)'nin genel tanımı; invaziv tümör sınırının dışında endotelyal hücrelerle kaplı bir boşlukta tümör hücrelerinin varlığıdır ancak LVSİ'nin kesin tanımı ve kapsamının etkisi tartışılmaktadır (8). LVSİ'nin lenf nodu metastazlarıyla yüksek ilişkisi mevcuttur (9). Erken evre EK'nde LVSİ pozitifliği yaklaşık %15 olarak görülmektedir (10). LVSİ bulunan EK hastalarında 5 yıllık sağ kalım oranı %64,5, LVSİ bulunmayan hastalarda ise bu oran %83 olarak bulunmuştur (11). Son yıllarda EK ve LVSİ ile ilgili yapılan çalışmaların sonuçları tartışmalıdır. Bazı çalışmalarda LVSİ bağımsız bir kötü prognostik faktör olarak değerlendirilmektedir (8-13).

Bu çalışmada EK'de LVSİ'nin tümör differansiasyon düzeyi (grade), miyometrial invazyon, lenf nodu metastazı ve tümör evresi gibi kötü prognostik faktörler ile ilişkisinin incelenmesi amaçlanmıştır.

GEREÇ VE YÖNTEMLER

Bu çalışmada Düzce Üniversitesi Sağlık Uygulama ve Araştırma Hastanesi Kadın Hastalıkları ve Doğum kliniğinde opere edilen EK tanılı hastaların medikal kayıtları Düzce Üniversitesi Tıp Fakültesi'nden 05.07.2021 tarihinde alınan 2021-164 numaralı etik kurul onayı ile retrospektif olarak incelenmiştir.

Kliniğimizde 2015-2021 yılları arasında EK nedeniyle ameliyat olan 44 hasta çalışmaya dahil edilmiştir. LVSİ olmayan 29 hasta kontrol grubu ve LVSİ olan 15 hasta çalışma grubu olarak belirlenmiştir.

Hastaların tümüne total histerektomi + bilateral salpingooferektomi + omentektomi ± pelvik ve/veya paraaortik lenfadenektomi uygulanmıştır. Adjuvan tedavi endikasyonları post operatif patoloji sonuçları ile konseyde görüşülerek ilgili branşlara konsülte edilmiştir.

Hastaların hem dosya hem otomasyon üzerinden kayıtlarına erişilmiştir. Olguların demografik ve klinikopatolojik özellikleri belirlenmiştir. Yaş, ameliyat tipi, gravida, parite, menopoz durumu, geçmiş malignite öyküsü, ailede malignite öyküsü, sistemik hastalık varlığı, ilaç kullanımı, operasyon öyküsü, başvuru şikayeti, preop endometrial örnekleme sonucu, yapılan ameliyatlar, patolojik tanısı, cerrahi evreleri ve patolojik prognostik parametrelerin değerlendirme sonuçları incelenerek kaydedilmiştir. Hastaların patolojik sonuçlarından kötü prognostik faktörler olarak kabul edilen histolojik grade, uterus boyutu, tümör boyutu, miyometrial invazyon durumu, alt uterin segment tutulumu, servikal tutulum, LVSİ durumu ve çıkarılan pelvik ve/veya paraaortik lenf nodu sayısı ve metastatik lenf nodu sayısı değerlendirilmiştir. Lenfovasküler invazyon histopatolojik olarak endoteli görülen damar yapılarında, gerektiğinde CD31, CD34 gibi markerlarla immünohistokimyasal olarak verifiye edildikten sonra var/yok olarak kaydedilmiştir.

İstatistiksel Analiz

Hastalar çalışma grubu ile kontrol grubu olmak üzere demografik özellikler ve klinikopatolojik özellikler olarak univaryan ve multivaryan analizler yapılarak karşılaştırılmıştır. Verilerin dağılımı Shapiro-Wilk testiyle incelenmiş, normal dağılım gösteren değişkenlerin karşılaştırılmasında Independent samples t test, normal dağılım göstermeyen değişkenlerin karşılaştırılmasında Mann-Whitney U test kullanılmıştır. Kategorik değişkenlerin analizinde Pearson chi-square, Fisher's exact ve Fisher-Freeman-Halton testleri kullanılmıştır. Beklenen değer kuralı sağlanmadığı durumlarda, 2x2 tablolarda Fisher's exact test kullanılırken daha büyük boyutlu rxc boyutlu tablolarda ise genelleştirilmiş hali olan Fisher-Freeman-Halton testi kullanılmıştır. Sayısal değişkenler için tanımlayıcı istatistikler dağılım şeklinde bağlı olarak ortalama±standart sapma veya ortanca, çeyreklikler ve minimum-maksimum değerler ile, kategorik değişkenler için sayı ve yüzde şeklinde verilmiştir. İstatistiksel analizler SPSS v.22 paket programı ile yapılmış ve anlamlılık düzeyi p<0,05 olarak dikkate alınmıştır.

BULGULAR

Çalışmamızda hastaların yaş ortalaması 62,43±10,92 olarak tespit edilmiştir. Hastalar yaş gruplarına göre incelendiğinde ≤49 yaş grubunda 4 hasta (9,1), 50-64 yaş grubunda 18 hasta (%40.9) ve ≥65 yaş grubunda 22 hasta (%50) olarak bulunmuştur. Meme kanser 6, mesane kanseri 1, meme kanseri ve tiroid kanseri ise 1 hastanın özgeçmişinde mevcuttur. LVSİ pozitif olan çalışma grubu ile kontorl grubu arasında geçirilmiş malignite öyküsü açısından istatistiksel olarak anlamlı fark bulunamamıştır (0,999 ve p<0,05). Çalışma ve kontrol grupları arasında yaş, gravida, parite, menopoz durumu, malignite öyküsü, malignite tipi, ailede malignite öyküsü ve tipi, sistemik hastalık varlığı, başvuru şikayeti, preoperatif endometrial örnekleme sonuçları, patolojiye gönderilen ana materyalde, uterus boyutu, tümör çapı, myometrial invazyon varlığı, alt uterin segment tutulumu, servikal tutulum, paraaortik lenf nodu tutulumu, batın yıkama sıvında tümör varlığı ve prognoz açısından sonuçları karşılaştırılmış ve istatistiksel olarak anlamlı fark bulunamamıştır (sırasıyla p=0.657; p=0.773; p=0.930; p=0.957;p=0.925; p=0.822; p=0.571; p=0.675; p=0.414; p=0.846; p=0.083; p=0.328 ve p<0.05). Hastaların temel demografik ve klinik özellikleri Tablo 1'de özetlenmiştir.

