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Publisher Contact
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Çağış Mah. Çağış B.M.Sk.
No:340/16 İç Kapı No:17
Bigadiç/ BALIKESİR,Türkiye
Phone: +90 532 605 56
85/+90 850 380 08 02
E-mail: info@cetuspub.com
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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.

2. Hakemlerin Dikkat Etmesi Gereken Hususlar

· Hakemler değerlendirmelerinde tarafsız olmalıdır.
· Hakemler araştırmayla, yazarlarla ve/veya araştırma fon sağlayıcılar ile çıkar çatışması içerisinde olmamalıdır.
· Hakemler araştırmayla ilgili yayımlanmış ancak atıfta bulunulmamış eserleri belirtmelidirler.
· Hakemler kontrol ettikleri makaleleri gizli tutmalıdır.

3. Editör/Editörlerin Dikkat Etmesi Gereken Hususlar

· Editörler bir makaleyi kabul ya da reddetmek için tüm sorumluluğa ve yetkiye sahiptir.
· Editörler kabul ettiği ya da reddettiği makaleler ile ilgili çıkar çatışması içerisinde olmamalıdır.
· 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.

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ORIGINAL ARTICLE/ORİJİNAL MAKALE

A New Ally in HPV and Cervical Cancer Screening: Age-Tailored Scenario-Based Analysis of ChatGPT

HPV ve Servikal Kanser Taramasında Yeni Müttefik: ChatGPT'nin Yaşa Duyarlı Senaryo Bazlı Analizi

Celal Akdemir[1]

[1] Izmir City Hospital, Department of Gynecologic Oncology, Izmir, Turkiye

ABSTRACT

Introduction: In recent years, large language models such as ChatGPT have gained increasing attention in the field of health education. However, their reliability in providing age-sensitive, accurate, and guideline-compliant information on human papillomavirus (HPV) and cervical cancer screening has not been sufficiently investigated. This study aimed to evaluate the performance of ChatGPT-4 in terms of informativeness and guideline compliance when responding to HPV and cervical screening questions tailored to different age scenarios

Methods: Thirty questions were developed based on three age scenarios (18, 30, and 45 years). Each question was submitted to the June 2025 version of ChatGPT-4. The responses were independently evaluated by a five-member panel consisting of three gynecologic oncology surgeons, one infectious diseases specialist, and one public health specialist. Evaluation was based on four criteria: scientific accuracy, clinical guideline compliance, comprehensibility (ease of understanding), and public health reliability. The term "comprehensibility" was used consistently throughout the study instead of "clarity". Each criterion was rated on a 5-point Likert scale.

Results: The overall mean score across all criteria was 4.19 ± 0.51. The highest mean score was for guideline consistency (4.22 ± 0.48), followed by public health reliability (4.20 ± 0.54), scientific accuracy (4.19 ± 0.50), and comprehensibility (4.16 ± 0.53). The 30-year-old scenario received the highest overall scores, particularly for scientific accuracy (4.34) and guideline consistency (4.26). The 18-year-old scenario scored highest in comprehensibility (4.28) but slightly lower in public health reliability (4.12). The 45-year-old scenario achieved the highest public health reliability score (4.32) but had marginally lower ratings for scientific accuracy (4.16) and comprehensibility (4.10). Expert comments highlighted ChatGPT's strengths in health communication and combating misinformation, while pointing out the lack of clinical details and explicit guideline references in some responses.

Conclusion: ChatGPT-4 appears to be an effective tool for promoting HPV vaccination and providing public health information, particularly in younger age groups. However, due to its limitations in clinical decision-making and guideline-based content, its use in patient education should be accompanied by expert oversight. Further research should encompass different model versions, additional evaluation metrics, and user perspectives.

Keywords: ChatGPT, Large Language Models, HPV, Cervical Cancer Screening, Age-Sensitive Information, Scenario-Based Analysis, Expert Evaluation, Health Education, Public Health Communication, Clinical Guideline Compliance

ÖZET

Giriş: Son yıllarda ChatGPT gibi büyük dil modelleri sağlık eğitiminde önemli bir ilgi odağı haline gelmiştir. Ancak insan papilloma virüsü (HPV) ve serviks kanseri taramasında yaşa duyarlı, doğru ve kılavuza uyumlu bilgi sunmadaki güvenilirliği yeterince incelenmemiştir. Bu çalışma, farklı yaş senaryolarına uyarlanmış HPV ve servikal tarama sorularına ChatGPT-4'ün verdiği yanıtların bilgilendiricilik ve kılavuza uyum açısından performansını değerlendirmeyi amaçladı.

Yöntem: On sekiz, otuz ve kırk beş yaş olmak üzere üç yaş senaryosuna dayalı otuz soru hazırlandı. Her soru, ChatGPT-4'ün Haziran 2025 sürümüne sunuldu. Yanıtlar; üç jinekolojik onkoloji cerrahı, bir enfeksiyon hastalıkları uzmanı ve bir halk sağlığı uzmanından oluşan beş kişilik bir panel tarafından bağımsız olarak değerlendirildi. Değerlendirme; bilimsel doğruluk, klinik kılavuza uyum, anlaşılırlık (netlik ve kolay anlaşılabilirlik) ve halk sağlığı güvenilirliği olmak üzere dört ölçüte göre yapıldı. "Anlaşılırlık" kavramı çalışmada tutarlılık sağlamak amacıyla "comprehensibility" terimi ile ifade edildi. Her kriter 5 puanlık Likert ölçeği ile puanlandı.

Bulgular: Tüm kriterlerde genel ortalama puan 4,19 ± 0,51 idi. En yüksek ortalama puan kılavuza uyumda (4,22 ± 0,48) elde edildi; bunu halk sağlığı güvenilirliği (4,20 ± 0,54), bilimsel doğruluk (4,19 ± 0,50) ve anlaşılırlık (4,16 ± 0,53) izledi. Otuz yaş senaryosu, özellikle bilimsel doğruluk (4,34) ve kılavuza uyum (4,26) açısından en yüksek puanları aldı. On sekiz yaş senaryosu anlaşılırlıkta en yüksek puanı (4,28) elde etti ancak halk sağlığı güvenilirliği puanı biraz daha düşüktü (4,12). Kırk beş yaş senaryosu halk sağlığı güvenilirliğinde en yüksek puana ulaştı (4,32) ancak bilimsel doğruluk (4,16) ve anlaşılırlık (4,10) puanları biraz daha düşüktü. Uzman yorumları, ChatGPT'nin sağlık iletişimi ve yanlış bilgilendirmeyle mücadelede güçlü yönlerini vurgularken, bazı yanıtlarda klinik detayların ve açık kılavuz atıflarının eksikliğine dikkat çekti.

Sonuç: ChatGPT-4, özellikle genç yaş gruplarında HPV aşılamasını teşvik etme ve halk sağlığı bilgisi sağlama açısından etkili bir araç gibi görünmektedir. Ancak, klinik karar verme ve kılavuza dayalı içerikteki sınırlılıkları nedeniyle, hasta eğitiminde kullanımının uzman denetimiyle birlikte yürütülmesi önerilir. Gelecek araştırmalarda farklı model sürümleri, ek değerlendirme ölçütleri ve kullanıcı perspektifleri ele alınmalıdır.

Anahtar Kelimeler: ChatGPT, Büyük Dil Modelleri, HPV, Serviks Kanseri Taraması, Yaşa Duyarlı Bilgi, Senaryo Bazlı Analiz, Uzman Değerlendirmesi, Sağlık Eğitimi, Halk Sağlığı İletişimi, Klinik Kılavuz Uyumu

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Correspondence: Celal Akdemir, İzmir City Hospital, Department of Gynecologic Oncology, Istanbul, Türkiye. E-mail: akdemircelal@gmail.com

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INTRODUCTION

Human papillomavirus (HPV) is one of the most important causes of various gynecological and anogenital malignancies, including cervical, vulvar, vaginal, and anal cancers. However, one of the main factors limiting the effectiveness of current vaccination programs is the incomplete or incorrect public perception that HPV is associated only with cervical cancer. In a systematic review by Cangelosi et al. (1), it was emphasized that the success of HPV vaccination programs is adversely affected by knowledge gaps and misconceptions. This underscores the need for targeted, evidence-based educational interventions to increase community-based acceptance of preventive strategies in gynecologic oncology.

In recent years, large language models (LLMs) have emerged as potential tools in public health education. ChatGPT, one of the most well-known applications in this field, is increasingly used in areas such as patient education, clinical counseling, and raising public health awareness (2). However, Shen et al. (2) described such models as a "double-edged sword," reporting that they may occasionally produce information of questionable accuracy, insufficient clinical details, and fabricated references (hallucinations).

Studies conducted in the context of HPV reveal both the potential and the limitations of ChatGPT. Patel et al. (3) evaluated responses to patient questions about HPV in terms of scientific accuracy, content completeness, and educational value; they found that only 45% of the responses were scientifically accurate and noted deficiencies particularly in guideline-based clinical management and follow-up recommendations. Nevertheless, the model's ability to convey basic information in clear and understandable terms suggests it could serve as a complementary tool in public health communication. Similarly, Deiana et al. (4) highlighted that ChatGPT is generally accurate when addressing myths and misconceptions about vaccination, but its outputs may lack contextual nuance and consistent source validation, underscoring the need for professional oversight.

The use of ChatGPT in healthcare is not limited to public health education. Skryd and Lawrence (5) demonstrated that ChatGPT could serve as a potential educational tool for medical students and residents in clinical decision-making processes. In their study, the model was able to generate reasonable responses to complex clinical scenarios, but it was highlighted that expert supervision was essential for patient safety. Likewise, in a comprehensive systematic review, Li et al. (6) classified ChatGPT's healthcare applications, identifying multiple potential areas such as patient education, clinical decision support, research processes, and public health communication, while also listing accuracy, source reliability, and contextual appropriateness as major limitations.

Studies investigating the direct impact of AI-based interventions on HPV vaccination rates are also available. Hou et al. (7) reported that a vaccine chatbot developed for parents significantly increased HPV vaccination rates among middle school-aged girls. This finding suggests that digital and AI-based tools could be effective in public health campaigns. However, ChatGPT's performance may remain limited on HPV topics requiring detailed clinical knowledge. Bellamkonda et al. (8), in evaluating responses to frequently asked patient questions about HPV-positive oropharyngeal carcinoma, found that while the model performed well on some basic information, it lacked sufficient

detail particularly in clinical management steps.

Message framing and persuasiveness are important factors influencing HPV vaccine acceptance. In a comparative study by Xia et al. (9), some pro-vaccine messages generated by ChatGPT were found to be more persuasive than those written by humans. This suggests that, when appropriate content and language tailored to the target audience are used, AI-based messages can be powerful tools in public health communication. These findings indicate that ChatGPT alone may not be sufficient, particularly in scenarios of vaccine hesitancy driven by cultural or belief-related factors.

In this context, evaluating ChatGPT's HPV-related outputs in age-specific scenarios based on criteria such as scientific accuracy, guideline compliance, comprehensibility, and public health reliability is important from both clinical and public health perspectives. This study aims to analyze ChatGPT-4's responses to HPV-related questions in 18-, 30-, and 45-year-old scenarios through a multi-criteria expert assessment.

MATERIALS AND METHODS

Study Design

This study was conducted using a content analysis methodology. The June 2025 version of the ChatGPT-4 model (ChatGPT Plus version) was used to address a total of 30 HPV-related questions structured according to three different age groups. Responses were recorded without any modifications. Since no data were collected from real individuals, ethics committee approval was not required.

Question Structure and Age Scenarios

Questions were developed according to three thematic age groups:

- 18 years: HPV vaccination, vaccine hesitancy, family pressure
- 30 years: Pap smear, transmission routes, partner trust
- 45 years: CIN classifications, colposcopy, follow-up recommendations

The content of the questions was based on patient knowledge gaps and common misconceptions about HPV identified in previous literature (4,6). Additionally, frequently asked questions from online patient forums, popular health platforms, and social media content were reviewed to reflect prevalent public knowledge gaps and misconceptions.

The full list of 30 questions and their sources is provided in Supplementary Table S1 to ensure transparency and reproducibility (Table S1).

Evaluation Panel and Criteria

Responses generated by ChatGPT were independently evaluated by a five-member panel consisting of three gynecologic oncology surgeons, one infectious diseases specialist, and one public health specialist. Each expert scored each response on a 5-point Likert scale across four domains:

1. Scientific accuracy
2. Guideline consistency (WHO, CDC, and up-to-date national/international guidelines)
3. Comprehensibility
4. Public health reliability

Although the panel included diverse subspecialists, the absence of patient representatives or primary care physicians may limit the assessment of comprehensibility from a broader audience perspective.

Data Analysis

For each question, the scores given by the five experts across the four criteria were compiled, resulting in a total of 600 evaluations. Data were analyzed by age group and criterion, and mean ± standard deviation values were calculated. Findings were supported with graphical and tabular presentations.

Reporting Principles

The methodological framework adhered to recommendations from prior systematic evaluations of ChatGPT in healthcare contexts (6). For consistency, the term "clarity" used in earlier drafts was standardized to "comprehensibility" to denote the ease of understanding of ChatGPT's responses.

RESULTS

A total of 600 individual ratings were collected from the five-member expert panel for 30 HPV-related questions, each evaluated across four predefined criteria: Scientific Accuracy, Guideline Consistency, Comprehensibility, and Public Health Reliability. Each criterion was scored on a 1–5 scale, with higher values indicating better performance.

The overall mean score for ChatGPT's responses across all criteria and experts was 4.19 ± 0.51, with 82% of all ratings in the 4–5 range, indicating generally accurate and educationally adequate content. No response received the lowest score of 1. Among the four criteria, Guideline Consistency achieved the highest mean score (4.22 ± 0.48), followed by Public Health Reliability (4.20 ± 0.54), Scientific Accuracy (4.19 ± 0.50), and Comprehensibility (4.16 ± 0.53). For consistency, the term "comprehensibility" is used throughout the manuscript to denote the ease of understanding of ChatGPT's responses. All numerical values correspond to those presented in Table 1.

Table 1. Overall Mean Scores

Criterion	Mean Score ± SD
Scientific Accuracy	4.19 ± 0.50
Guideline Consistency	4.22 ± 0.48
Comprehensibility	4.16 ± 0.53
Public Health Reliability	4.20 ± 0.54
*Overall Mean	4.19 ± 0.51

When stratified by age scenario, the 30-year-old scenario received the highest overall scores, particularly for Scientific Accuracy (4.34) and Guideline Consistency (4.26). The 18-year-old scenario achieved the highest score in Comprehensibility (4.28) but slightly lower in Public Health Reliability (4.12). The 45-year-old scenario scored highest in Public Health Reliability (4.32) but marginally lower in Scientific Accuracy (4.16) and Comprehensibility (4.10) (Table 2). When tested with the Kruskal–Wallis test, no statistically significant differences were observed between the three age groups across any of the four evaluation criteria (all $p > 0.05$).

Table 2. Age-Specific Mean Scores

Age Group	Scientific Accuracy	Guideline Consistency	Comprehensibility	Public Health Reliability
18 years	4.08	4.16	4.28	4.12
30 years	4.34	4.26	4.10	4.16
45 years	4.16	4.24	4.10	4.32

* Values are presented as mean scores. Kruskal–Wallis test showed no statistically significant differences between the three age groups across any of the four evaluation criteria (all $p > 0.05$).

Mean scores per criterion according to expert specialty are shown in Table 3. Gynecologic oncology specialists consistently rated Guideline Consistency and Scientific Accuracy

Table 3. Expert-Based Average Scores per Evaluation Criterion

Criterion	Gynecologic Oncology 1	Gynecologic Oncology 2	Gynecologic Oncology 3	Infectious Diseases	Public Health
Scientific Accuracy	4.23	4.30	4.07	4.17	4.20
Guideline Consistency	4.47	4.27	4.07	4.30	4.00
Comprehensibility	4.07	4.10	4.10	4.13	4.40
Public Health Reliability	4.20	4.33	4.30	4.27	3.90

*Values are presented as mean scores. Inter-rater reliability analysis demonstrated low-to-fair agreement, with intraclass correlation coefficients (ICC) ranging from 0.14 to 0.22 across the four evaluation criteria.

Supplementary Table S1. List of HPV-Related Questions by Age Scenario and Their Sources

No	Age Scenario	Question	Source/Origin
1	18 years	Is it too late to get the HPV vaccine after the age of 18?	Guideline (WHO, CDC)
2	18 years	Does the vaccine cause infertility?	Common misconception / Social Media (YouTube comments, Twitter/X)
3	18 years	Can I get vaccinated without my parents' consent?	Patient forum (MedHelp, Reddit)
4	18 years	Is it only for women? Is it necessary for men as well?	Online Q&A (Quora, Google search results)
5	18 years	Can I have sexual intercourse immediately after vaccination?	Social Media (YouTube comments, Twitter/X)
6	18 years	Is it true that the HPV vaccine can be started at age 9?	Guideline (CDC, WHO)
7	18 years	I read on the internet that the HPV vaccine is dangerous; is that true?	Misconception / Social Media (YouTube comments, Twitter/X)
8	18 years	Do I need to have any other tests after the vaccination?	Guideline (CDC)
9	18 years	Where can I find the most reliable information about HPV?	Public health resources
10	18 years	Is the HPV vaccine covered by the government?	National health policy (country-specific)
1	30 years	My smear test is normal but I am HPV positive; what does this mean?	Common misconception / Social Media (YouTube comments, Twitter/X)
2	30 years	If I have HPV, does that mean my partner definitely cheated?	Patient forum / misconception (YouTube comments, Twitter/X)
3	30 years	Is it more dangerous if I have multiple HPV types?	Literature (HPV risk stratification studies)
4	30 years	If the screening test is positive, how often should I have follow-up?	Guideline (WHO, CDC)
5	30 years	Can HPV be transmitted from men to women?	Guideline (CDC)
6	30 years	Do condoms protect against HPV?	Literature + Guideline (WHO, CDC)
7	30 years	If I am HPV negative, does that mean I will never get cancer?	Patient forum (MedHelp, Reddit)
8	30 years	Can HPV be transmitted without sexual intercourse (e.g., swimming pool, toilet)?	Patient forum (MedHelp, Reddit)

9	30 years	Is a smear test the same as an HPV test?	Public health FAQ
10	30 years	Should I postpone pregnancy because I have HPV?	Social Media (YouTube comments, Twitter/X)
1	45 years	If I am HPV 16 positive, what is my cancer risk?	Literature (high-risk HPV studies)
2	45 years	What is the difference between CIN 1, 2, and 3?	Guideline (WHO classification)
3	45 years	Can HPV become active again years later?	Literature (HPV persistence/reactivation)
4	45 years	Is it mandatory to take a biopsy during colposcopy?	Patient forum (MedHelp, Reddit)
5	45 years	If HPV clears with immunity, does it leave any trace?	Literature (HPV natural history)
6	45 years	I am 45 and have never had a smear test; is it too late?	Guideline (WHO/CDC screening age limits)
7	45 years	If I am HPV positive, do I need a hysterectomy?	Misconception / Patient forum (MedHelp, Reddit)
8	45 years	Until what age should HPV screening be done?	Guideline (WHO/CDC, national protocols)
9	45 years	How often should I go for follow-up in HPV monitoring?	Guideline (WHO, CDC)
10	45 years	If HPV is contagious, how should my partner and I protect ourselves?	Guideline (WHO/CDC + public health FAQ)

the highest (mean range: 4.07–4.47). Public Health Reliability was rated highest by both gynecologic oncology and infectious diseases specialists (4.20–4.33), while the public health specialist assigned the highest Comprehensibility score (4.40). Variability between experts was generally low; however, the public health specialist rated Public Health Reliability slightly lower (3.90) compared with other panel members. The inter-rater reliability analysis demonstrated low-to-fair agreement between experts, with ICC values ranging from 0.14 to 0.22 across the four evaluation criteria.