Tablo 1. Hastaların temel demografik, klinik ve obstetrik özellikleri ile tümör klinikopatolojik özellikleri

	Ort±SS (min-max)	%
Yaş	62.43±10.92 (38-90)	
Gravida	3 (1-4) [0-9]	
Parite	2,5 (1-3,8) [0-9]	
Menopoz Durumu, n (%)		
Postmenopozal	35	79.5
Premenopozal	9	20.5
Malignite Öyküsü, n (%)		
Yok	36	81.8
Var	8	18.2
Sistemik Hastalık, n (%)		
Yok	7	15.9
Var	37	84.1
Başvuru Şikayeti, n (%)		
Postmenopozal Kanama	31	70.5
Anormal Uterin Kanama	8	18.2
Pelvik Kitle	1	2.3
Tamoxifen kullanımı nedeniyle kontrolde Entometrial Hiperplazi	3	6.8
Kontrol sırasında endometrial hiperplazi	1	2.3

Preop Endometrial Örnekleme sonucu, n (%)		
Endometrioid Karsinom	32	72.7
Endometrioid Karsinom/Endometrial Intraepitelyal Neoplazi ayrımı yok	1	2.3
Atipili Endometrial Hiperplazi	4	9.1
Andiferansiye komponentli endometrial karsinom	1	2.3
High grade adenokarsinom	2	4.5
Seröz endometrial karsinom	1	2.3
Yaygın eozinofilik sinsityal metaplazi	1	2.3
Endometrial polip	1	2.3
Az diferansiye endometrioid karsinom	1	2.3
Ana Materyal Patoloji Sonuçları, n (%)		
Endometrioid karsinom	35	79.5
Fokal Squamöz Diferansiasyonlu Endometrioid Karsinom	2	4.5
Malign mikst müllerien tümör	3	6.8
Yaygın Squamöz Diferansiasyonlu Endometrioid Karsinom	1	2.3
Mikst karsinom(%60 seröz+%40 endometrioid karsinom)	1	2.3
İyi diferansiasyonlu endometrioid karsinom	1	2.3
Endometrial Stromal Sarkom	1	2.3

Çalışma grubunu oluşturan LVSİ pozitifliği (+) 15 (%34.1) hastada mevcutken, kontrol grubunu oluşturan 29 (%65.9) hastada LVSİ saptanmamıştır. Her iki gruba ana materyalde tümöral grade açısından bakıldığında çalışma grubunda istatistiksel olarak anlamlı olacak şekilde daha fazla oranda grade 3 tümöre sahip olduğu tespit edilmiştir (p=0.001 ve p<0.05) (Tablo 2). LVSİ pozitif olan çalışma grubunda istatistiksel olarak kontrol grubuna göre daha fazla nükleer grade 3 tümöre sahip olduğu bulunmuştur (p=0.001 ve p<0,05) (Tablo 2.).

Miyometrial invazyon varlığı açısından her iki grup arasında istatistiksel olarak anlamlı farklılık bulunamamış (p=0.999 ve p<0.05) olmasına rağmen çalışma grubunda miyometrial invazyon derinliğinin anlamlı olarak ½'den daha fazla olduğu tespit edilmiştir (p=0.001 ve p<0.05) (Tablo 2.).

Çalışma grubunda istatistiksel olarak anlamlı olacak şekilde sağ pelvik lenf nodu tutulumu daha fazla izlenmiştir (p=0·003 ve p<0·05). Her iki grup sol pelvik lenf nodu tutulumu açısından karşılaştırıldığında çalışma grubunda 4 hastada (%26·7) sol pelvik lenf nodu tutulumu tespit edilirken kontrol grubunda hiç sol pelvik lenf nodu tutulumu izlenmemiştir (p=0,001 ve p<0·05) (Tablo 2.).

Kontrol grubunda ana materyal cerrahi evrelendirmesi 16 hastada (%55.2) evre 1A tespit edilmiştir. Çalışma grubunda ise 3 hastada (%20) evre 3C1 tespit edilmiştir. Her iki grup istatistiksel olarak karşılaştırıldığında LVSİ pozitif olan çalışma grubundaki hastaların ana materyal cerrahi evrelendirme açısından daha ileri evreye sahip olduğu tespit edilmiştir (p=0.009 ve p<0.05) (Tablo 2).