Overall, experts agreed that ChatGPT's responses were well-aligned with current scientific guidelines and were presented in a clear, understandable manner. Noted limitations included the absence of explicit citations to guidelines, the lack of direct clinical directives, and occasional superficiality in complex clinical scenarios (e.g., CIN classification and colposcopy guidance). No response was deemed misleading, contradictory, or clinically unsafe.

DISCUSSION

This study presents an original content analysis evaluating ChatGPT-4's responses to HPV-related questions in terms of scientific accuracy, guideline compliance, comprehensibility, and public health reliability, based on age-specific scenarios. The findings indicate that the model performs particularly well in delivering age-tailored public health messages, but demonstrates limited guideline-based informational depth in complex clinical scenarios.

In our study, the highest mean scores were obtained in questions related to the 30-year-old group, particularly for scientific accuracy and guideline consistency. These scenarios often addressed issues of Pap smear interpretation, HPV transmission, and partner-related concerns, which may have allowed ChatGPT to generate more guideline-aligned and accurate responses.

The 18-year-old group achieved the highest comprehensibility score, reflecting the model's strength in delivering clear and accessible public health messages, especially regarding HPV vaccine safety, efficacy, and family-related hesitancy. Similarly, in the literature, Hou et al. (7) reported in a randomized controlled trial that digital information tools targeting specific groups increased HPV vaccination rates. This suggests that AI-based tools such as ChatGPT could be a strong complement to public health communication, particularly in younger populations.

Conversely, the 45-year-old group demonstrated comparatively lower scores in scientific accuracy and comprehensibility, underscoring the model's limitations in addressing more complex clinical topics. Evaluations by Patel et al. (3) and Bellamkonda et al. (8) likewise identified deficiencies in ChatGPT's recommendations for clinical management and follow-up. In particular, the absence of guideline-referenced information on CIN classifications, colposcopy referrals, and follow-up protocols for older patients parallels our findings.

Comprehensibility emerged as a relatively strong criterion across all age groups. This finding is consistent with the observations of Deiana et al. (4), who highlighted ChatGPT's ability to provide accurate yet oversight-dependent content, and Xia et al. (9), who showed that its pro-vaccination messages can even surpass human-written texts in persuasiveness. However, both Deiana et al. (4) and Passanante et al. (10) emphasized that expert supervision remains essential, particularly to ensure contextual appropriateness in clinical communication. Therefore, in gynecologic oncology practice, ChatGPT should function only as a supportive tool rather than an autonomous source of patient education.

The literature on the use of LLMs in gynecologic oncology-specific domains is limited. Kuerbanjiang et al. (11) evaluated LLM performance in cervical cancer management and found that while basic information delivery was adequate, clinical decision support was limited. Similarly, Angyal et al. highlighted the potential of LLMs in cervical cancer screening education. Together with our findings, these studies indicate that AI tools can be powerful for education and awareness-raising purposes but should be used cautiously for clinical decision support.

One of the strengths of our study is the multidisciplinary nature of the evaluation panel. Notably, the public health specialist assigned a slightly lower score for Public Health Reliability compared with other experts, possibly reflecting the application of stricter criteria for population-level reliability and evidence integration. Perspectives from specialists in obstetrics and gynecology, infectious diseases, and public health provided a multidimensional analysis of ChatGPT's responses. However, certain limitations should be acknowledged. First, the evaluation was limited to GPT-4; no comparisons were made with GPT-3.5 or future models. Second, the analysis was based solely on expert assessments, without incorporating patient or public perspectives. Furthermore, the reliability and traceability of references in the responses were not systematically evaluated. This omission is relevant given the well-documented "hallucination" phenomenon in large language models, which refers to the generation of inaccurate or fabricated information despite confident presentation (2,4,12,13). Previous studies have highlighted that such inaccuracies may undermine clinical reliability, particularly when AI outputs are used without expert oversight,

underscoring the importance of systematic reference verification in future research. These limitations, including the lack of patient or lay perspectives, the restriction to GPT-4, and the absence of systematic reference verification, are of critical importance as they directly affect the reproducibility and generalizability of our findings

Overall, our study shows that ChatGPT has high potential for age-specific preventive health messaging on HPV, especially in younger age groups, but its limitations in producing guideline-based content in gynecologic oncology should be noted. In clinical practice, ChatGPT should be used under professional supervision for educational and awareness purposes, and positioned as a complementary rather than a directive tool in clinical decision-making. Future research should include comparative analyses of different LLM versions, evaluations incorporating patient and public perspectives, and applications in other areas of gynecologic oncology. These approaches will contribute to enhancing the reliability and effectiveness of AI-based educational tools, while addressing current limitations that constrain reproducibility and generalizability.We would like to express our sincere gratitude to the evaluation experts who contributed their time and expertise to this study. Their constructive feedback and valuable perspectives greatly enriched our analysis.

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Conflicts of interest

The authors have no conflicts of interest.

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Ethical approval

This study did not involve human participants or patient data; therefore, ethical approval was not required.

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ORIGINAL ARTICLE/ORİJİNAL MAKALE

Prediction of Para-Aortic Lymph Node Metastasis Using Metastatic Pelvic Lymph Node Diameter in Patients With Locally Advanced Cervical Cancer

Lokal ileri evre serviks kanserli hastalarda metastatik pelvik lenf nodu çapı kullanılarak para-aortik lenf nodu metastazının öngörülmesi

Belma Gozde Ozdemir[1], Fazıl Avcı[1], Mehmet Kulhan[1], Abdul Hamid Guler[1], Mete Can Ates[1], Cetin Celik[1], Ahmet Bilgi[1]

[1] Selcuk University Faculty of Medicine, Department of Gynecology and Obstetrics, Konya, Türkiye

ABSTRACT

Objectives: Investigation of the prediction of para-aortic lymph node (LN) metastasis by metastatic pelvic lymph node diameter in patients with locally advanced cervical cancer.

Methods: Between 28 December 2010 and 30 March 2021, 57 patients with locally advanced cervical cancer (2B-4A 2018 FIGO) at Selcuk University Faculty of Medicine were enrolled in this retrospective analysis. The involvement of pelvic and para-aortic LN in patients with surgical staging and outcomes were assessed.

Results: The average age of 57 patients was 56 (33-78) years. Of patients, 73.7% were stage 2b, 12.3% were stage 3 and 14.0% were stage 4a. Of samples, 91.2% had histological type squamous cells. The mean number of LNs collected was 4 (0-49) and 10 (7-37) in patients with pelvic and para-aortic LN involvement, respectively. Para-aortic LN was positive in 9 patients and negative in 48 patients according to ROC analysis. Para-aortic LN involvement was predicted by metastatic pelvic LN cut-off diameter of 0.75 cm with 100% sensitivity and 89.6% specificity [AUC=0.959, p=0.001 [95% CI, 0.912-1.000].

Conclusion: The cut-off for pelvic LN dissection and metastatic pelvic LN diameter in locally advanced cervical cancer was accepted as 0.75 cm for predicting para-aortic LN involvement.

Keywords: Cervix Cancer, Lymph Node Diameter, Prediction, Surgery

ÖZET

Amaç: Lokal ileri servikal kanserli hastalarda metastatik pelvik lenf nodu (LN) çapına göre para-aortik lenf nodu lenf nodu metastazının tahmininin araştırılması.

Gereç ve Yöntemler: 28 Aralık 2010 ile 30 Mart 2021 tarihleri arasında Selçuk Üniversitesi Tıp Fakültesi'nde lokal olarak ilerlemiş servikal kanserli 57 hasta (2B-4A 2018 FIGO) bu retrospektif analize dahil edildi. Cerrahi evreleme ve sonuçları olan hastalarda pelvik ve para-aortik LN tutulumu değerlendirildi.

Bulgular: 57 hastanın ortalama yaşı 56 [33-78] yıldı. Hastaların %73,7'si evre 2b, %12,3'ü evre 3 ve %14,0'ı evre 4a idi. Örneklerin %91,2'sinde histolojik tip skuamöz hücreler vardı. Pelvik ve para-aortik LN tutulumu olan hastalarda toplanan ortalama LN sayısı sırasıyla 4 [0-49] ve 10 [7-37] idi. ROC analizine göre para-aortik LN 9 hastada pozitif, 48 hastada negatifti. Para-aortik LN tutulumu %100 duyarlılık ve %89,6 özgüllük ile 0,75 cm'lik metastatik pelvik LN kesme çapı ile tahmin edildi [AUC=0,959, p=0,001 [95% CI, 0,912-1,000].

Sonuç: Lokal ileri servikal kanserde pelvik LN diseksiyonu ve metastatik pelvik LN çapı için kesme değeri, para-aortik LN tutulumunu tahmin etmek için 0,75 cm olarak kabul edildi.

Anahtar Sözcükler: Serviks Kanseri, Lenf Nodu Çapı, Tahmin, Cerrahi

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Correspondence: Belma Gozde Ozdemir, Selcuk University Faculty of Medicine, Department of Gynecology and Obstetrics, Konya, Turkey. E-mail: gzdgrgn35@gmail.com

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INTRODUCTİON

Cervical cancer is the fourth most common female cancer among gynecological cancers in terms of morbidity and mortality (1). The most common histological types are squamous cell types (about 70%), along with adenocarcinoma (25%) and other rare types (5%) (2). The cervical cancer FIGO staging system was recently revised and patients with pelvic and para-aortic lymph node (LN) metastases proven by imaging or histopathology were classified as stage IIIC1 and stage IIIC2, respectively (3). Extended field radiation chemotherapy treatment is applied in cases with para-aortic lymphatic spread (4).

LN involvement is one of the primary prognostic factors in locally advanced cervical cancer (5,6). Five-year event-free survival is approximately 57% in LN-negative patients, whereas it decreases to 34% and 12% in pelvic-positive and para-aortic LN-positive patients, respectively (7). Para-aortic LN involvement is found in 17-24% of locally advanced cervical cancer patients (8). Para-aortic LN metastases are present in 15% [1B2/2B FIGO 2009] and 40% [3B/4 FIGO 2009] patients with locally advanced cervical cancer (9). The major challenge in locally advanced cervical cancer is identifying patients with para-aortic LN metastases who may be candidates for ancillary therapy with extended field radiotherapy or chemotherapy or immunotherapy after standard chemoradiation (10).

Cervical cancer spreads primarily to regional pelvic LNs. Pelvic LN involvement is a known risk factor for para-aortic LN metastasis. Para-aortic LN involvement generally occurs as a result of extensive pelvic LN metastases (11-14) . Rarely, para-aortic LN metastasis can occur without pelvic LN metastasis. The possible route of spread may be the posterior cervical trunk, which drains into sacral LNs, common iliac LNs, and para-aortic LNs, but cervical cancer cells spread primarily with pelvic lymphatics before reaching the para-aortic LNs (15). We aimed to investigate histopathological metastatic pelvic lymph node diameter for predicting para-aortic lymph node metastasis in patients with locally advanced cervical cancer.

METHODS

In this retrospective study, 57 patients diagnosed with locally advanced cervical cancer [IIB-IVA 2018 FIGO] between 28 December 2010 and 30 March 2021 in our clinic were included in the study (16). Pelvic and para-aortic LN involvement of all the patients with surgical staging and outcomes were evaluated. This study was approved by Selçuk University Faculty Of Medicine, Ethics Committee with protocol number 2022/337.

The cases were evaluated according to age, surgical stage, histological type [squamous and non-squamous] and lymph node status [number of pelvic and para-aortic lymph nodes, metastasis and diameter]. Inclusion criteria were histological diagnosis of stage IIB-IVA and squamous and non-squamous type carcinoma according to the FIGO 2018 system (17). Exclusion criteria were non-surgical staging and without pelvic and para-aortic lymph node dissection. Signed values are not taken into account. The histopathological results were evaluated according to pelvic and para-aortic LN involvement after extraperitoneal LN dissection. The short-axis diameter of metastatic pelvic LNs was measured in mm.

2.1 Pelvic and para-aortic lymph node surgical staging

Extraperitoneal LN dissection with a laparotomic J incision was performed in all patients. When

entering the abdomen, pelvic lymphadenectomy was performed in both external iliac, obturator and bilateral common iliac lymph nodes. Para-aortic lymphadenectomy was performed in the aortacaval space, vena cava and left and right para-aortic area, up to the left renal vein, and caudally up to both common iliac bifurcation and both psoas muscles.

2.1.1 Statistical analysis

SPSS version 21 [IBM SPSS Statistics, IBM Corporation, Armonk, NY, USA] was used for all statistical computations. Categorical variables are presented as frequencies and percentages, while quantitative variables are given as median and minimum-maximum. ROC analysis was performed for the cut-off, sensitivity and specificity of the data. Statistical significance was accepted as $p<0.05$.

RESULTS

The median age of 57 patients included in the study was 56 [33-78] years (Table 1). Of patients, 73.7% were evaluated as stage 2b, 12.5% as stage 3 and 13.3% as stage 4a. Squamous cell histological type was detected in 91.2%. Pelvic and para-aortic LN involvements were detected in 10 [17.5%] and 9 [15.8%] patients, while the median number of LNs collected was 4 [0-49] and 9 [0-35], respectively. Metastatic LN involvements were detected only in the pelvic area in 5 [8.8%] patients, only in the para-aortic area in 4 [7,0%] patients, and in the pelvic and para-aortic areas in 5 [8.8%] patients.

In the ROC analysis, para-aortic LN was positive in 9 patients and negative in 48 patients (Figure 1). When the metastatic pelvic LN diameter cut-off was accepted as 0.75 cm, the sensitivity was 100% and specificity was 89.6% for predicting para-aortic LN involvement [AUC=0.959, p=0.001 [95% CI, 0.912 1.000]. If the metastatic pelvic LN diameter cut-off was assumed to be 1.55 cm, sensitivity of 88.9% and specificity of 91.7% were found. If the diameter cut-off was 2.1 cm, the sensitivity was 77.8% and the specificity was 93.8%, and if the diameter cut-off was 3.1 cm, the sensitivity was 44.4% and the specificity was 97.9% for predicting para-aortic LN metastasis.

Table 1: Characteristics of cases according to 2018 cervical cancer staging

Variables		[n=57] Median	[%]
Age, years		56 [33-78]	
Stage			
	IIb	42	73.7
	III	7	12.3
	IVA	8	14.0
Histologic type			
	Squamous	52	91.2
	Non-squamous	5	8.8
Pelvic lymph node involvement, n		10	17.5
Total pelvic lymph node count		5 [0-49]	
Para-aortic lymph node involvement, n		9	15.8
Total para-aortic lymph node count		10 [7-37]	
Lymph node involvement, n			
	Pelvic	5	8.8
	Para-aortic	4	7.0
	Pelvic and para-aortic	5	8.8

n=number of patients

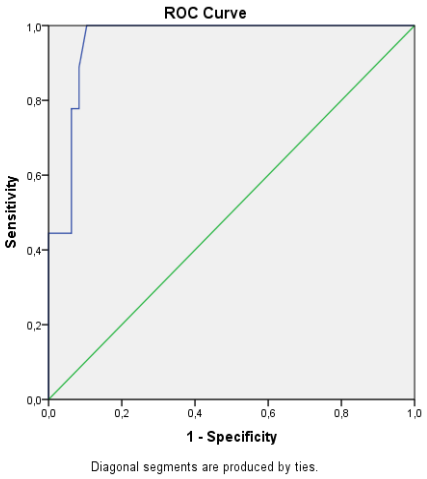

Figure 1: *ROC analysis of metastatic lymph node diameter in predicting para-aortic lymph node involvement*

DISCUSSION

Currently, since LN involvement is accepted as a prognostic factor in cervical cancer, treatment of cervical cancer is planned according to LN involvement. However, pelvic and para-aortic LN involvement is detected by imaging methods or surgically by pathological diagnosis (16). When evaluating LN involvement, studies evaluating para-aortic LN metastasis according to metastatic pelvic LN diameter surgically and giving a metastatic pelvic LN cut-off value are limited. In this study, the prediction of para-aortic lymph node involvement by metastatic pelvic lymph node diameter after extraperitoneal LN dissection was investigated in locally advanced cervical cancer. 9 patients must have had paln due to the rarity of the cases.

While para-aortic LN metastasis is thought to be correlated with pelvic LN metastasis, the skip LN metastasis rate is reported to be below 4% in studies (18,19). The study by Ayhan et al. (20) 522 patients, 2009 FIGO stage IB1-IIA2] included cases with aver age of 50 years med[23-81], 79.1% squamous cell histological type, and 37% stage 3c. They collected median pelvic LN number of 30.0 [10–97] and median para-aortic LN 11.0 [5–52] and identified pelvic LN metastasis in 190 patients [36.4%], para-aortic LN metastasis in 48 patients [9.2%], isolated para-aortic LN metastasis in 4 patients [0.8%] and both pelvic and para-aortic LN metastases in 44 patients [8.4%]. In this study, the median of the patients was 56 med [33-78] years, 12.3% of the patients were stage 3, 91.2% squamous cell histological type with pelvic and para-aortic LN involvement in 10 [16.7%] and 9 [15.0%] patients, respectively. The median number of LNs collected was 4 [0-49] and 9 [0-35], respectively. Metastatic LN involvement was detected only in the pelvic area in 5 [8.8%] patients, only in the para-aortic area in 4 [7.0%] patients, and in the pelvic and para-aortic areas in 5 [8.8%] patients. The significant difference between these studies is due to including locally advanced cervical cancer patients and the low number of patients in our study.

Because of the higher incidence of para-aortic LN metastases in the case of pelvic LNs, para-aortic lymphadenectomy or sampling is recommended when suspicious enlargement of the pelvic LNs is found by intraoperative palpation (21). Tsuruga et al. observed a positive effect of para-aortic lymphadenectomy on the surgical treatment of cervical cancer with extensive iliac LN metastases. Intraoperative frozen analysis can be a useful method to identify diffuse iliac LN metastases during surgery (22) . In the study by Matsuo et al., (11) the incidence of intraoperative ≥1 cm metastasized LN or multiple pelvic LN metastases and para-aortic LN was 16.7% and 18.2%, respectively. Likewise, Ayhan et al. [20] reported that metastatic pelvic LN size >1 cm [OR: 4.51, 95% CI: 1.75–11.64; p = 0.002] was among the independent risk factors identified for para-aortic LN involvement. Moreover, this

result suggests that patients with pelvic LN metastases may be best suited for para-aortic LN dissection as a diagnostic procedure, given that the benefits of staging surgery should outweigh any possible morbidity[23]. It is worth noting that while a positive common iliac LN strongly suggests para-aortic LN status, negative common iliac LN does not necessarily guarantee negative para-aortic LN. Likewise, in the study by Gouy et al.(13) , para-aortic LN involvement was observed in the histological analysis of 22 patients [9%] in LACC, while PET/CT results in false negatives. The false negative rate in the para-aortic LN region was 18% [16/90] and 4% [6/150] in PET/CT in patients with and without pelvic LN involvement, respectively. Likewise, Benedetti-Panic et al. found 80% of metastatic LNs were <1.0 cm in greatest dimension in LN-positive cervical carcinoma patients[24]. Belhocine et al. (25) found 80% [8 LN] of their metastatic LNs were micrometastatic LN and only 2 LN >1.0 cm. In addition, in the systematic review and meta-analysis by Thelissen et al.(26) , in the absence of suspicious para-aortic LNs on PET-CT or MRI, para-aortic LN dissection occurred in 11-12% of all patients with LACC and 21% of patients with pelvic LN metastases. They concluded that patients with pelvic LN metastases had significantly higher staging rate after para-aortic LN dissection than an unselected cervical cancer case group [21% vs 11-12%], confirming the predictive power of pelvic LN involvement for para-aortic LN involvement. In the light of the literature, pelvic LN dissection may be chosen under suitable conditions, because it has high predictive value for para-aortic LN involvement. In this study, para-aortic LN was positive in 9 patients and LN was negative in 48 patients. When the cut-off diameter of the metastatic pelvic LN was accepted as 0.75 cm, the sensitivity was 100% and the specificity was 89.6% for predicting para-aortic LN involvement. The significant difference in the studies is related to the surgical evaluation of LNs. Evaluation of pelvic lymph node metastasis to predict peroperative para-aortic lymph node metastasis may provide inspiration for further studies.

The limitations of this study are that it is retrospective, included a small number of patients, the diameter of lymph nodes was measured on the formalin-fixed paraffin-embedded samples and not fresh or frozen, and it included a single center. The strengths of the study are that all patients had surgical dissection of locally advanced LN, and metastatic LN diameters were examined with ROC analysis to predict para-aortic LN involvement. As a result, the cut-off value of metastatic pelvic LN diameter for the prediction of paraaortic LN metastasis in locally advanced cervical cancer can be accepted as 0.75 cm.

The findings of this study demonstrate that setting the metastatic pelvic lymph node (LN) diameter threshold at 0.75 cm provides a highly valuable clinical marker for predicting the risk of para-aortic LN metastasis in patients with locally advanced cervical cancer. Based on ROC analysis, this cut-off value yielded a sensitivity of 100% and a specificity of 89.6% in identifying para-aortic LN involvement, indicating that it is both a reliable and balanced predictor—capable of detecting all true positive cases while keeping the false positive rate low. This suggests that the 0.75 cm threshold can serve as a key criterion in determining which patients may benefit from surgical evaluation of the para-aortic region during staging procedures.

From a clinical perspective, the 0.75 cm metastatic pelvic LN cut-off has the potential to play a critical role in standard treatment planning. In particular, in cases where

suspicious enlargement of pelvic LNs is detected intraoperatively, this measurement can help guide the decision to perform para-aortic lymphadenectomy or sampling. By applying this criterion, unnecessary surgical interventions—and the associated risk of morbidity—can be minimized, while ensuring that patients with para-aortic metastases are correctly identified and directed toward the appropriate treatment field. Furthermore, this finding highlights that histopathological measurements can serve as a valuable complement to imaging modalities, especially in situations where imaging alone may not provide sufficient accuracy for decision-making.

CONCLUSİON

In conclusion, adopting the 0.75 cm metastatic pelvic LN diameter as a threshold offers a practical, evidence-based, and highly accurate parameter for guiding both surgical staging and diagnostic para-aortic lymphadenectomy. This measure represents a simple yet effective prognostic tool that clinicians can confidently integrate into individualized patient management strategies.

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ORIGINAL ARTICLE/ORİJİNAL MAKALE

İleri Evre Over Kanserinde Kolonoskopinin Yeri ve Mukozal Barsak Metastazı Saptanan Hastaların Özelliklerinin İncelenmesi

The Role of Colonoscopy in Advanced Stage Ovarian Cancer and Examination of the Characteristics of Patients with Mucosal Intestinal Metastases

Yavuz Çiçek[1], Ganim Khatib[2], MehmetAli Vardar[2]

[1]Medical Park Seyhan Hastanesi, Kadın Hastalıkları ve Doğum Anabilim Dalı, Adana, Türkiye
[2] Çukurova Üniversitesi Tıp Fakültesi, Kadın Hastalıkları ve Doğum Anabilim Dalı, Adana, Türkiye

ABSTRACT

Aim: This study investigated the sensitivity of colonoscopy in detecting bowel metastases of ovarian cancer, its contribution to surgical and oncological outcomes, and the patient groups for whom its use would be appropriate.

Materials and Methods: A total of 676 patients diagnosed with advanced-stage ovarian cancer were retrospectively analyzed. Statistical analyses were performed using SPSS version 23. The Chi-square test and Fisher's exact test were used for the comparison of categorical variables. Categorical data were expressed as numbers and percentages, while continuous variables were presented as mean ± standard deviation and minimum–maximum values. A p-value of <0.05 was considered statistically significant.

Results: Colonoscopy was performed in 234 patients, and malignancy was detected in 17 of them. When patients with and without malignancy were compared, no significant differences were found in terms of age, clinical findings, or comorbidities. The most common symptoms in patients with malignancy were abdominal pain and bloating. In addition, CA125 levels were significantly higher in patients with malignancy compared to those without. Ascites was observed in 64.7% of patients with malignancy and minimal ascites in 35.3% (p=0.017). The primary tumor diameter was larger in patients with malignancy than in those without. When patients who underwent colonoscopy were compared with those who did not, no significant difference was found in terms of mean overall survival. Similarly, no significant difference in mean survival was observed between patients with and without malignancy detected by colonoscopy.

Conclusion: Based on our findings and in line with previous studies, it can be concluded that instead of performing routine colonoscopy in all patients diagnosed with ovarian cancer, a risk-adapted approach to colonoscopy would be a more appropriate strategy.

Keywords: Ovarian cancer, Screening, Colonoscopy

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ÖZET

Amaç: Bu çalışmada kolonoskopi taramasının over kanserinin bağırsaklara metastazlarını saptamadaki duyarlılığı ve cerrahi ve onkolojik sonuçlara katkısı ile hangi hasta gruplarında uygulanmasının uygun olacağı araştırılmıştır.

Gereç ve Yöntem: İleri evre over kanseri tanısı almış 676 hasta retrospektif olarak incelendi. Verilerin istatistiksel analizinde SPSS 23 programı kullanıldı. Kategorik değişkenlerin karşılaştırılmasında Ki-kare testi ve Fisher'ın kesinlik testi uygulandı. Kategorik veriler sayı ve yüzde olarak, sürekli değişkenler ise ortalama ± standart sapma ve minimum–maksimum değerleriyle ifade edildi. Tüm testlerde istatistiksel anlamlılık düzeyi p<0,05 olarak kabul edildi.

Bulgular: Toplam 234 hastaya kolonoskopi uygulandı ve bu hastaların 17'sinde malignite saptandı. Malignite saptanan ve saptanmayan gruplar karşılaştırıldığında yaş, klinik bulgular ve komorbidite açısından anlamlı bir fark bulunmadı. Malignite tespit edilen hastalarda en sık görülen semptomların karın ağrısı ve şişkinlik olduğu belirlendi. Ayrıca bu grupta CA125 düzeyi, malignite saptanmayanlara göre anlamlı derecede yüksek bulundu. Malignite tespit edilen grupta %64,7 oranında belirgin asit, %35,3 oranında ise minimal asit görüldü (p=0,017). Bu hastalarda primer tümör çaplarının, malignite saptanmayan hastalara kıyasla daha büyük olduğu saptandı. Kolonoskopi yapılan ve yapılmayan hastalar karşılaştırıldığında ortalama sağkalım süresi açısından anlamlı bir fark izlenmedi. Benzer şekilde, kolonoskopide malignite saptanan hastaların ortalama yaşam süreleri ile saptanmayanlarınkiler arasında da anlamlı bir fark bulunmadı.

Sonuç: Bulgularımız ve literatürdeki benzer çalışmalar birlikte değerlendirildiğinde, over kanseri tanısı almış tüm hastalara rutin kolonoskopi uygulanması yerine risk faktörlerine göre uyarlanmış kolonoskopi yapılmasının daha uygun bir yaklaşım olacağı sonucuna varılmıştır.

Anahtar Sözcükler: Over kanserleri, Over kanserlerinde tarama, Kolonoskopi

Sorumlu Yazar: Yavuz Çiçek, Medical Park Seyhan Hastanesi, Kadın Hastalıkları ve Doğum Anabilim Dalı, Adana, Türkiye
E-mail: dr.yavuzcicek@gmail.com

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GİRİŞ

Over kanseri, jinekolojik kanserler içerisinde en mortal seyreden türdür (1). Over kanseri, kadınlarda görülen kanserlerin yaklaşık %4'ünü oluşturur. Hastalığın bulgu ve belirtileri geç ortaya çıktığı için genellikle ileri evrede tanı almaktadır. Bu nedenle hastaların prognozu yüz güldürücü değildir. Genel sağkalım oranı ortalama %41'dir (2). Epitelyal over kanseri en sık görülen alt tip olup tüm olguların %85–90'ını oluşturur.

Over kanserinde prognostik faktörlerin en önemlisi, tanı anındaki evredir (3). Son 20 yılda tıp ve teknoloji alanlarında önemli ilerlemeler kaydedilmiş olsa da over kanseri mortalitesinde kayda değer bir azalma sağlanamamış, beş yıllık yaşam süresi %47 düzeylerinde kalmıştır.

Over kanserine özgü belirgin semptomların olmaması ve hastalığın hızlı ilerleme ve metastaz eğilimine sahip olması nedeniyle olguların büyük çoğunluğu Evre III ve Evre IV'te tanı almaktadır. Bu sebeple mortalite ve morbidite oranları oldukça yüksektir (4). Erken evrede tanı alan hastalarda beklenen yaşam süresi artmaktadır. Ancak, hastaların yalnızca %19'u erken evrede tanı alabilmektedir. Güncel cerrahi teknikler ve kemoterapi ilaçları sağkalım oranında kısmi bir artış sağlasa da istenilen düzeye ulaşılamamıştır. Erken evre over kanserinde beş yıllık sağkalım oranı %90 iken, ileri evrelerde bu oran %30'lara düşmektedir (4).

Epitelyal over kanserlerinde güncel tedavi protokolü; primer sitoredüksiyon ve platin bazlı kemoterapidir. Sitoredüktif cerrahinin amacı, makroskopik olarak görülen tüm tümör dokularını çıkarmak ve geriye sıfır makroskopik tümör rezidüsü bırakmaktır (5). Cerrahi sonrası rezidü tümör dokusu kalmaması, sağkalıma en önemli katkıyı sağlayan prognostik faktördür (6). Bu nedenle metastaz odakları dikkatle araştırılmalı; bağırsak metastazı saptanan olgularda rezidü tümör dokusu bırakmamak için bağırsak rezeksiyonu uygulanmalıdır (7). Mevcut kanıtlar, rezidü tümör dokusu bırakılmayan hastalarda sağkalımın belirgin şekilde daha uzun olduğunu göstermektedir (7,8).

Kolonoskopi, kalın bağırsak hastalıklarının tanı ve tedavisinde kullanılan bir görüntüleme yöntemidir. Bu yöntemle terminal ileum ve kolon mukozası ayrıntılı olarak değerlendirilebilmekte ve bazı girişimsel işlemler de uygulanabilmektedir. Kolonoskopide etkin bir görüntüleme ve değerlendirme için işlem öncesi kolon temizliği mutlaka sağlanmalıdır.

Kolonoskopi over kanseri hastalarına rutin olarak yapılmamakla birlikte, kolon metastazı düşünülen veya senkron kolorektal tümörden şüphelenilen olgularda birçok klinikte uygulanmaktadır.

Bu çalışmada kolonoskopi taramasının over kanserinin bağırsak metastazlarını saptamadaki duyarlılığı, cerrahi ve onkolojik sonuçlara katkısı ve hangi hastalara uygulanmasının uygun olduğu araştırılmıştır.

GEREÇ VE YÖNTEM

Bu çalışma, Çukurova Üniversitesi Tıp Fakültesi Etik Kurulu onayı ile Çukurova Üniversitesi Tıp Fakültesi Kadın Hastalıkları ve Doğum Anabilim Dalı, Jinekoloji-Onkoloji Bilim Dalı'nda gerçekleştirildi.

Araştırmaya, Evre II–IV arasında over kanseri tanısı alan toplam 676 hasta retrospektif olarak dahil edildi. Çalışmaya yalnızca operasyonları, preoperatif ve postoperatif tetkikleri ile medikal tedavileri hastanemizde yapılan hastalar alındı.

Hastalar değerlendirilirken şu parametreler incelendi: Kolonoskopi yapılan hastalarda

malignite varlığı, yaş aralığı, vücut kitle indeksi, komorbidite durumu, menopoz durumu, tümör belirteçleri (CA125, CA15-3, CA19-9, CEA), preoperatif tümör çapı, preoperatif asit miktarı, tanı anındaki semptomlar, tümör histolojisi, histolojik grade, tümör evresi.

Ayrıca kolonoskopi yapılan ve yapılmayan hastaların ortalama sağkalım süreleri ile kolonoskopide malignite saptanan ve saptanmayan hastaların ortalama sağkalım süreleri karşılaştırıldı. Bunun yanı sıra, malignite tespit edilen ve edilmeyen hastalar ile bağırsak rezeksiyonu yapılan ve yapılmayan hastaların hastalıksız yaşam süreleri değerlendirildi.

Hastanemizde kolonoskopi, Dahiliye-Gastroenteroloji Bölümü'nde deneyimli öğretim üyeleri tarafından uygulandı. Kullanılan cihazlar Pentax EG-290 KP, Fujifilm EG-600 WR ve Fujifilm EG-760 LT idi.

Verilerin istatistiksel analizinde SPSS 23 programı kullanıldı. Kategorik değişkenlerin karşılaştırılmasında Ki-kare testi ve Fisher'ın kesinlik testi uygulandı. Kategorik veriler sayı ve yüzde, sürekli değişkenler ise ortalama ± standart sapma ve minimum–maksimum değerleriyle ifade edildi. Tüm testlerde p<0,05 istatistiksel olarak anlamlı kabul edildi.

BULGULAR

Çalışmaya toplam 676 hasta dahil edildi. Bu hastaların 234'üne kolonoskopi uygulandı.

Table 1: Kolonoskopi taramasında malignite saptanan ve saptanmayan hastaların incelenmesi

	Frekans (n)	Yüzde (%)
Kolonoskopi taraması		
Malignite var	17	2,5
Malignite yok	217	32,1

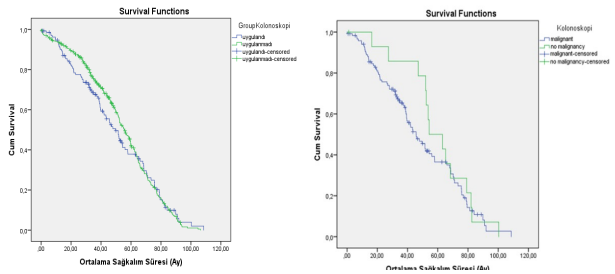
234 hastaya kolonoskopi taraması yapıldı. Kolonoskopi taraması yapılan hastaların 17 tanesinde (%2,5) malignensi saptandı.