Tablo 2. Kontrol ve çalışma grubuna ait klinik ve klinikopatolojik özellikler

	Kontrol (n=29)	%	Çalışma (n=15)	%	p değeri
Ana Materyal Tümör Grade β					
1	**12**	**41.4**	0	0.0	***0.001****
2	14	48.3	7	46.7	
3	3	10.3	**8**	**53.3**	
Ana Materyal Histoloji Grade β					
1	**12**	**41.4**	0	0.0	***0.001****
2	14	48.3	7	46.7	
3	3	10.3	**8**	**53.3**	
Uterus en büyük boyutu Ω	9.52±4.09		10.49±1.94		0.388
Tümör Çapı Ω	3.81±1.72		4.59±1.83		0.174
Myometrial İnvazyon β					
(-)	1	3.4	0	0.0	0.999
(+)	28	96.6	15	100	
Myometriuma İnvazyon Derinliği β					
<½	**19**	**67.9**	2	13.3	
=½	1	3.6	0	0.0	
>½	8	28.6	**13**	**86.7**	***0.001****
Alt Uterin Segment Tutulumu β					
(-)	21	72.4	7	46.7	0.111
(+)	8	27.6	8	53.3	
Servikal Tutulum β					
(-)	26	89.7	12	80.0	0.647
(+)	3	10.3	3	20.0	
Sağ PLN Tutulumu β					
(-)	29	100	10	66.7	***0.003****
(+)	0	0.0	**5**	**33.3**	
Sol PLN Tutulumu β					
(-)	29	100	11	73.3	***0.001****
(+)	0	0.0	**4**	**26.7**	
Paraaortik Lenf Nodu Tutulumu β					
(-)	29	100	14	93.3	
(+)	0	0.0	1	6.7	0.341
Ana Materyal Cerrahi Tümör Evresi β					
Evre1A	**17**	**58.6**	2	13.3	***0.009****
Evre1B	7	24.1	7	46.7	
Evre2	3	10.3	2	13.3	
Evre3A	1	3.4	0	0.0	
Evre3C1	0	0.0	**3**	**20.0**	
Evre3C2	0	0.0	1	6.7	
Evre4	1	3.4	0	0.0	
Prognoz β					
Regrese	24	82.8	10	66.7	0.299
Cuff metastazı	1	3.4	0	0.0	
Batın ön duvarı metastazı (+)	0	0.0	1	6.7	
Exitus	3	10.3	3	20.0	
Diğer nedenlerle exitus	1	3.4	0	0.0	
Akciğer metastaz	0	0.0	1	6.7	

*P<0.05 değeri ististiksel olarak anlamlı kabul edilmiştir. Ω :ortalama±SS; β : n (%); PLN: pelvik lenf nodu

TARTIŞMA

EK'nin evrelemesi cerrahi olarak yapılmaktadır. Ameliyat piyesinin histopatolojik olarak incelenmesi ile tümörün oluşturduğu solid yapıların yüzdesi ve nükleer özelliklere göre gradeleme, myometrial invazyon, servikal tutulum ve lenf nodu metastazı gibi belirteçler hastalığın kesin evresi ve prognozu hakkında bilgi vermektedir (14). Hasta yaşı, tümörün reseptör durumu, tümörün histolojik alt tipi, tümör diferansiasyon derecesi (grade), miyometrial invazyon, alt uterin segment tutulumu, servikal tutulum ve lenf nodu tutulumunun kanserin tekrarlamasını öngörmede başlıca olumsuz prognostik faktörler olarak tanımlanmıştır (15).

Çalışmamızda hastalarımızın yaş ortalaması EK ile ilgili yapılan diğer çalışmalara benzer şekilde 62·43±10·92 olarak bulunmuştur (16-17). EK nedeniyle opere ettiğimiz hastaların en sık başvuru şikayetinin postmenopozal kanama olduğu çalışmamızda gösterilmiştir ve yapılan çoğu çalışmada da en sık başvuru şikayetinin bu olduğu görülmektedir (18-19). Endometrioid adenokarsinom, tüm EK'lerinin yaklaşık %80'inde saptanan ve en sık tespit edilen histolojik alt tipidir (16,20-21). Ana materyal patoloji sonuçlarına bakıldığı zaman çalışmamıza dahil olan hastaların %79.5'inde endometrioid adenokarsinom olduğu tespit edilmiştir. EK'de histolojik ve nükleer grade'in prognoz ile güçlü bir ilişkisi bulunmaktadır (22). Çalışmamızda 44 hastanın 12'sinde (%27.3) nükleer grade 1, 21'inde (%47.7) grade 2 ve 11 hastada (%25) grade 3 tümör bulunmuştur. Beş yıllık sağkalım grade 1 tümörlerde %92, grade 2 tümörlerde %86, grade 3 tümörlerde bu oran %64 olarak bildirilmektedir ve tümörlerin nükleer gradelerine göre sıklıklarını inceleyen çalışmalar ile sonuçlarımız benzerdir (23-25). Çalışmamızda ana materyal tümöral histolojik grade açısından bakıldığında LVSİ pozitif olan grupta istatistiksel olarak anlamlı şekilde daha fazla oranda grade 3 histolojiye sahip olduğu bulunmuştur (p=0.001 ve p<0.05). LVSİ pozitif olan EK'de histolojik grade'in kontrol grubuna göre daha yüksek grade olmasına dair bulduğumuz sonuç (p=0.001 ve p<0.05) LVSİ'nin prognoz ve rekürrensle ilişkisi olduğunu iddia eden daha önce yapılmış çalışmaları da desteklemektedir (26-28).

Bu çalışmada miyometrial invazyon varlığı açısından kontrol ve çalışma grubu arasında istatistiksel olarak anlamlı farklılık bulunamamıştır (p=0,999 ve p<0,05), ancak miyometrial invazyon varlığında LVSİ pozitif olan çalışma grubunda miyometrial invazyon derinliğinin anlamlı olarak ½'den daha fazla olduğu bulunmuştur (p=0,001 ve p<0,05). LVSİ pozitif olan grupta %97,7 oranında miyometrial invazyon bulunmuştur. Miyometriyal invazyon EK'nde evreyi yükselten ve aynı zamanda sağkalımı düşüren prognostik faktördür (29-30). LVSİ varlığında myometrial invazyonun daha sık olmaktadır (8) ancak LVSİ bulunan hastalarda derin myometrial invazyonun daha sık olduğuna dair çalışamıza benzer şekilde daha önce yapılmış ülkemizden yapılmış bir çalışma dışında çalışma sayısı kısıtlıdır mevcuttur (31).