Table 2: Kolonoskopi taraması yapılan hastaların yaş, klinik bulgu, tm marker, preop asit,komorbidite ve preop tm çapı bulgularının incelenmesi

	Kolonoskopi		
	Malignite var (n=17)	Malignite yok (n=217)	p
	n(%)	n(%)	
Yaş aralığı			
<50	7 (41,2)	73 (33,6)	0,450
50-65	9 (52,9)	106 (48,8)	
>65	1 (5,9)	38 (17,5)	
Klinik bulgular			
Asemptomatik	1 (5,9)	3 (1,4)	0,278
Karın şişliği	2 (11,8)	54 (24,9)	
Karın ağrısı	14 (82,4)	142 (65,4)	
Vajinal kanama	-	10 (4,6)	
Diğerleri	-	8 (3,7)	
Komorbidite	2 (11,8)	68 (31,3)	0,090
CEA	1 (1-1)	1,3 (0,25-905)	0,881
Ca19.9	11,2 (11,2-11,2)	11,53 (0,38-1433)	0,810
Ca15.3	10,2 (10,2-10,2)	46 (4,8-851,3)	0,548
Preop CA125	301 (88-3312)	260,75 (6-11130)	0,621
Postop CA125	184 (14,28-2323)	111 (2,31-2843)	0,018
Preop asit			
Yok	-	71 (32,7)	0,017*
Minimal	6 (35,3)	45 (20,7)	
Belirgin	11 (64,7)	101 (46,5)	
Preop Tm Çapı	8 (5-30)	7 (2-30)	
			0,031*

* p<0,05, ** p<0,001, ki-kare testi, b: Mann whitney u testi

Kolonoskopi taramasında malignite saptanan ve saptanmayanlar karşılaştırıldığında; yaş aralığı ve klinik bulgular ile komorbidite durumları açısından anlamlı fark saptanmadı. Kolonoskopi taramasında malignite tespit edilen hastalarda en sık görülen semptomların karın ağrısı ve şişkinlik olduğu görüldü. Hastaların kolonoskopi taramasında malignite varlığı ve yokluğu ile laboratuvar bulguları arasındaki farklılıklarının karşılaştırılmasında postoperatif CA125 değeri malignite saptanan hastalarda, saptanmayanlara göre anlamlı şekilde daha yüksek bulundu. Diğer marker değerlerinde her iki grup arasında anlamlı fark tespit edilmedi. Kolonoskopi taramasında malignite görülen hasta grubunda %64,7 oranında belirgin asit, %35,3 oranında da minimal asit tespit edildi(p=0,017). Kolonoskopi taramasında malignite saptanan hasta grubunun malignite saptanmayan hastalar ile kıyaslamasında primer tümör çaplarının daha büyük olduğu görüldü.



***Şekil 1**: Kolonoskopi taraması yapılan ve yapılmayan hastaların ortalama sağ kalım süreleri ile kolonoskopi de malignite saptanan ve saptanmayan hastaların ortalama sağ kalım sürelerinin karşılaştırılması.*

Kolonoskopi yapılan hastalarla yapılmayan hastalar karşılaştırıldığında ortalama sağ kalım süresinde istatiksel olarak anlamlı bir fark saptanmadı.

Kolonoskopi taramasında malignite saptanan hastaların ortalama yaşam süresinin 49,33 ay olduğu görüldü. Kolonoskopi taramasında malignite görülmeyen hastalarda ise ortalama yaşam süresi 60,24 ay olarak görüldü. (p=0,425)

Kolonoskopide malignite saptanan hastaların ortalama yaşam süreleri, malignite saptanmayan hastalarla kıyaslandığında istatiksel olarak aralarında anlamlı bir fark saptanmadı. Tablo 3'de Bağırsak metastazı bulunan hastaların ortalama sağkalım süresinin daha düşük olduğu tespit edildi. (p=0,008)

Tablo 3'de Bağırsak metastazı görülmeyen hasta grubunda ortalama hastalıksız sağ kalım süresi 19,32 ay, bağırsak metastazı görülen hasta grubunda ise ortalama hastalıksız sağ kalım süresi 17,99 ay (p=0,548) olarak bulundu. Bağırsak rezeksiyonu gerekliliği olan ve bağırsak rezeksiyonu yapılan hasta grubunda hastalıksız sağ kalım süresinin 16,42 ay, bağırsak rezeksiyonu gerekliliği bulunmayan ve yapılmayan hasta grubunda ise hastalıksız sağ kalım süresinin 19,21 ay (p=0,384) olduğu görüldü.

Table 3: Hastaların hastalıksız sağ kalım süresi bulguları ile gruplar arasındaki farklılıklarının incelenmesi

	Ortalama	Standart sapma	95% Güven Aralığı		p
			En Düşük Değeri	En Yüksek Değeri	
Kolonoskopi Taraması					
Var	16,86	1,73	13,55	20,36	0,108
Yok	20,25	1,27	17,75	22,75	
Bağırsak metastazı					
Var	17,99	1,55	14,94	21,04	0,548
Yok	19,32	1,27	16,82	21,82	
Bağırsak rezeksiyonu					
Var	16,42	2,79	10,94	21,91	0,384
Yok	19,21	1,09	17,06	21,36	

* p<0,05, p<0,001, Kaplan meier sağkalım analizi, Log rank testi

TARTIŞMA

Erken evre over kanserlerinde evreleme ameliyatları yapılırken, ileri evre over kanseri vakalarında sitoredüktif cerrahi ön plana çıkar. İleri evre over kanseri vakalarında genellikle çeşitli metastaz odakları bulunduğundan, bağırsak rezeksiyonu ve stoma oluşturma gibi gastrointestinal sistemdeki metastazlara yönelik işlemler de uygulanmaktadır (9). İleri evre over kanserlerinde cerrahi operasyon sırasında barsak rezeksiyonu gerekliliği %41,5 ve stoma gerekliliği %11 olarak tahmin edilmektedir (10). Barsak metastazından şüphelenildiğinde, durum tespitinin operasyon öncesi yapılması önem arz eder. Kolonun değerlendirilmesinde altın standart görüntüleme yöntemi kolonoskopi taraması olarak kabul edilir (11).

Çalışmamızda, ileri evre over kanseri hastalarında karın ağrısı (%71,2) ve karında şişkinlik (%22,3) gibi semptomların daha yüksek oranda görüldüğü tespit edilmiştir. Kolonoskopi taramasında malignite saptanan hastaların ise çok büyük bir bölümünde karın ağrısı veya karında şişkinlik gibi semptomlar gözlenmiştir (%94,2). Renata ve arkadaşlarının yaptığı çalışmada, bizim çalışmamıza paralel olarak, karın ağrısı ile şişkinlik gibi semptomlar ön planda olup az bir hasta grubunda bulantı, kusma, kabızlık ve ishal gibi semptomlar saptanmıştır. Benzer başka bir çalışmada, over kanseri olan ve barsak metastazı bulunup stoma gerekliliği olan 68 hasta incelendiğinde, %71 hastada spesifik semptomlar, %28 hastada ise nonspesifik semptomlar saptanmıştır. Bağırsak rezeksiyonu gerekliliği bulunan başka bir hasta grubunda ise %42 oranında spesifik, %58 oranında nonspesifik semptomlar gözlenmiştir (12,13). Yaptığımız çalışmada ve diğer çalışmalarda paralel şekilde, barsak metastazı saptanan hastalarda karın ağrısı ve karında şişkinlik gibi semptomların ağırlıklı olarak görüldüğü tespit edilmiştir (14,15).

Çalışmamızda, bağırsak metastazı tespit edilen hastaların büyük bir kısmında (%81,2) preoperatif asit saptanmıştır. Kolonoskopide malignite saptanan hasta grubunun tamamında preoperatif asit tespit edilmiştir. Petru ve arkadaşlarının yaptığı çalışmada da bizim çalışmamıza paralel olarak, over kanseri olan hastaların %70'inde asit saptanırken, metastatik over kanseri olan hasta grubunun %83'ünde asit tespit edilmiştir (16).

Çalışmamızda kolonoskopide malignite tespit edilen hastaların primer tümör çapının, malignite saptanmayan hastalarla kıyaslandığında daha büyük olduğu gözlenmiştir. Petru ve arkadaşlarının çalışmasında, preoperatif tümör çapı 10 cm üzerinde olan hastalar incelendiğinde, bu hasta grubunun %40'ını metastatik over kanseri olan hastaların oluşturduğu saptanmıştır. Gouchen Liu ve arkadaşlarının yaptığı benzer bir çalışmada ise kolonoskopide malignite tespit edilen hastaların tümör çapının diğer hasta gruplarına göre daha büyük olduğu tespit edilmiştir (13,16). Çalışmamızdan ve diğer çalışmalardan elde edilen veriler ışığında, belirgin asiti olan ve preoperatif tümör çapı büyük olan hastalarda barsak metastazının daha yüksek oranda görüldüğü sonucuna varılabilir.

Bağırsak metastazı saptanan hastaların %64,8'i Evre 3c, bağırsak rezeksiyonu yapılan hastaların ise %72,1'i Evre 3c olarak tespit edilmiştir. Ravizza ve arkadaşlarının yaptığı benzer bir araştırmada 144 hasta incelenmiş ve kolonoskopide over kanseri metastazı tespit edilen hastaların çoğunluğunun ileri evre over kanseri olduğu görülmüştür (13,14). Çalışmamız ve benzer diğer çalışmaların sonuçlarına göre, barsak metastazlarının ileri evre over kanserlerinde

daha sık görüldüğü tespit edilmiştir.

Yaptığımız çalışmada, ileri evre over kanserlerinde ortalama hastalıksız sağkalım süresi 18,99 ay olarak belirlenmiş; kolonoskopi taramasında malignite saptanan hastalarda ise ortalama hastalıksız sağkalım süresi 41,26 ay olarak tespit edilmiştir. Benzer çalışmalarda ortalama yaşam süresi ve ortalama hastalıksız sağkalım süresine değinilmemiştir. Ancak literatürde belirtilen ileri evre over kanserlerinde ortalama yaşam süresi ve hastalıksız sağkalım süresi değerlerinin, çalışmamızdan elde edilen verilerle paralel olduğu görülmüştür.

Over kanser tanılı hastalarda preoperatif kolonoskopi taraması ile ilgili çalışmalar sınırlıdır ve bu çalışmaların elde ettiği veriler bazı çelişkiler içermektedir. Tüm bu çalışmalar ve bulgularımız ayrı ayrı analiz edildiğinde; 50 yaşın üzerinde, klinik olarak şüpheli semptomları olan, CEA ve CA125 değerleri yüksek, ultrasonografik muayenede bilateral veya büyük adneksiyal kitle bulunan, preoperatif belirgin asiti olan ve sitolojide pozitiflik saptanan hastalara barsak metastazı açısından şüphe ile yaklaşılmalıdır. Bu hastalara preoperatif veya peroperatif kolonoskopi yapılması uygun bir yaklaşım olacaktır.

Sonuç olarak, over kanserinde şu an için rutin bir tarama protokolü bulunmamakta olup, birçok klinikte, over kanseri kolon metastazı düşünülen hastalara tarama amaçlı kolonoskopi uygulanmaktadır. Over kanserinin bağırsak metastazları genellikle seromüsküler tutulum gösterdiğinden, kolonoskopinin taramada duyarlılığı yeterli düzeyde olmamaktadır. Ek olarak kolonoskopi taraması yüksek maliyetli olup, invaziv bir işlem olması nedeniyle bazı komplikasyon risklerini de beraberinde getirmektedir. Ancak ileri evre over kanseri vakalarında genellikle uzak metastaz ve barsak metastazı bulunduğundan, optimal sitoredüksiyon gerçekleştirmek için bağırsak rezeksiyonu ve stoma oluşturma gibi cerrahi işlemler gerekli olabilmektedir. Bağırsaklara yönelik böyle bir gereklilik söz konusuysa, durum tespitinin ve planlamanın operasyon öncesi yapılması gerekmektedir; bu noktada kolonoskopi taraması ön plana çıkmaktadır. Ayrıca kolonoskopi taraması yalnızca malignite içeren lezyonların değil, premalign ve polipler gibi neoplastik olmayan lezyonların da tespit edilip çıkarılmasına olanak sağlamaktadır.

Tüm bunlar değerlendirildiğinde, over kanseri tanısı almış tüm hastalara rutin kolonoskopi taraması yapmak yerine, risk faktörlerine göre uyarlanmış kolonoskopi taraması uygulanmasının hastalar için çok daha makul bir yaklaşım olacağı sonucuna varılmıştır.

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Evaluation of Clinical and Pathological Characteristics in Recurrent Endometrial Cancer

Rekürren Endometriyum Kanserinde Klinik ve Patolojik Özelliklerin Değerlendirilmesi

Elif Iltar[1], Fatma Ceren Guner [1], Muge Ates Tikiz [1] Selen Dogan [1], Aykut Tuncer[1], Tayup Simsek[1]

[1]Akdeniz University, Faculty of Medicine, Gynecological Onkology, Department of Gynecology and Obstetrics, Antalya, Turkiye

ABSTRACT

Aim: This study aims to evaluate the clinical and pathological characteristics of patients with recurrent endometrial cancer.

Methods: This retrospective observational study included 52 patients with histologically or radiologically confirmed recurrence among 475 endometrial cancer cases treated between January 2014 and December 2024 at Akdeniz University Hospital. Data on demographics, histological subtypes, molecular markers, recurrence sites, and clinical presentation were collected from medical records.

Results: The recurrence rate was 10.9% (52/475). The mean age at diagnosis was 63.2 ± 10.1 years and at recurrence was 65.0 ± 9.7 years. Recurrence was symptomatic in 53.8% and asymptomatic in 46.2% of cases. The most frequent recurrence site was the vaginal cuff (23.1%), followed by widespread intra-abdominal recurrence and lung metastases (each 13.5%). Endometrioid adenocarcinoma was the most common histological subtype (46.2%), but non-endometrioid types collectively accounted for over 50% of cases. Significant LVSI was observed in 64.4% of patients, and P53 mutation was detected in 50% of tested cases. Peritoneal cytology was positive in 19.2%, and omental metastasis was present in 15.4% of patients. Comparison of local (vaginal) and distant (pulmonary) recurrences revealed distinct patterns in age, symptomatology, and molecular profiles

Conclusion: Our findings demonstrate that advanced age, non-endometrioid histology, positive peritoneal cytology, significant LVSI, and molecular alterations such as P53 mutation are associated with recurrence in endometrial cancer. Notably, nearly half of the recurrences were asymptomatic, underscoring the importance of structured follow-up protocols.

Keywords: Endometrial cancer, Recurrence, Vaginal cuff

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ÖZET

Amaç: Bu çalışmanın amacı, rekürren (nüks) endometrial kanserli hastaların klinik ve patolojik özelliklerini değerlendirmektir.

Yöntem: Bu retrospektif gözlemsel çalışmada, Ocak 2014 ile Aralık 2024 tarihleri arasında Akdeniz Üniversitesi Hastanesi'nde tedavi edilen 475 endometrial kanser vakası arasından histolojik veya radyolojik olarak nüks tanısı konulan 52 hasta değerlendirilmiştir. Demografik veriler, histolojik alt tipler, moleküler belirteçler, nüks bölgeleri ve klinik başvuru şekli hasta kayıtlarından elde edilmiştir.

Bulgular: Nüks oranı %10.9 (52/475) olarak hesaplanmıştır. Tanı anındaki ortalama yaş 63.2 ± 10.1 yıl, nüks anındaki ortalama yaş ise 65.0 ± 9.7 yıldır. Nükslerin %53.8'i semptomatik, %46.2'si ise asemptomatik olarak tespit edilmiştir. En sık nüks bölgesi vajinal kaf (%23.1) olup, bunu yaygın intraabdominal nüks ve akciğer metastazları (%13.5'er) takip etmiştir. En yaygın histolojik alt tip endometrioid adenokarsinom (%46.2) olsa da, non-endometrioid tipler toplu olarak vakaların %50'sinden fazlasını oluşturmuştur. Hastaların %64.4'ünde belirgin LVSI, test yapılanların %50'sinde ise P53 mutasyonu saptanmıştır. Hastaların %19.2'sinde peritoneal sitoloji pozitifliği, %15.4'ünde ise omentum metastazı mevcuttu. Lokal (vajinal) ve uzak (pulmoner) nüksler karşılaştırıldığında, yaş, semptomatoloji ve moleküler profiller açısından belirgin farklılıklar gözlenmiştir.

Sonuç: Bulgularımız; ileri yaş, non-endometrioid histoloji, pozitif peritoneal sitoloji, belirgin LVSI varlığı ve P53 mutasyonu gibi moleküler değişikliklerin endometrial kanser nüksü ile ilişkili olduğunu göstermektedir. Nükslerin yaklaşık yarısının asemptomatik olması, yapılandırılmış ve düzenli takip protokollerinin önemini bir kez daha ortaya koymaktadır.

Anahtar Sözcükler: Endometrial kanser, Rekürrens, Vajinal cuff

Sorumlu Yazar: Elif Iltar, Akdeniz University, Faculty of Medicine, Gynecological Onkology, Department of Gynecology and Obstetrics, Antalya, Turkiye

E-mail: dktr_elif@hotmail.com

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INTRODUCTION

Endometrial cancer is the most common malignancy of the female genital tract, and its incidence is steadily increasing. It accounts for approximately 6% of all cancers diagnosed in women. Most patients are diagnosed at an early stage and achieve high cure rates with surgical treatment and adjuvant therapies. However, in a subset of patients, the disease recurs, which has a markedly negative impact on overall survival. In patients without recurrence, the 5-year overall survival rate has been reported to exceed 90% (1,2). However, in cases with distant metastases, the 5-year overall survival rate may decline to as low as 15–20% (1,3).

Recurrence rates in endometrial cancer are closely associated with several prognostic factors, including disease stage, histological subtype, lymphovascular space invasion (LVSI), depth of myometrial invasion, and adjuvant therapy. While endometrioid adenocarcinoma is typically associated with a more favorable prognosis, non-endometrioid subtypes such as serous carcinoma and carcinosarcoma are linked to higher recurrence and mortality rates[4]. In a large population-based study, approximately 8% of patients with endometrioid endometrial cancer were found to develop recurrence and the five-year overall survival rate in these patients was reported to be below 50% (1). In a study evaluating geriatric patients with endometrial cancer, the five-year overall survival rate after recurrence was reported as 35.7%, and at these poatients lung was identified as the most common site of recurrence (5). A review focusing on advanced stage and recurrent endometrial cancer reported that recurrence rates range from 10–15% in early-stage disease to 40–70% in advanced stages (3).

Typical sites of recurrence in endometrial carcinoma include the pelvic and para-aortic lymph nodes, vagina, peritoneum and lungs. However, recurrence can also occur in intra-abdominal organs, bones, brain and at atypical locations such as abdominal wall and muscle (2). The diagnosis of recurrence is most often made during patients symptomatic presentations. The most commonly reported symptoms include vaginal bleeding, pelvic pain, fatigue, and respiratory distress. Among the symptoms related to distant metastases, findings such as skeletal pain are also reported as reasons for clinical admission (1,5). On the other hand, recurrence diagnoses are also made in asymptomatic patients during planned follow-ups; however, this situation is less common compared to presenting with symptoms (4–6).

MATERIALS AND METHODS

This retrospective observational study was conducted to evaluate the clinical, pathological, and demographic characteristics of patients with recurrent endometrial cancer who were followed at the Gynecologic Oncology Unit of Akdeniz University Faculty of Medicine between January 2014 and December 2024, following primary surgical treatment.