Hem sağ (p=0.003 ve p<0.05) hem sol (p=0.001 ve p<0.05) pelvik lenf nodu tutulumu LSVİ olan hastalarda daha fazla izlenmiştir. Benzer şekilde paraaortik lenf nodu tutulumu LVSİ pozitifliğinde daha fazladır (p=0.341 ve p<0.05). Stålberg ve ark. 2019 yılında yaptıkaları çalışmalarında lenf nodu metastazları için en güçlü bağımsız risk faktörü olarak LVSİ varlığını tespit etmişlerdir ve bu durumun endometrioid adenokarsinomlu hastalarda sağkalımı azalttığını göstermişlerdir (8). Ayhan A ve ark. ülkemizde gerçekleştirdikleri güncel bir çalışmalarında LVSİ pozitif olan kadınların 5 yıllık genel sağkalım oranını, LVSİ negatif olanlara göre önemli ölçüde daha düşük bulmuşlardır (sırasıyla %88.2'ye karşılık %98.5; p<0.001) (31). Şahin ve ark. 2020 yılında yaptıkları çalışmalarında yüksek histolojik grade sahibi hastalarda LVSİ pozitifliği daha sık tespit etmişlerdir (32). Sadozye ve ark. yaptıkları derlemede LVSİ ile ilgili mevcut literatürü gözden geçirdiklerini ve uzak nüks kadar nodal metastaz için de LVSİ'nun bağımsız bir risk

faktörü olduğunu göstermişlerdir (33).

Çalışmamızda LVSİ pozitif olan olguların kontrol grubuna göre daha ileri cerrahi tümör evresine sahip olduğu tespit edilmiştir (p=0·009 ve p<0·05). Neal ve ark. 2016 yılında yayınlanan çalışmalarında LVSİ'nin evre, grade ve myometrial invazyona göre daha zayıf bir prognostik faktör olduğu bildirilmiştir (34). Ancak Ayhan ve ark. yapmış oldukları kapsamlı çalışmada LVSİ pozitif olan grupta daha ileri evre hastalığın saptandığı bildirilmiştir (31). Gemer ve ark. LVSİ pozitif olan hastaların daha ileri evre hastalık, daha yüksek rekürrens oranı ve daha kötü 5 yıllık sağkalıma sahip olduklarını bildirmişlerdir (35).

SONUÇ

Çalışmamızda EK olgularında LVSİ varlığında yüksek histolojik grade, derin miyometrial invazyon, lenf nodu tutulumu ve daha ileri evrede hastalık tespit ettik. Ancak LVSİ'nun rutin bir prognostik belirteç olarak kullanılabilmesi için daha geniş kapsamlı, prospektif, randomize kontrollü çalışmalara gereksinim olduğu kanaatindeyiz.

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Fikir: AY, Tasarım: CÜ, Gözetim: AY, Araç gereç: CÜ, Veri toplama ve işleme: CÜ, SKC, Analiz ve yorumlama: CÜ, SKC, Literatür tarama: CÜ, Yazma: CÜ, Eleştirel inceleme: SKC

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REVIEW/DERLEME

Mismatch repair defects in endometrial cancer

Mismatch repair gen defektlerinin endometrium kanserindeki önemi

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ABSTRACT

Endometrial cancer is the most commonly diagnosed gynecologic malignancy among women worldwide and may be classified on the basis of different molecular, pathologic and genetic alterations. Identification of mismatch repair-deficient (MMRd), which occur in up to 30% of all endometrial cancers (EC), has become unavoidable for therapeutic management, clinical desicion making, and prognosis. Although microsatellite instability is associated with a more favorable outcome in colorectal cancer, its relationship with prognosis in EC is not yet clear.

Keywords: Endometrial Cancer, Mismatch Repair, Prognosis

ÖZ

Endometrium kanseri dünya genelinde en yaygın görülen jinekolojik kanserdir ve farklı moleküler, patolojik ve genetik değişikliklere göre sınıflandırılır. Yaklaşık %30 oranında görülen mismatch repair defekti (MMRd)'nin tespiti, tedavi yönetimi, klinik karar verme süreci ve prognoz ile ilişkisinden dolayı vazgeçilmez bir duruma gelmiştir. Kolorektal kanserlerde mikrosatellit instabilite daha iyi prognozla ilişkili olmasına rağmen, bu ilişki endometrium kanserinde henüz netlik kazanmamıştır.

Anahtar Kelimeler: Endometrial Kanser, Mismatch Repair, Prognoz

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INTRODUCTION

Endometrial cancer (EC) is the most common gynecological cancer among women in developed countries and the fourth most common malignancy overall. (1) This type of cancer mostly develops in postmenopausal women. (2) The mean age at diagnosis of patients with endometrial cancer is 63 years and 70% is limited to the corpus uteri at diagnosis. Also, up to 14% of cases (2) occur in premenopausal women as a result of a high body mass index (BMI). (3) The lifetime incidence is 3%, and although most women present at an early stage and have a good prognosis, some women present with advanced disease, experience relapses, and have a poor prognosis. (1) Patients with advanced and recurrent EC constitute a major therapeutic challenge, with 5-year overall survival rates of only 17% in patients with distant organ involvement. (4) Approximately 80% of women with early-stage EC have a favorable prognosis, with 5-year overall survival rates of 95%. (5)

The standard treatment for endometrial cancer is surgery that includes bilateral salpingoophorectomy and total hysterectomy with evaluation of the lymph nodes. (6) Clinical and surgical histopathological features help stratify according to risk categories to determine the type and need for adjuvant therapy. (6) The major diagnostic challenge is to determine which patients with early stage EC have low-risk disease with a <5% risk of recurrence and to decide whether they can be treated with surgery alone as opposed to patients with high-risk disease who need adjuvant therapy. (7)

Over the past decade, numerous studies have investigated prognostic factors, including pathologic type, histologic grade, lymphovascular involvement, and tumor staging, but were insufficient to determine reproducibility. Therefore, research has turned to gene carcinogenesis, such as molecular changes, to provide a new prognostic classification. (8)

Understanding the molecular alterations involved in endometrial cancer provides an opportunity to (1) improve upon the current histologic classification system, (2) enhance diagnostic testing modalities, and (3) personalize treatments through the incorporation of targeted therapies. Here, we highlight from a clinical perspective, the implications of emerging molecular characteristics on classification of subtypes, development of diagnostic testing, and therapeutic options.