As part of the study, a total of 475 patients diagnosed with endometrial cancer who underwent hysterectomy and surgical staging followed by completion of adjuvant therapy were retrospectively reviewed. Among these, 52 patients who developed either symptomatic or asymptomatic recurrence confirmed by pathological or radiological evaluation during follow-up were included in the study group. All surgical procedures were performed by physicians from the gynecologic oncology department.

Following diagnosis, patients were routinely scheduled for outpatient visits every 3 months

during the first 2 years, every 6 months for the subsequent 3 years and annually thereafter. During these follow-up visits, symptom assessments were conducted, gynecological examinations were performed and imaging studies were ordered when necessary. Recurrence was diagnosed during these visits in patients with no evidence of residual disease after primary treatment. The diagnosis was confirmed by biopsy from suspicious areas amenable to histopathological sampling (e.g., vaginal cuff, lung); in cases where biopsy was not feasible, imaging modalities such as computed tomography (CT), magnetic resonance imaging (MRI), or positron emission tomography (PET) were utilized for diagnostic confirmation.

All patients' age, FIGO stage at diagnosis, histopathological subtype, presence of lymphovascular space invasion (LVSI), history of adjuvant treatment, time to recurrence, site of recurrence and presenting symptoms at the time of recurrence were retrospectively retrieved from medical records. Histological subtypes were classified according to the World Health Organization (WHO) criteria, while staging was reassessed based on both the 2009 and 2023 FIGO staging systems.

Recurrence sites were categorized into anatomical regions such as the vaginal cuff, pelvic lymph nodes, para-aortic lymph nodes, omentum, liver, lungs, brain, bone, subcutaneous tissue and widespread intra-abdominal recurrence. In addition, whether the patients presented with symptoms at the time of recurrence diagnosis, and if so, the specific presenting symptoms (e.g., vaginal bleeding, dyspnea, pain, swelling, altered consciousness etc.) were meticulously recorded. Ethics committee approval for the study was approved by our local committee (Akdeniz University Clinical Research Ethics Committee Date: 29.05.2025, Decision no: TBAEK- 532)

All procedures performed comply with the ethical standarts of the institutional and/or national research committee and the Helsinki declaration and its subsequent amendments or comparable ethical standards.

Statistical analyses were performed using SPSS software version 23.0. Continuous variables were presented as mean ± standard deviation (SD), while categorical variables were expressed as frequencies and percentages.

RESULTS

Between January 2014 and December 2024 a total of 475 patients diagnosed with endometrial cancer at a tertiary care center were screened. Among them, 52 patients (10.9%) who had completed surgical and adjuvant treatments and subsequently developed recurrence during follow-up were retrospectively evaluated. The mean age at the time of initial diagnosis was 63.2 ± 10.1 years, while the mean age at the time of recurrence was calculated as 65.0 ± 9.7 years. Among 50 patients whose final pathology reports included tumor size data, the mean tumor diameter was calculated as 4.93 ± 3.74 cm.

In 53.8% of the patients, the diagnosis of recurrence was made based on clinical symptoms, while in 46.2%, asymptomatic recurrences were detected during routine follow-up after the completion of treatment. Among the symptomatic cases, the most commonly reported symptom was postmenopausal vaginal bleeding, observed in 12 patients (23.1%), followed by dyspnea in 8 patients (15.4%). In the majority of asymptomatic cases, the diagnosis was established during scheduled follow-up visits through radiological imaging.

Among the patients with available data on recurrence sites, the most frequently observed site was the vaginal cuff, detected in 12 patients (23.1%). This was followed by abdominal widespread metastasis and lung metastasis, each identified in 7 patients (13.5%). Other common recurrence sites included the liver in 4 patients (7.7%) and pelvic lymph nodes in 3 patients (5.8%). This distribution indicates that recurrences can occur in both local and distant regions, reflecting significant clinical heterogeneity. Table 1 summarizes the clinical and pathological characteristics of the patients with recurrent endometrial cancer included in this study.

Table 1: Clinical and Pathological Characteristics of Patients with Recurrent Endometrial Cancer

Parameter	n (%) or mean ± SD
Age at diagnosis (mean ± SD)	63.2 ± 10.1
Age at recurrence (mean ± SD)	65.0 ± 9.7
Tumor size (mean ± SD, cm)	4.93 ± 3.74
Symptomatic recurrence	28 (53.8%)
Asymptomatic recurrence	24 (46.2%)
Vaginal cuff	12 (23.1%)
Abdominal widespread metastasis	7 (13.5%)
Lung metastasis	7 (13.5%)
Liver metastasis	4 (7.7%)
Pelvic lymph node metastasis	3 (5.8%)
Positive peritoneal cytology	10 (19.2%)
Omental metastasis	8 (15.4%)
Significant LVSI	29/45 (64.4%)
MMRd	3/25 (12.0%)
POLE mutation evaluated	0 (0.0%)
FIGO stage I–II (old)	65%
FIGO stage I–II (new)	46%
FIGO stage III–IV (new)	54%
FIGO stage III–IV (old)	35%

Among patients included in the study, the most frequently observed histological subtype was endometrioid adenocarcinoma, detected in 24 cases (46.2%). This was followed by serous carcinoma in 11 patients (21.2%), mixed carcinoma in 5 (9.6%), carcinosarcoma in 5 (9.6%), anaplastic/undifferentiated carcinoma in 3 (5.8%), clear cell carcinoma in 2 (3.8%) and dedifferentiated carcinoma in 2 patients (3.8%). This distribution indicates that both endometrioid and non-endometrioid histological subtypes are significantly represented among patients who developed recurrence. The histological subtype distribution is detailed in Table 2.

Table 2: Histological Subtypes of Recurrent Endometrial Cancer

Histological Subtype	n (%)
Endometrioid adenocarcinoma	24 (46.2%)
Serous carcinoma	11 (21.2%)
Mixed histology	5 (9.6%)
Carcinosarcoma	5 (9.6%)
Anaplastic/undifferentiated carcinoma	3 (5.8%)
Clear cell carcinoma	2 (3.8%)
Dedifferentiated carcinoma	2 (3.8%)
Total	52 (100%)

Following surgical staging, final cytologic assessments revealed that 10 patients (19.2%) had positive peritoneal cytology. In contrast, 38 patients (73.1%) had negative cytology results, while cytological evaluation was not performed in 4 patients (7.7%). This distribution indicates that approximately one in five patients who experienced recurrence had positive peritoneal cytology at the time of initial staging.

Upon reviewing the omental pathology reports of the 52 patients, omental metastasis at initial diagnosis was identified in 8 patients (15.4%). No omental metastasis was observed in 40 patients (76.9%), while in 4 patients (7.7%),

the omental status could not be evaluated due to the absence of omentectomy or lack of histopathological assessment. Among the 8 patients with omental metastasis, the most frequently observed histological subtype was serous carcinoma, found in 3 patients (37.5%). The remaining cases consisted of mixed endometrial carcinoma, endometrioid adenocarcinoma, carcinosarcoma, clear cell carcinoma, and undifferentiated carcinoma each accounting for 12.5% of the cases.

Among the 45 patients for whom lymphovascular space invasion (LVSI) status could be evaluated, significant LVSI was identified in 29 cases (64.4%), while 16 patients (35.6%) exhibited absent or focal LVSI. In 7 patients (13.5%), LVSI status was not reported in the pathology records. These findings indicate a high prevalence of marked LVSI among patients with recurrent disease, suggesting that LVSI may serve as a potential prognostic indicator in endometrial cancer.

Among the 26 patients whose P53 immunohistochemical staining results were available, a mutant P53 expression pattern was identified in 13 cases (50.0%), while the remaining 13 patients exhibited a wild-type P53 profile. The other 26 patients did not undergo P53 immunohistochemical evaluation.

Immunohistochemical evaluation of MMR (Mismatch Repair) protein expression was performed in 25 patients, revealing MMR deficiency (MMRd) in 3 cases (12.0%), while the remaining 22 patients (88.0%) retained MMR protein expression. All patients with MMRd exhibited endometrioid histology and were classified within FIGO stage I–II. POLE mutation analysis was not performed in any of the patients included in this study.

In our study, the distribution of patients was evaluated according to both the former and updated FIGO staging systems. Under the previous staging system, 65% of patients were classified as stage I–II, whereas this proportion decreased to 46% with the updated system. Conversely, the rate of stage III–IV disease increased from 35% to 54% according to the new FIGO classification.

Our findings suggest that local (vaginal) and distant (pulmonary) recurrences exhibit distinct clinical profiles in terms of age at recurrence, clinical presentation and symptomatology as demonstrated in Table 3

Table 3: Clinical profiles in recurrent endometrial cancer

Parameter	Vaginal Cuff Recurrence (n=12)	Lung Metastasis (n=7)
Mean Age at Diagnosis (years)	61.1 ± 9.5	66.3 ± 10.4
Mean Age at Recurrence (years)	62.6 ± 9.3	68.2 ± 10.2
Mean Tumor Size (cm)	4.25 ± 3.8	5.1 ± 3.7
Symptomatic Recurrence	6 (50.0%)	6 (85.7%)
Asymptomatic Recurrence	6 (50.0%)	1 (14.3%)
Positive Peritoneal Cytology	1 (8.3%)	2 (28.6%)
Omental Metastasis	1 (8.3%)	2 (28.6%)
Significant LVSI	6/11 (54.5%)	5/6 (83.3%)
Mutant P53 Pattern	3/6 (50.0%)	2/3 (66.7%)
MMRd	0/5 (0.0%)	1/4 (25.0%)

DISCUSSION

Recurrence in endometrial cancer is one of the most critical prognostic factors influencing the course of the disease. According to the literature, the overall recurrence rate ranges between 8% and 10% with the majority of cases occurring within the first three years after diagnosis and typically presenting in extra-pelvic sites (1,2,3). In our study, the mean age at initial diagnosis

among patients who developed recurrence was calculated as 63.2 years, while the mean age at the time of recurrence was 65.0 years.

In our study, the mean tumor diameter reported in the final pathology of patients with recurrence was 4.93 ± 3.74 cm. This finding is in line with previously reported data in the literature. In an analysis by Gülseren et al. focusing on elderly patients with endometrial cancer, it was reported that the mean tumor size was significantly larger in cases that developed recurrence[3].The mean tumor size observed in our study appears to be relatively large.

The diagnosis of recurrence was established based on symptomatic presentation in 53.8% of patients with vaginal bleeding was the most common complaint. This finding is consistent with the literature; Akesson et al. similarly reported that the majority of recurrences were detected in patients presenting with symptoms (1). In our cohort, the proportion of asymptomatic cases was 46.2%, underscoring the critical importance of scheduled follow-up visits after completion of primary treatment in detecting recurrences at an early stage.

When evaluated in terms of histological subtypes, endometrioid adenocarcinoma was the most commonly observed type; however, non-endometrioid tumors collectively accounted for more than half of the recurrent cases in our cohort. This finding aligns with existing literature, which indicates that non-endometrioid tumors, particularly serous carcinomas and carcinosarcomas, exhibit a more aggressive clinical course and are associated with higher mortality rates following recurrence. In the study by Cosgrove et al. the post-recurrence mortality rate was reported as 4% for patients with endometrioid tumors, whereas it increased to 36.4% for serous carcinomas and 45.5% for carcinosarcomas (4).

In terms of recurrence site, the most commonly observed locations in our study were the vaginal cuff, pelvic/abdominal regions and pulmonary metastases. The mean age of the seven patients who developed lung recurrence was 64.6 ± 9.9 years. The relatively advanced age of patients with pulmonary recurrence in our cohort suggests that older age may be a potential risk factor for distant metastasis. Similarly, in the study by Gülseren et al. focusing on elderly patients, the lung was also reported as the most frequent site of recurrence, observed in 40.5% of cases (4). A population-based study reported that recurrences most commonly occurred in the vaginal or pelvic region (57.2%), followed by distant metastases (25.3%) and in some cases, both local and distant sites were involved simultaneously (17.4%) (1).

Positive peritoneal cytology is another prognostic indicator associated with lymphovascular invasion and dissemination potential in endometrial cancer. In our study, 19.2% of patients with recurrence had positive cytology at the time of initial diagnosis. Although positive cytology has been excluded as a staging criterion in current guidelines, literature suggests that it may still aid in predicting recurrence risk, particularly in patients with advanced-stage disease or high-risk histologic subtypes (1,3). In the study conducted by Gülseren et al. evaluating elderly patients with endometrial cancer, the rate of positive peritoneal cytology was reported as 21.6% and this condition was emphasized as one of the factors increasing the risk of recurrence (5). Moreover, in the multicenter study by Demir et al. positive peritoneal cytology was shown to be more frequently observed in serous and clear cell tumors and when evaluated together with LVSI, it significantly increased

the risk of recurrence[6]. Tronconi et al. also identified positive cytology as one of the factors associated with an increased risk of peritoneal dissemination in advanced-stage endometrial cancer, emphasizing that this finding should not be overlooked in treatment planning (3). In our study, the rate of positive cytology was similarly 19.2% and its more frequent occurrence in non-endometrioid tumors supports this notion. Therefore, cytological findings should be considered a supportive parameter in identifying patients at high risk of recurrence.

Omental metastasis is considered a hallmark of advanced-stage endometrial cancer and is known to significantly impact prognosis. In our study, omental involvement was identified in 15.4% of patients with recurrence. Tronconi et al. reported that omental dissemination was more frequently observed in serous and mixed histologic subtypes and this pattern was associated with peritoneal spread and poor prognosis (3). In our study, the majority of cases with omental metastasis were associated with high-risk histologic subtypes, further supporting the findings in the literature. Routine assessment of the omentum during surgical staging is crucial for more accurate risk stratification and for guiding adjuvant treatment planning in patients at elevated risk of recurrence.

The presence of lymphovascular space invasion (LVSI) was observed in 64.4% of the patients with recurrence in our series. This rate is consistent with the 56.8% reported by Gülseren et al. in their study on elderly patients with endometrial cancer (5). Furthermore, in the multicenter study conducted by Demir et al., LVSI was identified as an independent prognostic factor for recurrence risk in endometrial cancer. These findings support the notion that LVSI is a significant predictor of recurrence and should be taken into account, particularly in identifying high-risk patients[6]. Both Akesson and Cosgrove emphasized in their studies that LVSI is strongly associated with recurrence in endometrial cancer (1,4).

The notably high rate of P53 mutations observed in our cohort of patients with recurrent disease is striking. According to The Cancer Genome Atlas (TCGA) classification, molecular subtypes exhibiting P53 abnormalities—referred to as “serous-like” tumors—are identified as the subgroup with the poorest prognosis in endometrial cancer. These subtypes have been reported to carry a significantly increased risk of recurrence and mortality (7). Therefore, the high rate of P53 mutations observed in our study further emphasizes the prognostic importance of molecular profiling in patients who develop recurrence.

In contrast, no patient in our study underwent POLE mutation analysis. However, TCGA data indicate that the POLE-ultramutated subgroup is associated with the most favorable survival outcomes, underscoring the critical importance of identifying this subgroup in order to select patients who may safely forgo adjuvant therapy (7).

The newly published ESGO–ESTRO–ESP guidelines recommend integrating molecular classification into staging and treatment planning, selecting adjuvant therapy, and selecting patients for clinical trials. It also emphasizes that evaluating molecular data together with classical pathological factors such as LVSI, histological subtype, and tumor size provides a more personalized approach to patients (8).

In terms of FIGO staging, 65% of patients were classified as stage I–II according to the previous system, whereas this proportion decreased to

46% under the new system; conversely, the proportion of advanced-stage (stage III–IV) patients increased to 54%. This shift reflects the improved prognostic stratification capability of the updated FIGO classification. Similarly, studies by Akesson and Demir have emphasized that recurrence rates are higher and survival is significantly poorer among patients with advanced-stage disease (1,6).

LImItatIons of the Study

This study has several limitations. First, due to its retrospective design, the data were obtained from past medical records, which may have led to incomplete or non-standard reporting of certain pathological and molecular parameters. For instance, the fact that p53, MMR and POLE analyses were not performed in all patients POLE analysis is not a routine practice in our hospital ant this is limited the ability to comprehensively evaluate the prognostic impact of molecular subtypes..The main methodological limitation of our article is the lack of follow-up period and survival data . Additionally, the single-center nature of the study and the relatively small sample size restrict the generalizability of the findings. Due to the retrospective design of this study and the limited availability of long-term follow-up data, information regarding post-recurrence survival, median time to recurrence, and overall survival could not be obtained. This limitation should be taken into account when interpreting the prognostic implications of the findings. This study primarily aimed to investigate the demographic, clinical, pathological, and molecular characteristics of patients with recurrent endometrial cancer. Detailed information regarding the management or treatment modalities of recurrence was not within the scope of this analysis. Therefore, the post-recurrence treatment strategies were not evaluated.

CONCLUSION

This study comprehensively evaluated the clinical, pathological and molecular characteristics of patients who developed recurrence following surgical treatment for endometrial cancer. Our findings indicate that advanced age, non-endometrioid histology, substantial LVSI, high FIGO stage and the presence of distant metastases are the main factors associated with poor prognosis after recurrence. Moreover, the fact that approximately half of the recurrences were asymptomatic highlights the importance of regular and structured follow-up protocols. Although molecular analyses were performed in a limited number of cases, biomarkers such as p53 mutation and MMR deficiency (MMRd) appear to have prognostic value and warrant further investigation, particularly in recurrent cases. Patients were not grouped according to the TCGA classification (POLE ultramutated, MMRd, p53-aberrant, NSMP). The fact that this classification was not done systematically and this limits the prognostic implications of the studyThe results support the need for individualized follow-up and treatment strategies in high-risk endometrial cancer patients. Larger, prospective studies are needed to validate these findings.

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Investigation Of The Effect Of Nutrition In Gynecologic Malignancy On The Early Genitourinary And Gastrointestinal Side Effects Profile Of Patients Receiving Pelvic Radiotherapy

Jinekolojik Malignitelerde Beslenmenin Pelvik Radyoterapi Alan Hastaların Erken Genitoüriner ve Gastrointestinal Yan Etki Profiline Etkisinin Araştırılması

Belma Gozde Ozdemir [1], Burak Deli [2], Anara Madinaeva [1], Hamit Basaran[2], Cagdas Yavas [2], Ahmet Bilgi [1] Cetin Celik [1]

[1]Selçuk University Faculty Of Medicine, Obstetrics And Gynecology Department, Konya, Turkiye
[2] Selçuk University Faculty Of Medicine, Radiation Oncology Department, Konya, Turkiye

ABSTRACT

Aim: The The role of therapeutic or adjuvant radiotherapy in gynecological cancers is crucial. Genitourinary and gastrointestinal symptoms can occur in these diseases due to the anatomical relationships in the pelvic region. To prevent these complications, enriching the intestinal flora and microbiota, as well as providing supplementation with trace elements, vitamins, and minerals, has been shown to reduce side effects. This study aimed to investigate the early gastrointestinal and genitourinary side effect profiles in patients receiving nutritional support (NS) and radiotherapy.

Material and Methods: Patients who presented to the Department of Obstetrics and Gynecology and Radiation Oncology Department at Selçuk University Faculty of Medicine between 2023 and 2024 and received pelvic radiotherapy for gynecological malignancy were evaluated. Nutritional support is routinely provided in the clinic, and the study was designed as a retrospective study. The Radiation Therapy Oncology Group's Radiation Toxicity Index was used for side effect scoring. A total of 120 patients were included in the study. Based on nutritional support, Group 1 (n=60) included those who received nutritional support, and Group 2 (n=60) included those who did not receive nutritional support.

Results: There was a difference in the distribution of genitourinary side effects among patients receiving radiotherapy according to their use of nutritional support ($p<0.05$). It was observed that the use of NS had the potential to reduce genitourinary side effects. There was a difference in the distribution of gastrointestinal side effects in patients receiving radiotherapy according to their NS use ($p<0.05$). Gastrointestinal side effects were less common in patients receiving NS.

Conclusion: Nutritional support is thought to reduce genitourinary and gastrointestinal side effects in gynecologic cancer patients undergoing pelvic radiotherapy. Individualized approaches are essential, regardless of nutritional index.

Keywords: Radiotherapy, Hysterectomy, Side effect, Nutrition, Malignancy

ÖZET

Amaç: Jinekolojik kanserlerde radyoterapinin rolü çok önemlidir. Pelvik bölgedeki anatomik ilişkiler nedeniyle bu hastalıklarda genitoüriner ve gastrointestinal semptomlar ortaya çıkabilir. Bu çalışmada beslenme desteği (ND) alan hastalarda erken gastrointestinal ve genitoüriner yan etki profillerinin araştırılması amaçlanmıştır.

Materyal ve Metod: Selçuk Üniversitesi Tıp Fakültesi Kadın Hastalıkları ve Doğum Anabilim Dalı ve Radyasyon Onkolojisi Anabilim Dalı'nda 2023-2024 yılları arasında başvuran ve jinekolojik malignite tanısıyla pelvik radyoterapi alan hastalar değerlendirildi. Klinikte rutin olarak beslenme desteği verilmekte olup, çalışma retrospektif olarak tasarlandı. Yan etki skorlaması için Radyasyon Terapisi Onkoloji Grubu'nun Radyasyon Toksisite İndeksi kullanıldı. Çalışmaya toplam 120 hasta dahil edildi. Beslenme desteğine göre Grup 1 (n=60) beslenme desteği alanlar, Grup 2 (n=60) ise beslenme desteği almayan hastalardan oluşturuldu.

Bulgular: Radyoterapi alan hastalarda beslenme desteği kullanımına göre genitoüriner yan etkilerin dağılımında farklılık görüldü ($p<0,05$). ND kullanımının genitoüriner yan etkileri azaltma potansiyeline sahip olduğu görüldü. Radyoterapi alan hastalarda ND kullanımına göre gastrointestinal yan etkilerin dağılımında farklılık görüldü ($p<0,05$). ND alan hastalarda gastrointestinal yan etkiler daha az yaygın olarak raporlandı.

Sonuç: Pelvik radyoterapi uygulanan jinekolojik kanser hastalarında beslenme desteğinin genitoüriner ve gastrointestinal yan etkileri azalttığı düşünülmektedir. Beslenme indeksi ve ek hastalıklara göre kişiye özel yaklaşımlar esastır.

Anahtar Sözcükler: Radyoterapi, Histerektomi, Yan etki, Beslenme, Malignite

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Corresponding Author: Belma Gözde Ozdemir, MD ,PhD cand. Selcuk University Alaeddin Keykubat Campus Selçuk University Faculty of Medicine Hospital, Selçuklu/Konya , Post Code: 42130

E-mail: gzdgrgn35@gmail.com

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INTRODUCTION

Gynecologic malignancies are a heterogeneous group of tumors that pose a significant burden of morbidity and mortality worldwide in terms of both incidence and mortality rates (1). This group includes malignancies originating from the cervix, endometrium, ovary, vagina, and vulva, each characterized by unique pathophysiological mechanisms, clinical course, and treatment algorithms (2). Current oncological treatment approaches utilize surgery, chemotherapy, and radiotherapy, either alone or in multimodal combinations. Pelvic radiotherapy, in particular, is a highly preferred treatment modality with demonstrated evidence-based efficacy in the treatment of locally advanced disease and adjuvant treatment strategies (3). However, the ionizing radiation effect of pelvic radiotherapy on healthy pelvic tissues outside the target volume poses a significant clinical problem in terms of its early (acute) toxicity profile. Symptoms such as dysuria, pollakiuria, urinary retention, and hematuria in the genitourinary system, and diarrhea, rectal bleeding, abdominal cramping, and mucositis in the gastrointestinal system are frequently observed during or within the first 90 days following treatment (4,5). These adverse effects not only negatively impact quality of life but can also indirectly limit treatment effectiveness by reducing treatment compliance (6). In recent years, increasing scientific evidence has been reported that nutritional status and dietary modifications may be determining variables in the toxicity profile associated with pelvic radiotherapy (7,8). In particular, the effects of diet on the composition of the gut microbiota, mucosal barrier integrity, inflammatory response, and hydration balance have the potential to modulate the incidence and severity of gastrointestinal and genitourinary toxicities (9). Randomized controlled trials and prospective cohort analyses report that modification of fiber intake, lactose restriction, low-FODMAP diet practices, probiotic and prebiotic supplementation, and optimal fluid intake provide clinically significant reductions in the severity of symptoms such as diarrhea, abdominal discomfort, and urinary tract irritation (10,11). This study aimed to investigate the early gastrointestinal and genitourinary side effect profiles in patients receiving nutritional support (NS).

MATERIALS AND METHODS

This is a retrospective study conducted at the Department of Obstetrics and Gynecology and Radiation Oncology, Selcuk University Faculty of Medicine. Patients aged 46-79 who received pelvic radiotherapy for gynecological malignancy between 2023 and 2024 were evaluated.

A total of 120 patients were evaluated in the study, and two randomized groups were formed with 60 patients in each group.

Group 1: Pelvic radiotherapy, nutritional support (n=60)

Group 2: Pelvic radiotherapy, nutritional support (n=60)

Groups were classified according to age, parity, comorbidities, previous surgery, the type of cancer and the treatment modalities they received laboratory parameters (WBC, Hemoglobin, Platelet count), medication, pathology results, radiotherapy duration and dose, surgery type, grading of genitourinary (GU) and gastrointestinal (GI) side effect profiles on the seventh day after pelvic radiotherapy, and nutritional support status. The Radiation Therapy Oncology Group/ European Organization for Research and

Treatment of Cancer (RTOG/EORTC) Radiation Toxicity Grading System guide was used for grading.

The RTOG/EORTC acute radiation toxicity assessment system was developed to standardize the classification of adverse events occurring during radiotherapy or within 90 days following its completion. This assessment examines changes in various organ and tissue groups, including the skin, mucosa, gastrointestinal system, genitourinary system, lungs, blood counts, nervous system, and heart. Skin erythema, edema, peeling, or ulcers; mucosal redness, ulceration, or bleeding; gastrointestinal diarrhea, abdominal pain, or bleeding; urinary frequency, burning sensation, or hematuria; lung cough and shortness of breath; blood counts of leukocytes, platelets, and hemoglobin; nervous system headache, neurological deficits, and seizures; and cardiac ECG changes, arrhythmias, or signs of heart failure.

Check-ups are performed weekly throughout treatment and every 2–4 weeks for 90 days after the end of treatment. Scoring is performed separately for each organ system and ranges from Grade 0 (no toxicity) to Grade 4 (life-threatening toxicity). Grade 1 represents mild symptoms that do not require treatment; Grade 2 represents significant symptoms and the need for medical treatment; Grade 3 represents severe symptoms that interfere with daily life and often require hospitalization; and Grade 4 represents life-threatening complications that require urgent intervention (12). This form is routinely used in wards to report the side effect scale. Protein and energy, containing arginine, omega-3 fatty acids, RNA (dietary nucleotides) and soluble fiber (Nestlé Impact Oral, Novartis, Switzerland) the nutritional supplement routinely used in the clinic, is three suspension per day (237 ml/sus) for 5-7 days. It is a food formula for medical purposes containing 341 kcal, arginine, omega-3 fatty acids, RNA (dietary nucleotides), and soluble fiber. Each 237 ml serving contains approximately 18 g protein (21% energy), 44.8 g carbohydrate (53% energy), 9.2 g fat (24% energy), and 3.3 g fiber (2% energy); it also provides 4.3 g arginine, 1.4 g omega-3 fatty acids, and 0.43 g RNA. Its osmolarity is 680 mOsm/L. Mineral content includes (mg/100 ml) Na 150, Zn 2.1, Ca 114, P 101, Cl 169, Mg 32, Fe 1.7, and K 190.

All patients in this study were treated using advanced Intensity-Modulated Radiation Therapy (IMRT). In a total of 120 cases, radiotherapy was administered to the pelvic region in the range of 45–50.4 Gy, according to international guidelines and our clinic's standard treatment protocols. The treatment schedule was planned at 1.8 Gy per fraction, which represents the standard dose range widely accepted in the literature for oncological efficacy in irradiating the pelvic lymphatic spaces.

Exclude Criteria

Patients with inflammatory bowel disease, irritable bowel syndrome, interstitial cystitis, and chronic painful bladder syndrome were excluded from the study.

Statistics

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) 26.0 Statistics package program. Categorical data for female patients receiving radiotherapy are presented as numbers and percentages, and numerical variables are presented as mean, standard deviation, minimum, and maximum. The conformity of the female patients' age, WBC,

Hb, and PLT values to a normal distribution was determined by examining the skewness and kurtosis values. Except for WBC values, age, Hb, and PLT values were observed to conform to the rules of normal distribution. The reference value taken for a normal distribution is between ±1.96 (12). The Chi-Square test was used to compare comorbidities, surgical history, pathology results, surgery types, side effects, and gastrointestinal monitoring results of female patients receiving radiotherapy according to their formula use status. The Independent Samples T Test was used to compare age, Hb, and PLT values, and the Mann-Whitney U Test was used to compare WBC values. Significance levels throughout the study were calculated using values of 0.05 and 0.01 (13).

RESULTS

The mean age of patients who did not use Formula was 63.75 years, while the mean age of patients who used Formula was 63.47 years. According to these findings, no difference was observed between the mean ages of female patients receiving radiotherapy based on their formula use status (p>0.05).

Whole blood cell counts were measured at an average of 10.19 in the non-formula group and 10.91 in the formula-using group. Hemoglobin levels were measured at an average of 11.95 in non-formula patients and 12.26 in formula-using patients. Platelet counts were measured at an average of 260.37 in the non-formula group and 281.20 in the formula-using group.

Table 1: Comparison of Descriptive Characteristics of Female Patients Receiving Radiotherapy According to Formula Use Status

Parameter		Not using Formula (n: 60)		Using Formula (n: 60)		p
		Sayı	%	Sayı	%	
Medical State	No	27	45,0	37	61,7	0,100
	Yes	33	55,0	23	38,3	
Prior Operation	No	40	66,7	48	80,0	0,148
	Yes	20	33,3	12	20,0	
Patology	Endometrium cancer	42	70,0	43	71,7	0,452
	Cervical cancer	13	21,7	8	13,3	
	Serous Carcinoma	2	3,3	5	8,3	
	Others	3	5,0	4	6,7	
Surgery Type	Debulking	13	21,7	14	23,3	0,103
	Hys+Bso+Rplnd	18	30,0	18	30,0	
	Wertheım	8	13,3	8	13,3	
	Hys+Oop+LND+Omen	9	15,0	10	16,7	
	LS hys+Bso+Rplnd	1	1,7	7	11,7	
	Others	11	18,3	3	5,0	
		Mean.±S.D(Min.-Max.)		Mean .±SD (Min.Max.)		
Age		63,75±12,02 (30-86)		63,47±10,29 (28-85)		0,890

*p<0,05, **p<0,01, x^2: Chi-square test (Categorical data), t: Independent Sample T Test

Table 2: Comparison of Laboratory Findings of Female Patients Receiving Radiotherapy According to Formula Use Status

Laboratory findings	Not using Formula (n: 60) Mean.±S.D (Min.-Max.)	Using Formula (n: 60) Meant.±S.D (Min.-Max.)	
WBC (White Blood Cells) z	10,19±3,57 (2,5-21,1)	10,91±4,68 (3,77-31,8)	0,530
HB (Hemoglobin)t	11,95±1,66 (8,5-15,3)	12,26±1,49 (9,6-16,4)	0,286
PLT (Platelet)t	260,37±67,11 (151-452)	281,20±76,95 (111-460)	0,117

*p<0,05, **p<0,01, x^2: Chi-square test (Categorical data), t: Independent Sample T Test; z: Mann-Whitney U Test

These findings suggest that there was no significant effect on WBC, HB, or PLT levels in patients receiving radiotherapy (p>0.05).

In the non-formulated group, there were 42 patients with endometrial cancer, 13 with cervical cancer, 2 with ovarian serous carcinoma, and 3 with rare malignancies. In the formula-treated group, there were 43 patients with endothelial cancer, 8 with cervical cancer, 5 with ovarian serous carcinoma, and 4 with rare malignancies. A total of 27 patients underwent debulking, and 72 patients underwent Wertheim's disease, total hysterectomy, bilateral salpingo-oophorectomy ± omentectomy, and lymph node dissection.

Table 3: Comparison of Side Effects and Gastrointestinal Monitoring Results of Female Patients Receiving Radiotherapy According to Formula Use Status

Parameter		Not using Formula (n: 60)		Not using Formula (n: 60)		p
		No	%	No	%	
Genitourinary side effects	Grade 0	20	33,3	22	36,7	**0,000****
	Grade1	12	20,0	34	56,7	
	Grade 2	27	45,0	4	6,7	
	Grade 3	1	1,7	0	0,0	
Gastrointestinal side effects	Grade 0	22	36,7	23	38,3	**0,001****
	Grade 1	17	28,3	33	55,0	
	Grade 2	20	33,3	3	5,0	
	Grade 3	1	1,7	1	1,7	
Gastrointestinal transit	Grade 0	42	70,0	50	83,3	0,117
	Grade 1	15	25,0	10	16,7	
	Grade 2	3	5,0	0	0,0	
Transition during the day	Grade 0	36	60,0	44	73,3	0,217
	Grade 1	21	35,0	12	20,0	
	Grade 2	3	5,0	4	6,7	

*p<0,05, **p<0,01, x^2: Chi-square test (Categorical data)

The distributions of comorbidities, parity, surgical status, pathology results, and surgery types were similar in patients who received and did not receive radiotherapy (p>0.05).

A difference was observed in the distribution of genitourinary side effects among female patients receiving radiotherapy according to their formula use status (p<0.05). While 33.3% of non-formula patients experienced Grade 0 side effects, this rate was 36.7% in the formula-using group. The Grade 1 side effect rate increased to 56.7% in formula-using patients, while this rate was 20.0% in the non-formula-using group. Grade 2 side effects occurred in 45.0% of non-formula-using patients and only 6.7% in formula-using patients. Furthermore, Grade 3 side effects were observed in 1.7% of non-formula-using patients, while none were observed in the formula-using group. These findings suggest that formula use has the potential to reduce genitourinary side effects.

There was a difference in the distribution of gastrointestinal side effects among female patients receiving radiotherapy based on their formula use status (p<0.05). While 36.7% of non-formulated patients experienced Grade 0 side effects, this rate was 38.3% in the formula-using group. Grade 1 side effects were 55.0% in the formula-using group, compared to 28.3% in the non-formulated group. Grade 2 side effects were 33.3% in the non-formulated group and only 5.0% in the formula-using group. These findings suggest that formula use has the potential to reduce gastrointestinal side effects.

There was no difference in the distribution of gastrointestinal transit effects among female patients receiving radiotherapy based on their formula use status (p>0.05). Seventy percent of non-formula users experienced Grade 0 transit, compared to 83.3% in the formula-using group.

There was no difference in the distribution of daily transit effects among female patients receiving radiotherapy based on formula use status (p>0.05). Sixty percent of non-formula users experienced Grade 0 transit, compared to 73.3% in the formula-using group.

DISCUSSION

This study demonstrated that NS use reduced in gynecologic cancer the gastrointestinal and genitourinary side effect profiles of radiotherapy. This reflects the importance of nutritional support for the quality of life of oncology patients. The use of arginine and immunonutritional products in this study was motivated by the fact that short-term oral nutritional support enriched with immunomodulatory ingredients (arginine, omega-3, nucleotides, and soluble fiber) in patients with gynecological malignancies undergoing pelvic radiotherapy reduces early-stage genitourinary and gastrointestinal toxicity and is an integral component of nutrition in oncology. Medical nutritional support is recommended early and in a controlled manner to improve cancer care (14). Pathophysiologically, epithelial damage, microvascular dysfunction, immune system aggression, and gut microbiota dysbiosis all play a role in the pathogenesis of radiation enteropathy; this is a multifaceted condition that, in addition to short-term symptoms such as acute diarrhea, cramping, and bleeding, also paves the way for late effects such as progressive fibrosis and dysmotility (15). Therefore, concurrent NS formula feeding not only affects the acute phase but also has additional preventative effects in the late phase. On the toxicity side of GU, acute cystitis is characterized by mucosal inflammation and scarring, and in the late stage, by an obliterative process; this process can lead to short-term findings such as pollakiuria, dysuria, and

macroscopic hematuria, and over time, serious problems such as decreased bladder capacity, strictures, and fistulas can develop. Therefore, any intervention that reduces toxicity in the early stage has the potential to reduce the risk of late-term complications (16) indirectly. Metabolites of the gut microbiota, such as short-chain fatty acids (SCFAs; for example, butyrate), exert protective effects on epithelial integrity, mucus layer, occlusive junctions, and immune response. The association of pelvic radiotherapy with dysbiosis and SCFA reduction forms the basis for dietary and probiotic/prebiotic adjustments (17). The Formula used in this study did not contain probiotics, but it did contain prebiotic properties. Failure to provide probiotics appropriately leads to bacterial overgrowth, making this selection strategy potentially more effective. At the clinical level, randomized studies evaluating the effect of probiotics on radiotherapy-induced diarrhea—for example, studies with Lactobacillus-containing formulas showing a reduction in the incidence of diarrhea in pelvic radiotherapy (18) also support the superiority of probiotics over placebo in preventing radiotherapy-associated enteropathy in patients undergoing chemoradiotherapy (19). This association underscores the importance of supplementation.