HEREDITERY NON-POLYPOSIS COLORECTAL CANCER (LYNCH SYNDROME)

Lynch syndrome, also called hereditary non-polyposis colorectal cancer, is associated with pathogenic variants in mismatch repair (MMR) genes (MSH2, MLH1, MSH6 and PMS2). (9) Endometrial cancer is the second most common malignancy in patients with Lynch syndrome (after colorectal cancer). (10) It is inherited autosomal dominantly, composes for 2-5% of all endometrial cancers (11) and occurs 10 years earlier. In 2007 the Society of Gynecologic Oncology (SGO) published guidelines to assist in identifying patients for whom genetic risk assessment might be useful (Table 1). (12) The SGO specifically recommended risk assessment for women with a greater than approximately 20-25% probability of having Lynch syndrome, and also identified the class of patients at 5-10% risk for Lynch syndrome where genetic risk assessment might be useful.

Table 1. Risk of Malignancy Criteria for Genetic Risk Assessment for Lynch Syndrome

Patients with a greater than approximately 20-25% probability of having Lynch syndrome and for whom genetic risk assessment is recommended:
• Patients with endometrial or colorectal cancer who meet the amended Amsterdam criteria: ▪ At least three relatives with Lynch-related cancer in a lineage (colorectal cancer, cancer of the endometrium, small intestine, ureter, or renal pelvis); ▪ An affected person must be a first-degree relative of the other two; ▪ At least two consecutive generations must be affected; ▪ At least one Lynch-related cancer must be diagnosed before age 50. • Patients with synchronous or metachronous endometrial and colorectal cancer diagnosed with the first cancer before the age of 50. • Patients with synchronous or metachronous ovarian and colorectal cancer diagnosed with their first cancer before the age of 50. • Patients with colorectal or endometrial cancer with evidence of MMR gene defect (microsatellite instability (MSI) or immunohistochemical (IHC) loss of MLH1, MSH2, MSH6 or PMS2 expression). • Patients with a first- or second-degree relative with a known MMR gene mutation.
Patients with a greater than approximately 5-10% probability of having Lynch syndrome and for whom genetic risk assessment may be useful:
• Patients with endometrial or colorectal cancer diagnosed before age 50. • Patients of any age with endometrial or ovarian cancer with synchronous or metachronous colon or other Lynch syndrome-associated tumors. • Patients with endometrial or colorectal cancer and first-degree relatives with Lynch syndrome-related tumor[1] diagnosed before age 50. • Patients with colorectal or endometrial cancer diagnosed at any age, with two or more first-degree relatives[2] with tumors associated with Lynch syndrome,[1] regardless of age. • Patients with a first- or second-degree relative[2] who meet the above criteria.

[1]Tumors associated with Lynch syndrome include tumors of the colorectal, endometrial, stomach, ovary, pancreas, ureter, and renal pelvis, biliary tract, and brain (glioblastoma, as often seen in Turcot syndrome), sebaceous gland adenomas and keratoacanthomas in Muir-Torre syndrome, and carcinoma of the small intestine. [2]First and second degree relatives are parents, siblings, children, aunts, uncles, nieces, grandparents, and grandchildren.

While family history remains an important component in identifying individuals who may benefit from genetic risk assessment for Lynch syndrome, tumor testing for MMR defect is increasingly used to triage patients who may be at risk for germline DNA mutation. (13) These tumor tests include IHC and MSI analysis for four MMR proteins (MLH1, MSH2, MSH6 and PMS2). For IHC-based triage, the absence of a specific MMR protein in the tumor is considered abnormal. Both tumor and normal tissues are required for MSI-based triage.

Immunohistochemistry can also guide which of the four DNA MMR genes should be sequenced. This can be performed in most pathology laboratories and has become the approach of choice for the initial assessment of the MMR pathway in endometrial cancers. In 2014, the American College of Obstetricians and Gynecologists (ACOG) published an application with an IHC-based algorithm to assess the likelihood of Lynch syndrome in endometrial tumors (Figure 1). (14)

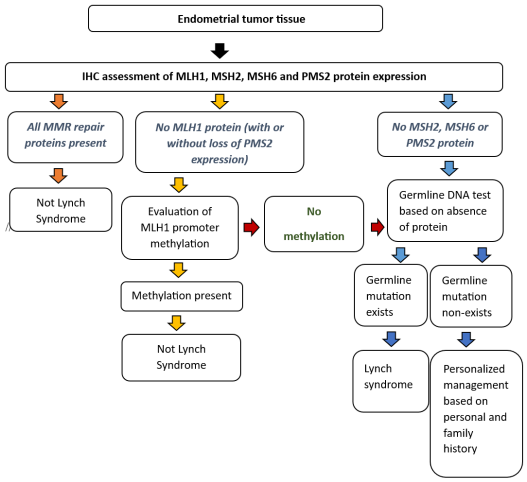

Figure 1. Algorithm for using IHC assessment of MMR protein expression to triage endometrial tumors for the possibility of Lynch Syndrome.

MMR DEFICIENT (MMRd) ENDOMETRIAL CANCER

Most endometrial cancers are sporadic, though some hereditary cases are caused by germline mutations, predominantly in MMR genes. (15) The MMR deficient (MMRd) molecular group represents 20–30% of EC cases, and is analogous to MSI in the initial genomic classification. (16)

Microsatellite instability (MSI) is defined by the expansion or contraction of the length of microsatellite pathways in the tumor compared to the corresponding DNA from the germline or normal tissues and is detected using polymerase chain reaction (PCR) based methods. (17) Microsatellites show the same number of nucleotide repeats of tumor and healthy tissue in the same individual, but can cause diffuse changes in the number of repeats in case of MMR loss.(18) MSI testing categorizes tumors as having high microsatellite instability (MSI-high), low microsatellite instability (MSI-low), or as being microsatellite stable (MSS).(19)

Tumors that are MMRd or MSI-high can originate through three pathways: germline MMR mutations in DNA mismatch repair proteins MLH1, PMS2, MSH2, MSH6, named Lynch syndrome; somatic MMR gene mutations occasionally labelled as Lynch-like; and homozygous methylation of the MLH1 gene promoter named sporadic.(20) MSI-test is more laborious, requires non-neoplastic tissue, is more expensive, and does not provide information on the gene affected both approaches (MMRd by IHC and MSI-test) require the analysis of MLH1 promoter methylation status in cases with loss of MLH1/PMS2 expression. Several studies have compared MSI testing and MMR assessment in endometrial cancer patients, and found reasonable concordance between the two methodologies. Discordance between MSI-high and MMR deficiency ranged from 2–8% in several studies from different institutions. (21) The International Society of Gynecological Pathology (ISGyP) guidelines therefore recommend MMR-IHC as the preferred test. (22) Tumors considered to be MSI-low are of much lower prevalence and not as well understood, but in practice these tumors are usually considered to be similar to MSS tumors.[23] MSI-low tumors, which comprise approximately 3% of endometrial tumors. (24)

Testing for MMR status/MSI in endometrial carcinoma patients has been shown to be relevant for four reasons:

(1) diagnostic, as MMRd/MSI is considered a marker for endometrioid type endometrial carcinoma;

(2) pre-screening to identify patients at higher risk for having Lynch syndrome;

(3) prognostic, as identified by The Cancer Genome Atlas (TCGA);

(4) predictive for potential utility of immune checkpoint inhibitor therapy.

Clinically, many studies have sought to evaluate other characteristics of MSI-high or MMR deficient endometrial tumors. (23) Histologically, some patterns have emerged. (23) Tumors with MMR deficiency or MSI-high are more commonly associated with endometrioid histology (25) and may be more frequently associated with poor prognostic factors such as advanced stage, deep myometrial invasion, high grade and lymphovascular space invasion (LVSI) (26) and has been found to be associated with an intermediate prognosis for EC. (16) From a demographic perspective, there was no age group or BMI association with MMRd. (27) Some studies show better survival outcomes (26-28), some show worse survival outcomes (29-30), and many show no association at all. (31-32)

The role of adjuvant chemotherapy in MMRd EC has been questioned by the molecular analysis of PORTEC-3. (7) This trial assessed chemotherapy used in addition to adjuvant radiation in high-risk EC. (7) The molecular analysis found no benefit with the addition of chemotherapy in the MMRd group, with the

5-year overall survival 84% in the radiation only group versus 79% in the chemoradiation group (p=0.445). (33) Adjuvant radiation on the other hand, may play a more important role in MMRd EC, compared with other EC molecular subtypes. (7) Pre-clinical work has shown increased sensitivity to radiation in MSH2 deficient cell lines. (34) In a review of 128 patients with stage Ib/II grade 3 endometrioid endometrial cancer, Reijnen et al. showed that adjuvant radiation was associated with improved disease specific survival in the MMRd group, but not in MMR-proficient cases. (35) A more recent study compared adjuvant chemotherapy and radiation with chemotherapy alone in advanced MSI-high EC, and found an improved progression-free survival with the addition of radiation. (36) There is so far insufficient evidence for the role of MMR status for response to radio or chemotherapy. (35) This evidence suggesting MMRd EC may have an increased sensitivity to radiation needs to be validated in prospective studies.

Cancers that have a high mutational burden have a substantially increased production of tumour mutated antigens (neoantigens), which correlates significantly with improved patient survival. (37) The increased neoantigens results in a high abundance of tumour-infiltrating lymphocytes (TIL), in particular CD8+ cytotoxic T cells, with an upregulated T-cell mediated antitumour response. (38) Cancer cells have two mechanisms to avoid the host immune response; the first involving the cytotoxic Tlymphocyteassociated protein 4 (CTLA-4) pathway, and the second linked with programmed cell death-1 (PD-1) and PD ligand (PD-L1). (39) Activated T cells express PD-1, and its interaction with PD-L1 decreases T cell activity. (40) Expression of PD-L1 on the surface of tumor cells causes the tumor to avoid host T-cell activity. (41) Therefore, blocking of the PD-1 interaction with PD-L1 in such cancers is likely to enhance the host immune response and have an antitumor effect. (42) Pembrolizumab (anti-PD-1) was the first immune checkpoint inhibitor shown to have favourable objective response rates (ORR) in metastatic or recurrent MMRd colorectal and non-colorectal cancers. (43-44) A subsequent study by the same group evaluated 86 patients with MMR deficiency with 12 different tumor types, including 15 patients with endometrial cancer (second only to colorectal cancer). (43) Although survival estimates are not mature, the progression-free survival at two years for this study was estimated at 53%, which is significantly higher than what would be expected for this population. (43) Pembrolizumab, an anti-PD-1 drug, has received FDA approval for the treatment of recurrent MMR-deficient or MSI-high tumors based on impressive response. (43-45) In a recently published phase 3 trial: the combination of pembrolizumab and lenvatinib were shown to improve both overall survival (OS) and progression-free survival (PFS) when compared to second or subsequent line chemotherapy in MMR proficient patients. (46) Two very important recent studies regarding the combination of immunotherapy with chemotherapy in advanced endometrial cancer showed promising results for pembrolizumab (47) and dostarlimab. (48) Combination and maintenance therapy with both of aforementioned immune check-point inhibitors altered the standard regimen for advanced endometrial cancer.

In conclusion, MSI and MMR protein assessments have already been extensively evaluated in endometrial cancer patients. Over the years new methods have been developed to stratify EC patients into a low-, intermediate-, or high-risk category. These developments are promising in guiding individualized surgical and adjuvant treatment. Tailored EC treatment prevents under- and overtreatment, that can result in suboptimal survival or unnecessary complications and toxicity. Major progress has been made with the introduction of the molecular classification. However, with

implementation of new methods the proven traditional methods, such as surgical staging and certain clinic-pathological biomarkers (i.e., LVSI) should not be ignored. Especially stage, which, alone, has been the most important prognostic factor up till now. The future lies in combinations of traditional and new stratification methods. Based on the results of ongoing research, the method to accurately assess the risk category in each patient will continuously be refined.