Meta-analyses supporting these findings have reported that probiotics may be beneficial, particularly in reducing Grade ≥2 diarrhea, and have a favorable safety profile; however, standardization of strains, doses, and treatment duration remains necessary (20). Evidence suggests that immunonutrition formulas (arginine, omega-3, and nucleotide enrichment) of the type used in this study may reduce toxicity across the mucositis-enteritis spectrum by modulating epithelial repair, collagen synthesis, eicosanoid profile, and inflammatory signaling pathways, primarily in head and neck oncology and perioperative surgical populations. Although high-quality randomized controlled trials in pelvic radiotherapy patient groups are scarce, the findings are significant due to the biological rationale and similar mucosal targets (21,22). This is also believed to be the mechanism of action in this study.

Regarding dietary patterns, there are pilot randomized clinical trials and observational data suggesting that a low-FODMAP approach may help reduce intestinal gas and symptoms during pelvic radiotherapy (23,24). However, the ESMO (European Society for Medical Oncology) supportive care guideline emphasizes that an evidence-based standard for these diets has not yet been established and that they should be implemented on a personalized basis, with the guidance of a dietitian, and for short periods (25). An individualized approach goes beyond standard protocols. Formulas should be tailored to comorbidities.

Behavioral-dietary measures, such as maintaining hydration, avoiding bladder irritants such as caffeine, alcohol, and green tea, and symptom-based pharmacological support (e.g., alpha-blockers, alkalizing agents), are early steps recommended in clinical literature for GU toxicity and are not contradictory to nutritional support; instead, they complement it (26).

In this context, the lower incidence of Grade 2–3 GU/GU toxicity in our patients receiving NS may be explained by microbiota-mucosal barrier interactions. It may be more clinically significant, particularly in patients receiving concurrent chemotherapy, those at high risk for sarcopenia or cachexia, or those with marginal nutritional status at baseline (14,17,19,21).

However, to clarify the most effective composition of NS, timing of initiation (including neoadjuvant/induction), dose-duration, and target population, powered, multicenter randomized controlled trials blinded to RTOG/EORTC or CTCAE (Common Terminology Criteria for Adverse Events) are needed (15,19,25,26). In conclusion, individualized medical nutrition support, probiotic and prebiotic strategies, short-term dietary changes and programs, if necessary, combined with lifestyle recommendations including hydration and avoidance of irritants and modern radiotherapy techniques, have the potential to reduce early GI and GU toxicity associated with pelvic radiotherapy in gynecologic cancers. These strategies aim to maintain and improve treatment continuity and quality of life.

CONCLUSION

Appropriate nutritional support is believed to play a crucial role in the treatment process of gynecological cancer patients receiving pelvic radiotherapy. Research indicates that dietary modification may reduce side effects that may occur in the genitourinary and gastrointestinal systems. This is important for maintaining patients' quality of life and improving treatment compliance. The effectiveness of nutritional support is not solely dependent on a specific dietary index; each patient's needs, health status, and response to treatment may vary. Therefore, implementing personalized, individualized nutritional approaches is of great value. Comprehensive, multicenter studies encompassing larger patient groups are planned for the future, and the resulting data are expected to guide clinical practice.

Ethical Statement

Ethical approval was obtained from the Ethics Committee of Selçuk University Faculty of Medicine (Approval No: E-70632468-05004-905549). This study complies with the principles of the Declaration of Helsinki.

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REVIEW/DERLEME

Epitelyal Over Kanserlerinde Genetik Testler

Genetic Testing in Epithelial Ovarian Cancer

Tevfik Güvenal[1], Fuat Demirkıran[2], İlkkan Dündar[3]

[1] Prof. Dr., Department of Gynecologic Oncology, Celal Bayar University School of Medicine Manisa, Turkiye
[2] Prof. Dr., Department of Gynecologic Oncology, Cerrahpasa Faculty of Medicine, Istanbul University-Cerrahpasa, Istanbul, Türkiye
[3] Prof. Dr., Department of Gynecologic Oncology, Acibadem University, Istanbul, Türkiye

ABSTRACT

In the epithelial ovarian cancer, the most important risk factors are family history and the presence of some genetic mutations. The most known genetic mutations are BRCA1 and 2 gene mutations, which are in the homologous recombination repair gene family. Besides BRCA1-2, other gene mutations involved in homologous recombination repair are also risk factors. Gene mutations occur in the form of germ line and/or somatic mutations. Today, knowing these mutations in epithelial ovarian cancers, especially in high-grade serous tumors, is important both in guiding the treatment of the patient and in determining whether there is a risk in family members. In this review, the detection methods of these tests, their effectiveness in choosing treatment and management in women at risk will be discussed.

Keywords: Epithelial ovarian cancer, Genetic testing, BRCA1, BRCA2, Homolog recombinant repair

ÖZET

Epitelyal over kanserleri için en bilinen risk faktörü aile öyküsü ve genetik mutasyonların varlığıdır. Genetik mutasyonların en bilineni BRCA1 ve 2 gen mutasyonları olup bunlar homolog rekombinasyon onarım gen ailesindendir. Ayrıca BRCA1-2 dışında homolog rekombinasyon onarımında görevli diğer gen mutasyonları da risk faktörü oluşturmaktadır. Gen mutasyonları germ line ve/veya somatik mutasyonlar şeklinde olmaktadır. Günümüzde epitelyal over kanserlerinde, özellikle yüksek dereceli seröz tümörlerde bu mutasyonların bilinmesi, hem hastanın tedavisinin yönlendirilmesinde hem de aile bireylerinde risk olup olmadığının belirlenmesinde önemlidir. Bu derlemede bu testlerin saptanma yöntemleri, tedavi seçminde etkinliği ve riskli kadınlardaki yönetim tartışılacaktır.

Anahtar Kelimeler: Epitelyal over kanseri, Genetik testler, BRCA1, BRCAA2, Homolog rekombinasyon onarım

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Sorumlu Yazar: Tevfik Guvenal, Prof. Dr., Celal Bayar University School of Medicine, Department of Obstetrics and Gynecology, Manisa, Turkey. Email: tguvenal@yahoo.com

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GİRİŞ

Over kanseri (OK), dünyada 6.6/100,000 sıklıkla görülen, 2020 yılında 313,959 yeni tanı alan hastanın olduğu ve 207,252 hastanın da kaybedildiği bir kanserdir. Dünya genelinde kadın kanserlerinde ölümlerde yedinci sırada, ABD de ise beşinci sıradadır (1,2). Türkiye'de GLOBOCAN 2020 verilerine göre 7. en sık görülen kanserdir ve 100.000 kadının 9.5'inde görülmektedir. Ülkemizde yılda 4059 over kanseri ve 2730 buna bağlı ölüm meydana gelmektedir (3). Yaşam boyu bir kadında over kanseri gelişme riski ise 78 de 1, ve bu kanserden ölüm riski yaklaşık olarak 108 de 1'dir (2).

Over kanserlerinde en güçlü risk faktörü, ailede meme veya over kanseri görülme öyküsüdür ve yaklaşık olarak tüm over kanserlerinin %25'i kalıtsal genetik nedenlidir (4). Aile öyküsü olan kadınlarda over kanserlerinin yaklaşık %40'ını BRCA1 ve BRCA2 mutasyonları oluşturmakta ve yaklaşık dörtte birinde de BRCA1/2 dışındaki Fanconi anemi yolağı ve homolog rekombinasyon (HR) genlerdeki değişimler saptanmaktadır (4).

Kalıtsal over kanserinin görüldüğü diğer bir durum ise Lynch sendromu, önceki adıyla herediter nonpolipozis kolorektal kanserdir. Bu sendromda kolon kanseri dışında endometrium ve over kanseri riski de artmaktadır. Lynch sendromdaki mutasyonlar mismatch onarım genleri (MMR) olan MLH1, MSH2, MSH6 ve PMS2' nın birinde oluşmaktadır. MMR mutasyonu olan kadınlarda yaşam boyu over kanseri gelişme riski%3-13 tür (5).

Over kanserlerinin altında yatan moleküler ve genetik değişiklikler hakkında bilgi sahibi olmak, tanıda, hastalığı öngörmede, prognoz ve tedavi stratejilerinde kişiye özgü yaklaşımların geliştirilmesine ve aynı zamanda ailedeki bireylerin risklerinin belirlenmesine olanak sağlar.

Kanserde Mutasyonlar

Kanserler, genlerde oluşan mutasyonlar ya da genlerin DNA dizilimindeki zararlı değişiklikler sonucu kontrolsüz hücre büyümesinden kaynaklanmaktadır. Çoğu mutasyonlar, baz sıralamasında silinmeler, yer değiştirmeler, eklemeler ve kaymalar gibi değişiklikleri içermektedir. Mutasyonlar, somatik ve germline mutasyonlar olmak üzere ikiye ayrılır.

Somatik Mutasyonlar

Somatik ya da akkiz mutasyonlar kanserin en sık nedenidir. Bu mutasyonlar, bir kişinin yaşamı boyunca tek bir hücredeki genlerin zarar görmesinden kaynaklanır. Somatik mutasyonlar nedeniyle ortaya çıkan kanserler sporadik kanserler olarak adlandırılır. Bu mutasyonlar vücuttaki her hücrede bulunmaz ve ebeveynden çocuğa geçmez. Başka bir deyiş ile kuşaktan kuşağa aktarılmazlar. Somatik mutasyonlara neden olan bazı yaygın kanserojenler arasında tütün kullanımı, ultraviyole, radyasyon, virüsler, kimyasal maruziyetler ve yaşlanma bulunur.

Germline Mutasyonlar

Germline mutasyonlar daha az görülen mutasyonlardır. Bir germline mutasyonu, sperm ve yumurta hücresinde meydana gelir ve konsepsiyon sırasında doğrudan ebeveynden çocuğa geçer. Embriyo büyürken, sperm veya yumurta hücresinden gelen mutasyon vücuttaki her hücreye kopyalanır. Mutasyon üreme hücrelerini etkilediği için nesilden nesile geçebilir. Germline mutasyonlarının neden olduğu kansere kalıtsal veya herediter kanser denir ve tüm kanserlerin yaklaşık %5-10'unu oluşturur. Bir nesilden diğerine geçebilen 50'den fazla farklı kalıtsal kanser sendromu tanımlanmıştır.

Mutasyonu saptama teknikleri

DNA sıralama (sekans) teknikleri, DNA dizisini normal hücrelerdeki sıralama ile karşılaştırarak hem germline hem de somatik mutasyonları tanımlayabilir. Somatik mutasyonların saptanması için tümör dokusu gerekirken, germline mutasyonlar insanın ulaşılabilen herhangi bir hücresine (tükürük örneğinde bukkal hücreler ya da kandaki hücreler) ulaşmak yeterlidir. Germline ve somatik mutasyon test sonuçları birbirleri ile örtüşmeyebilir. Örneğin, tümör dokusunda somatik BRCA mutasyonu saptanan bir over kanserli kadında germline BRCA mutasyonunu olabilir veya olmayabilir. Bu nedenle mutasyonun kalıtsal (germline) olup olmadığını belirlemek için germline mutasyon testi yapmak gerekli olacaktır. Kanser türüne bağlı olarak, tedavi seçeneklerinin belirlenmesine yardımcı olmak için hem somatik hem de germline testleri kullanılır.

Over kanserlerinde BRCA1/2 mutasyonların bilinmesi hastalığın yaygınlığı, kemosensitivite ve sağkalım gibi birçok faktör hakkında klinisyene yol gösterebilir. Aynı zamanda sağlıklı bireylerde germline BRCA mutasyonunun varlığının bilinmesi oluşabilecek kanserin tanı yaşı konusunda da yol gösterici olur.

BRCA1/2 Mutasyonları ve Homolog Rekombinant Eksikliği (Homologous Recombination Deficiency; HRD)

Pek çok çalışmada over kanseri tanısı alan kadınların %13-15'inde BRCA1 ve BRCA2 germline ve %7'sinde de somatik mutasyonlarının olduğu bildirilmiştir (6-9). Aile öyküsünde meme ve/veya over kanseri olanlarda ve genç yaşta (<50 yaş) tanı alanlarda daha fazla oranda BRCA1/2 mutasyonu saptanır (10). BRCA1/2 mutasyonları en sık yüksek grade epitelyal over kanserlerinde görülmekle birlikte diğer histolojik tiplerde daha az oranda saptanmaktadır (11,12). Müsinöz ve düşük grade seröz over kanserlerinde ise bu mutasyonlar oldukça nadirdir.

Son zamanlarda over kanserlerinde BRCA1/2 mutasyonlarını da içine alan daha kapsamlı genetik değişiklikler gösteren homolog rekombinant eksikliği (HRD) gündeme gelmiştir. Kanser Genom Atlası (TCGA) projesinde, yüksek grade seröz over kanserli olguların yaklaşık %50'nde HRD pozitifliği bildirilmiştir (13). HRD'ye homolog rekombinasyon (HR) yolağındaki germline ya da somatik mutasyonlar neden olur. Germline ve somatik BRCA1/2 mutasyonları ve BRCA gen promotor metilasyonları, HRD'nin en sık bilinen nedenleridir, ancak HR yolağının diğer genetik anormallikleri de HRD'ye neden olabilir (13, 14). HRD'yi saptamak için BRCA mutasyon testi ve genomik instabilite skoru bakılmakta ve BRCA mutasyonu varsa ya da genomik instabilite skoru ≥42 ise HRD pozitif olarak kabul edilmektedir. HRD skoru artıkça sağ kalım oranları artmaktadır (15). Ancak HRD testlerinin doğruluğu konusunda tartışmalar devam etmekte ve daha iyi sonuçlar verebilecek ve olguların seçiminde doğru yönlendirebilecek testlere gereksinim bulunduğu da belirtilmektedir.

Genetik testlerin önemi

Over kanserlerinde genetik mutasyonların saptanması ile herediter over kanserli hastaların tanımlanması, tedavinin kişiselleştirilmesi yanında, aile üyelerinin riskinin belirlenmesine, mutasyon taşıyıcıların tanınmasına ve sonucunda risk azaltıcı yöntemlerin uygulanmasına ve uzun dönemde sonuçların iyileşmesine olanak sağlar. BRCA mutasyonları epitelyal over kanserli hastalarda yönetimini ve tedavi seçimini etkilediği için, bu mutasyonları

belirleyecek testler günümüzde optimal yönetimin rutin bir parçası olmaya başlamıştır. Bu mutasyonlara sahip olan hastalarda poly (ADP-ribose) polymerase (PARP) inhibitörleri (olaparib, niraparib, rucaparib ve veliparib gibi) ile hedefe yönelik tedaviler konusunda kanıtlar oluşmaya başlamıştır. FDA 2014 yılında germline BRCA1/2 mutasyonu olan, önceden üç dönem ya da daha fazla kemoterapi almış, rekürren over kanserli hastalarda monoterapi için olaparib kullanımı onaylanmıştır. Daha sonra iki dönem ya da daha fazla kemoterapi alan germline ve somatik BRCA1/2 mutasyonu olan rekürren over kanseri olguları için rucaparib kullanımını onaylanmıştır. Amerika Birleşik Devletleri dışında Avrupa Komisyonu tarafından platin duyarlı, rekürren BRCA-mutant (germlime ve/veya somatik) yüksek grade seröz epitelyal over, tüp veya primer periton kanseri olan ve platin bazlı kemoterapiye tam ya da kısmi yanıt veren olgularda monoterapi olarak olaparib satışı onaylanmıştır. Son zamanlarda ise niraparib'in platin duyarlı rekürren over kanserlerinde idame tedavisinde etkinliği gösterilmiştir. Bu çalışmalarda en fazla klinik yarar germline HRD mutasyonu olan olgularda görülmüştür (16).

Sonraki yıllarda yapılan çalışmalarda olaparib, niraparib ve veliparib gibi PARP inhibitörlerinin ilk basamak tedavi sonrası BRCA1/2 mutasyonu olan ve olmayan epitelyal over kanserli olgularda da etkili olduğu gösterilmiştir (SOLO 1, PAOLA 1, PRIMA ve VELIA çalışmaları) (17-20). Bu çalışmalar sonrası olarapib yüksek grade epitelyal over kanseri, tüp ya da primer periton kanseri olan ve BRCA mutasyonu (germline ve/veya somatik) olan olgularda ilk basamak tedaviye kısmi ya da tam yanıt veren olgularda idame tedavisi olarak FDA tarafından onaylanmıştır.

PARP inhibitörleri, DNA'daki tek iplikli kırılmaların onarımında rol oynayan proteinler olan poli (ADP-riboz) polimerazları hedefleyen ilaçlardır. BRCA mutasyona uğramış tümör hücrelerinde, homolog rekombinasyonla çift sarmallı kırılmaların onarımı eksiktir (HRD). PARP aktivitesinin inhibisyonu ile onarılmamış tek sarmallı kırılmalar çift sarmallı kırılmalara dönüşerek hücre ölümüne yol açar (21). Epitelyal over kanserleri, tuba ve primer peritoneal kanserlerdeki PARP inhbitörleri ile ilgili çalışmalar incelendiğinde, olaparib'in platinum duyarlı, relalps, yüksek rade seröz over kanserli olgularda plasebo ile karşılaştırıldığında daha uzun progresyonsuz sağkalım (PFS) sağladığı görülmüştür (8.4 ay vs. 4.8 ay, $p<0.001$) (22). Ayrıca randomize, plasebo kontrollü faz 2 bir çalışmada, BRCA mutasyonuna sahip platin duyarlı, rekürren seröz over kanserlerinde platin bazlı kemoterapi sonrası olaparip ile idame tedavisi alan olgularda daha uzun genel sağkalım ve PFS görülmüştür (23). 2018 de yapılan SOLO-1 çalışmasında (randomize, çift kör ve Faz 3 çalışma) platinum duyarlı BRCA pozitif yüksek grade, seröz ve endometrioid kanserler ile periton ve tuba kanserli olgularda first line kemoterapiden sonra idame tedavisi olarak olaparip kullanımı progresyon riski %70 oranında düşürdüğü saptanmıştır (17). Yine SOLO2, faz 3 çalışmasında da olaparip in rekürren ve platin duyarlı olgularda etkin olduğu görülmüştür (24). PAOLA-1 randomize faz 3 çalışmasında ileri evre, yüksek grade epitelyal over kanseri olan HRD pozitif olgularda (BRCA mutasyonu olan ve olmayan) bevacizumap içeren ilk basamak kemoterapiye idame olaparib eklenmesinin, PFS de anlamlı artış sağladığı bulunmuştur (18).