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Conflict of interest

Authors have no conflicts of interest relevant to this article.

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Ethical Decleration

Helsinki Declaration rules were followed to conduct this study.

Authorship Contributions

Concept: TS, NY, Design: TS, NY, Supervising: TS, NY, Financing and equipment: TS, NY, Data collection and entry: TS, NY, Analysis and interpretation: TS, NY, Literature search: TS, NY, Writing: TS, NY, Critical review: TS, NY

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CASE REPORT/OLGU SUNUMU

Asymptomatic ovarian metastasis of malignant melanoma in an adolescent

Adölesanda asemptomatik ovaryan malign melanom

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ABSTRACT

Malignant Melanoma (MM) is a tumor with an extremely poor prognosis and is very rare in adolescents. The prognosis of the disease in this population is different from that of adults. The condition can be diagnosed at a metastatic stage. Gynecological metastases of MMs often occur in the endometrium. More rarely, metastases can be detected in the ovaries. Although it is rare in adolescents, MM cases should be evaluated regarding ovarian metastases. It should be noted that adolescents can be asymptomatic no matter how large the mass is. This case report presents a case with a primary melanoma lesion in the leg and a metastatic ovarian mass detected in imaging studies performed five months after the initial diagnosis. The mass detected in the ovary in the case was removed by salphingoopherectomy. The diagnosis of metastasis was confirmed by immunohistochemical staining. Sentinel lymph node biopsy was performed concurrently with oophorectomy. Malignant melanomas may rarely metastasize gynecologically. Metastases should be considered in the differential diagnosis of adnexal mass in patients with melanoma, and the treatment plan should be arranged accordingly.

Keywords: Malignant Melanoma, Ovary, Adolescent, Chemotherapy, Sentinel

ÖZ

Malign Melanom (MM), son derece kötü prognoza sahip bir tümördür ve adölesanlarda çok nadir görülür. Bu popülasyonda hastalığın prognozu yetişkinlerden farklıdır. Durum metastatik evrede teşhis edilebilir. MM'lerin jinekolojik metastazları sıklıkla endometriyumda meydana gelir. Daha nadiren yumurtalıklarda metastazlar saptanabilir. Adölesanlarda nadir görülmesine rağmen MM olguları over metastazları açısından değerlendirilmelidir. Unutulmamalıdır ki, kitle ne kadar büyük olursa olsun adölesanlarda asemptomatik olabilir. Bu olgu sunumunda bacakta primer melanom lezyonu ve ilk tanıdan beş ay sonra yapılan görüntüleme tetkiklerinde metastatik over kitlesi saptanan bir olgu sunulmaktadır. Olguda overde saptanan kitle salfingooferektomi ile çıkarılıp metastaz tanısı immünohistokimyasal boyama ile doğrulandı. Ooferektomi ile eş zamanlı olarak sentinel lenf nodu biyopsisi yapıldı. Malign melanomlar nadiren jinekolojik olarak metastaz yapabilirler. Melanomlu hastalarda adneksiyal kitle ayırıcı tanısında metastazlar da düşünülmeli ve tedavi planı buna göre düzenlenmelidir.

Anahtar Kelimeler: Malign Melanom, Yumurtalık, Ergen, Kemoterapi, Sentinel

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INTRODUCTION

Malignant melanoma is a strongly malignant tumor with an unstable spread profile. MMs are rare in adolescents. (1) Melanoma diagnosis in adolescents is highly exacting due to the difficulties in differentiating benign lesions such as spitz nevi from malignant spitzoid melanomas, which they may strongly resemble .(2)

The majority of metastatic spread is lymphatic and peritoneal. Metastasis usually affects the lungs, the mediastinum, the brain, the liver, and the bones. The endometrium is the most common gynecological localization. (3) Metastasis presenting as a solitary ovarian tumor is unusual, and only a few cases have been reported.

Ovarian MMs often present with abdominal pain and swelling. But ovarian masses may be asymptomatic in adolescents. Here, we present a 18-year-old case with a giant mass in the left ovary in controls performed five months after MM was detected in the extremity.

CASE

An 18-year-old girl applied to an external center due to discoloration, crusting, and bleeding of her nevus on the inner side of the left leg. The nevus was removed, and nodular melanoma was detected. She had no history of tanning, sun damage, congenital or atypical nodules, and a family history of melanoma. The melanoma was removed by wide local excision with a tumor margin of 2 cm. The tumor's Breslow depth was 2 mm. After the diagnosis, the patient was referred to our hospital. The general physical examinations were regular. She provided no specific gynecologic history. A solid pelvic mass was felt during a pelvic exam. Ultrasound demonstrated a solid right adnexal mass with multiple anechoic locules with a prevailing solid and partially hyperechoic compound. The patient had no abdominal pain, swelling, or another complaint. A pelvic magnetic resonance imaging (MRI) scan showed a 160 x 120 mm pelvic mass in the right ovary location and suspected left inguinal lymph nodes (Fig.1a) The thorax CT scan and biologic laboratory tests, CA125, carcinoembryonic antigen (CEA), alpha-fetoprotein (AFP), lactate dehydrogenase (LDH) and human chorionic gonadotrophin (beta-HCG) levels were all normal.

Sentinel lymph node biopsy for the primary lesion scar site and concurrent laparotomy were planned. An approximately 18 cm mass was observed in the right ovary at laparotomy (Fig.1b) Lymphoscintigraphy was performed before the sentinel lymph node biopsy, and SLNB was performed (Fig.1c) Oophorectomy was performed. The left ovary and whole abdomen were normal. A pathological examination of the ovary revealed a tumoral infiltration with atypical mitoses, large, hyperchromatic nuclei, prominent nucleoli, large eosinophilic cytoplasm, and an array of islands. Positive staining with HMB45 and Melan A stains were detected in immunohistochemical examination (Fig.1d) The sentinel lymph node was negative. The patient was transferred to the medical oncology clinic in our hospital. A multidisciplinary tumor board evaluated the patient and decided to begin nivolumab therapy. The patient was transferred to our hospital's medical oncology clinic.

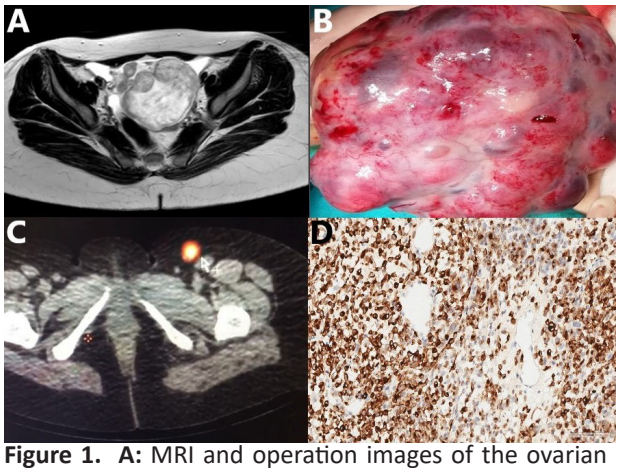

Figure 1. A: MRI and operation images of the ovarian mass. The ovary demonstrates a heterogeneous intensity on T2 **B:** Metastatic melanoma of the right ovary. **C:** Images of sentinel lymph node (SLN) SPECT / CT performed to determine the localization of SLNs observed in lymphoscintigraphy images before the operation (arrow in A) **D:** Positive staining with MelanA stain was detected in immunohistochemical examination (Melan A , focus 20 X)

DISCUSSION

Melanoma is extremely rare in the first two decades. In comparison to adults, there are fewer large series or reviews in the literature. (4,5) Studies evaluating MM in adolescents frequently compared this group with adult and childhood cases. Adolescent MM differs not only in terms of clinical presentation but also in terms of risk factors, etiology, natural history, and prognosis. (2) Xeroderma Pigmentosum, immunosuppression, inability to tan, freckles, family history, previous malignancy, numerous nevi, and congenital melanocytic nevi are all risk factors for pediatric and adolescent MM. (1) Our case did not have any risk factors. The absence of these risk factors made the initial diagnosis very difficult. Therefore, the referral of the patient to our tertiary hospital was delayed.

In terms of location, the lower limb was the most commonly affected region in adolescents in one study, followed by the head and neck region. (2) In our case, the primary lesion was on the left upper leg.

The prognosis of metastatic melanomas is inferior. Ovarian metastasis is difficult to diagnose. Patient age is also essential in this regard. Ovarian masses in adolescents are often asymptomatic. In most patients, tumor marker levels are non-discriminatory, as they were in our patient, who had normal CA125 levels. The lesion was unable to be classified using an ultrasound or CT scan. MRI scans could characterize the lesions, as melanin's presence rarely results in a peripherally increased signal on TI-weighted images. (6) These changes are visible only in areas with a high concentration of melanin. The MRI images of our patient was non-diagnostic for MM. As a result, MRI scans do not reliably identify lesions as melanomas in the majority of cases.

Breslow thickness, ulceration, increasing age, primary tumor location, lymph node involvement, satellite lesions, elevated lactate dehydrogenase, and metastatic disease are significant prognostic factors in adults. However, prognostic factors in young people were not well understood. (2) For patients aged 1 to 19, those with lesions bigger than 1.5 mm had a substantially better overall survival rate (OS) than patients aged 20 to 24. (7) Another study demonstrated that; young children aged 1 to 19 with thicker melanomas have a significantly higher survival rate than adults. (2) Adolescent patients were presented with a higher T classification than adults. (4) Although the precise cause for this remains unknown, variations in tumor biology, hormonal influences during puberty, genetics, and additional prognostic factors are likely to play a role. (1,2)

The time interval between primary malignant melanoma of the skin and metastatic ovarian tumor has been estimated to be between 15 and 228 months. (8) Our case is quite surprising, with a metastatic ovarian mass at a young age and shortly after diagnosing the primary lesion. We think this situation caused the delay in diagnosis in our patient, and by this time, the disease seems to have progressed.

The number and localization of metastases determine the treatment modality in MMs OS decreases significantly as the number of metastasis sites increases. (9) In our case, no further metastases were detected throughout the examination and scan, and the sentinel node was confirmed to be negative.

Sentinel lymph node biopsy (SLNB) is a staging procedure used to determine the lymph node status of patients with MM. There is a consensus on applying SLNB to patients with MM. In our patient, the mass detected in the adnexa was not thought to be metastasis due to the patient's age, and the patient underwent SLNB. However, once ovarian metastasis was identified, it became the determinant factor in adjuvant treatment.

Metastatic melanoma has a poor 5-year survival

rate for stage III and stage IV disease. For years, no traditional cytotoxic chemotherapeutic drug or regimen has improved overall survival in advanced and metastatic melanoma. (7) Single-agent chemotherapy, dacarbazine, and another cytotoxic agent, especially cisplatin, are used in systemic treatment. Biological therapy based on interferon-alpha, Ipilimumab, nivolumab was recently developed. Nivolumab, a monoclonal antibody that targets the programmed cell death protein 1 (PD-1), was approved in 2017 for adjuvant therapy in resected stage III and stage IV patients. (9) Nivolumab treatment was planned for our patient.

Conclusion: Although there are age-dependent differences, malignant melanoma may present asymptomatic but metastatic in adolescents. It should be kept in mind that any patient suspected or diagnosed with malignant melanoma to have metastasis should be referred to a comprehensive center on this subject before treatment. Thus, the deficiencies that may occur in the management of the patient will be prevented.

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Conflict of interest

Authors have no conflicts of interest relevant to this article.

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Ethical Decleration

Informed consent was obtained from the participant and Helsinki Declaration rules were followed to conduct this study.

Author contributions

Conceptualization and design: SS, SB; data acquisition; EK, MAN, ME, BBD, SS, drafting the manuscript: SS; supervision: SS, EK; review & editing: all authors.

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