ARIEL 3 (RCT, faz 3) çalışmasında da rucaparip platin duyarlı, rekürren over kanserlerde BRCA mutant olgularda PFS de, plaseboya göre anlamlı avantaj sağladığı görülmüştür (25). NOVA çalışmasında niraparib BRCA mutant, HRD

pozitif, yüksek grade, platin duyarlı, rekürren over kanserlerinde idame tedavisi olarak etkili bulunmuştur (16). PRIMA çalışmasında (RCT, faz 3), yeni tanı almış yüksek grade'li seröz ve endometrioid kanserlerli, BRCA mutasyonu olan ve olmayan olgularda (mutant ve wild tiplerde), ilk basamak kemoterapiye yanıt veren hastalarda idame niraparibin plaseboya göre anlamlı PFS avantajı sağladığı gösterilmiştir (19).

VELIA çalışmasında yüksek grade over kanserli olgularda, BRCA mutasyonu olan ve olmayan hastalarda, ilk basamak carboplatin/paclitaxel tedavisi sonrası veliparib ile idame tedavisi ile daha uzun hastalıksız sağkalım sağlanmıştır (20)

BRCA mutasyonlarının bilinmesi, sadece rekürren olgularda ilaç seçiminde kullanılan bir parametre değildir. Aynı zamanda hastalığın prognozu hakkında da bilgi verir. BRCA1/2 mutasyonu olan over kanserli kadınlarda BRCA wild tip ile karşılaştırıldığında tümör yükünün ve bulky lenf nodlarının daha fazla olduğu görülmüştür (26). Ancak bu grup hastalarda 5 yıllık sağkalımın daha yüksek oranlarda olduğu saptanmıştır. Epitelyal over kanserlerinde 5 yıllık sağkalım oranlarına bakıldığında; BRCA mutant olmayanlarda %36, BRCA1 mutantlarda %44 ve BRCA2 mutantlarda ise %52'dir (27). Diğer pek çok çalışmada da BRCA mutant hastalarda genel sağkalımın daha iyi olduğu doğrulanmıştır (8, 28). BRCA mutantlardaki sağkalım oranlarının iyi olması HRD'ye bağlı platin tabanlı tedavilere daha iyi yanıt vermesiyle açıklanabilir.

Over kanserli olgunun patojenik bir germline mutasyon taşıdığı doğrulandığında, birinci derece akrabaların aynı mutasyonu taşıma olasılığı %50, ve ikinci derece akrabaların ise %25 tir. BRCA mutasyonları taşıyan bireylerde yüksek oranda kanser görülme olasığı göz önüne alındığında, her yetişkinin birinci ve ikinci derece akrabalarının test edilmesinin gerekliliği ortaya çıkar (29).

Genetik Testler

Genetik testler, germline ve somatik genetik testler olarak ikiye ayrılır. İki testin avantajları ve dezavantajları vardır (30). Germline testler daha iyi bilinen bir tekniğe sahiptir. DNA ekstraksiyonu daha kolaydır. Germline mutasyonların prognostik ve öngörme özellliği vardır. Ancak somatik mutasyonlarda bu özellikler ile ilgili veriler sınırlıdır. Ayrıca germline mutasyonları çoklu kanser riskini artırdığından, farkındalığın artmasına ve risk azaltıcı işlemlerin yapılmasına ve aile üyelerinin riskinin belirlenmesine olanak sağlar.

Next Generation Sequencing (NGS) ile yapılan somatik testler, hedefe yönelik tedavilerin kullanılabileceği HRD'li hastaların belirlenmesine olanak verir. Bu nedenle tümör dokusunda somatik mutasyonları araştırılmasında büyük önemi vardır. Ayrıca germline testler ile atlanan (germline muasyonu olmayan) ve somatik mutasyonu olan hastalar vardır. Bunun yanında somatik testler genetik danışmanlık gerekmediğinden günlük pratikte kullanımları daha kolaydır. Pratik uygulamada somatik testler germline testler için bir triaj işlemi görür. Somatik mutasyonu olmayan olgulara germline test yapılmasına gerek yoktur.

Germline DNA sekansı en hassas yaklaşımdır. Germline DNA, BRCA mutasyonu için negatifse, tümör dokusundan DNA sekanslanmalıdır, çünkü olguların % 5'inde BRCA genlerinde somatik mutasyonlar vardır (23,31). Ancak tümör dokusunda somatik mutasyon araştırmaları için DNA'nın eksrakte edilmesinde teknik zorluklar vardır.

BRCA1/2 ve Homologous recombination deficiency (HRD) testi

BRCA1/2 testleri, periferik kanda etkinliği

belirlenmiş tekniklerle bakılmaktadır. BRCA genlerindeki mutasyonların spektrumu geniş olduğu için testlerin yorumlanmasında farklılıklar olabilir. Bu nedenle yorumlamanın belli standarlara göre yapılması önerilmektedir. Sonuçlar benign, olası benign, belirli olmayan, olası patojenik ve patojenik olarak rapor edilir (32).

Epitelyal over kanserlerin % 50'si, homolog rekombinasyon (HR) yolağındaki genlerinde genetik ve epigenetik değişikliklere bağlı olarak, homolog rekombinasyon (HR) yoluyla kusurlu DNA onarımı ve homologous recombination deficiency (HRD) oluşur (33). Homolog rekombinasyon gen ailesi BRCA1/2 genlerini de içeren çok sayıda geni barındırır. Bunlar; BRCA1, BRCA2, ATM, ATR, ATRX, BARD1, BLM, BRIP1, CHEK1, CHEK2, FANCA, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, FANCM, MRE11A, NBN, PALB2, RAD50, RAD51, RAD51B, RAD51C, RAD51D, RAD52, RAD54L, RPA1'dir. Yüksek grade seröz over kanserli olguların yaklaşık %50 de HRD pozitifliği görülür. HRD testi tümör dokusundan çalışılmaktadır.

dMMR testi

DNA mismatch repair (MMR) gen defekteri, epitelyal over kanserlerinin yaklaşık %10-12 de bulunur ve tüm histolojik alt tiplerde olmakla birlikte ağırlıklı olarak nonseröz histolojilerde görüldüğü bildirilmiştir (34-36). En yüksek dMMR oranları endometrioid (%19.2), müsinöz (%16.9), ve clear cell (%11.5) tümörlerde görülür. Dolayısıyla, dMMR'nin clear cell, endometrioid ve müsinöz over, fallop ve primer periton kanserlerinde rutin olarak test yapılmasının yararlı olacağı ve diğer histolojik tiplerde de yapılabileceği düşünülebilir. dMMR mutasyonunun saptanan rekürren epitelyal over kanserli olgularda pembrolizumab ile tedavi gündeme gelebilir.

Risk azaltıcı yöntemler

BRCA1 mutasyonu taşıyanlarda over kanseri riski %44, BRCA2 mutasyon taşıyıcılarında ise %17 dir (37). BRCA mutasyonlu hastalarda over kanserinin ortalama başlangıç yaşı, mutasyon olmayan hastalara göre 10 yıl daha erkendir (37). Bu yüksek riskli hastaların risk azaltma stratejilerine ilişkin multidisipliner yönetim ve bireysel danışmanlık zorunludur.

Mutasyon taşıyıcılara uygun tarama, kemoprevensiyon veya risk azaltıcı cerrahi gibi tedavi seçenekleri sunulmalıdır. ESMO, SGO ve NCCN tarafından yayınlanan uluslararası kılavuzlardaki bu güncel kanıtlara göre, BRCA 2 mutasyon taşıyıcılarına 40-45 yaşlarında, BRCA1 taşıyıcılarına ise 35 ila 40 yaş arasında risk azaltıcı cerrahiler (BSO, mastektomi, vb) önerilmelidir.

ÖNERİLER

Tüm epitelyal over, tuba ve primer periton kanseri olgularına BRCA1/2 için genetik testler (germline ve somatik), yaş, ve aile öyküsüne bakılmadan istenmelidir. Müsinöz histolojilerde ve borderline over tümörlerinde test yapmak için yeterli veri yoktur. Genetik testlerin (germline, mutasyon) tanı konduğunda yapılması önerilir. Önce germline, negatif ise somatik mutasyonmu aranmalı, yoksa önce somatik, negatif ise germline mutasyon aranmalıdır görüşleri, halen tartışmaya açıktır. Eğer tanı sırasında test yapılmamışsa, mümkün olan en kısa zamanda yapılmalıdır. Ayrıca ilk tedavisini tamamlamış takip döneminde olan hastalarda da, nüks olduğun BRCA1/2 somatik mutasyonların varlığı araştırılmalıdır. Başlangıçta germline testi yapılmış ve negatif veya anlamsız sonuç çıkmış olgularda da somatik mutasyon aranmalıdır. Çünkü germline test negatif olsa bile tümör

dokusunda somatik mutasyon olabilir. BRCA1/2 mutasyonları negatif olan olgularda diğer HRD gen mutasyonları olabilir. Bu nedenle tüm HRD genlerini içeren multigen panellerinin çalışılması uygun olabilir.

Germline veya somatik mutasyonları olan over kanserli kadınlara, ilgili otortiteler tarafından onaylanmış PARP inhibitörü gibi tedaviler önerilmektedir. Clear cell, endometrioid veya müsinöz over kanserli kadınlara, dMMR) için somatik tümör testi önerilmeli ve dMMR olan kadınlara da onay almış tedaviler sunulmalıdır. Ayrıca patojenik mutasyonlu over kanserli hastaların birinci veya ikinci derece kan akrabalarına, kişiye özel genetik risk değerlendirmesi, danışmanlık ve genetik test sunulmalıdır. Bazı derneklerin önerileri aşağıdaki tabloda sunulmuştur (38)

Dernek	Hedef populasyon	Kimlere genetik test	Hangi test	Test zamanı	Genetik danışmanlık
SGO	Epitelyal over, tuba ve periton kanseri tanısı alan kadınlar	Meme, over, tuba ve periton kanseri tanısı almış olan ve kalıtsal riski artmış olan hastalar.	Symptoms may mimic Bartholin cyst; solid, non-cystic mass without inflammation should raise suspicion	Kanser tanısı konduğunda	Meme, over, tuba ve periton kanseri tanısı almış olan ve kalıtsal riski artmış olan hastalara verilmeli
NCCN	Epitelyal over, tuba ve periton kanseri tanısı alan kadınlar	Over, tuba ve peritoneal kanseri olan kadınlara önceden bilinmiyorsa BRCA1/2 testi yapılmalı. Meme, over, tuba ve periton kanseri kalıtsal riski olan kadınlara yapılmalı	En az BRCA1/2 ve MSI veya DNA mismatch repair bakılmalı. HRD düşünülebilir	Tanı konduğunda Germline ve/veya somatik BRCA1/2	Tedaviyi geciktiren bir danışmanlık olmamalı
NICE	Meme veya over kanserli olgular, meme, over ya da ilişkili (prostat, pankreatik) kanser aile öyküsü olanlar	Meme veya over kanseri olan kadınların kombine BRCA1/2 mutasyon taşıyıcısı olma olasılığı %10 veya daha fazlaysa, uzman genetik kliniklerinde genetik testler önerin.		Başlangıç tedavi aşamasında ya da sonraki herhangi bir zamanda	Herhangi bir yaşta over kanseri akrabası olan ailelerin spesifik genetik kliniklerine gitmeleri önerilmekte

Dernek	Hedef populasyon	Kimlere genetik test	Hangi test	Test zamanı	Genetik danışmanlık
ACMG ve NSGC	Herediter meme -over kasner sendromu şüphesi olanlar	Ailesinde over, tüp ve periton kanseri olan olgular	Symptoms may mimic Bartholin cyst; solid, non-cystic mass without inflammation should raise suspicion	Herediter bir kanser sendromunu düşündüren kişisel veya aile öyküsü olan bireylere genetik testler önerilmelidir	
ESMO	Yüksek grade tümörü olan hastalar	Yüksek grade tümörleri olan hastalar germline BRCA mutasyonu için test edilmelidir. BRCA mutasyonu için somatik testler de düşünülebilir	MRI is helpful in assessing tumor grade and extent		Test öncesi bilgilendirilmiş onam formu ile genetik danışmanlık verilmelidir

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CASE REPORT/OLGU SUNUMU

A rare mass on the localization of Bartholin gland: Leiomyosarcoma

Bartholin bezi lokalizasyonunda nadir görülen bir kitle: Leiomyosarkom

Tugba Akcaoglu[1], Adeviye Elci Atılgan[2]

[1] Department of Plastic and Reconstructive Surgery, Johns Hopkins University, School of Medicine, Baltimore, Maryland, USA
[2] Department of Urogynecology, Istanbul Medipol University Faculty of Medicine, Istanbul, Türkiye

ABSTRACT

Vulvar leiomyosarcoma is a rare malignant tumor of the vulva originating from smooth muscle, yet it is the most common type of vulvar sarcoma. It often presents as a benign lesion, which can lead to misdiagnosis and delays in appropriate treatment. We present a case that was initially suspected to be an anal abscess or Bartholin gland abscess. Imaging revealed a solid vulvar mass with fibroid-like characteristics rather than a cystic structure. Following wide local excision, histopathological examination and immunohistochemical staining confirmed the diagnosis of vulvar leiomyosarcoma. Current literature emphasizes the lack of a standardized treatment algorithm due to the rarity of this tumor. This case highlights a personalized treatment approach enabled by interdisciplinary collaboration.

Keywords: leiomyosarcoma, Vulvar sarcoma, Vulvar leiomyosarcoma, Bartholin cyst

ÖZET

Vulvar leiomyosarkom, vulvanın düz kas dokusundan kaynaklanan nadir bir malign tümördür; ancak vulvar sarkomlar arasında en sık görülen tiptir. Genellikle iyi huylu bir lezyon izlenimi verdiğinden, yanlış tanıya ve tedavide gecikmelere yol açabilir. Bu yazıda, başlangıçta anal apse veya Bartholin apsesi olarak değerlendirilen bir olgu sunulmaktadır. Görüntüleme yöntemleriyle yapılan incelemede, kistik yapıdan ziyade miyomu andıran solid özellikte bir vulvar kitle saptanmıştır. Kitlenin geniş lokal eksizyonunun ardından gerçekleştirilen immünohistokimyasal boyama ve patolojik inceleme sonucunda vulvar leiomyosarkom tanısı konmuştur. Güncel literatürde, vulvar leiomyosarkomların oldukça nadir görülmesi nedeniyle standart bir tedavi algoritması bulunmadığı vurgulanmaktadır. Bu olguda, disiplinler arası iş birliğiyle hasta bazlı kişiselleştirilmiş bir tedavi yaklaşımı benimsenmiş ve vaka, mevcut literatürdeki yönetim stratejileriyle birlikte değerlendirilmiştir.

Anahtar Kelimeler: Leiomyosarkom, Vulvar sarkom, Vulvar leiomyosarkom, Bartolin kisti

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Correspondence: Tugba Akcaoglu, Department of Plastic and Reconstructive Surgery, Johns Hopkins University, School of Medicine, Baltimore, Maryland, USA. E-mail:drtugbaakcaoglu@gmail.com

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INTRODUCTION

In gynecological practice, soft tissue and visceral sarcomas are rare tumors, accounting for an estimated 4% of all gynecological malignancies.[1] They most frequently arise in the uterus (83%), followed by the ovaries (8%), vulva and vagina (5%), and other gynecological organs (2%) [2]

Leiomyosarcomas are classified as soft tissue sarcomas (STS) of smooth muscle origin, arising from the smooth muscle component throughout the body. They originate from mesenchymal tissue and typically occur in intra-abdominal organs, the retroperitoneum, and the walls of blood vessels.[2] They are not considered a distinct gynecological malignancy. Gynecologists are generally more familiar with uterine leiomyosarcomas than those occurring in the vulva.

Vulvar leiomyosarcomas (VLMS) are extremely rare, representing only 1% to 3% of all malignant vulvar tumors.[3] However, VLMS is the most common histological type among primary vulvar sarcomas. [1] It exhibits a bimodal age distribution in women, with the first peak occurring between 20 and 30 years of age and the second in women over 50. [4] The youngest reported case was 14 years old, and the oldest was 72.[4] VLMS most frequently occurs in the labia majora, followed by the Bartholin gland, clitoris, and labium minus, respectively.[3]

Clinically, VLMS typically presents as a painless mass near the Bartholin gland, often leading to an initial misdiagnosis as a Bartholin cyst or abscess.[5] Due to its rarity, there is currently no standardized guideline for the management of VLMS. Consequently, clinical decision-making relies primarily on case reports published in the literature. Herein, we report a case of VLMS and review the current literature regarding preoperative evaluation, diagnosis, treatment options, and follow-up.

CASE REPORT

A 44-year-old virgin woman presented with a growing mass on the left side of her vulva. She reported progressive swelling accompanied by pain while sitting, which had developed over the past six days. She had no history of systemic illness or prior surgery. The patient initially visited the general surgery outpatient clinic with a suspected anal abscess. However, following a rectal and anal examination, the general surgeon ruled out an anal abscess and referred her to a gynecologist with a presumptive diagnosis of a Bartholin abscess.

Gynecological examination revealed a well-defined, palpable mass measuring 7×6×7 cm on the left side of the vulva, located at the 5 o'clock position on the left labium majus. No palpable lymphadenopathy was detected. Transabdominal ultrasound showed a normal uterus and ovaries. On translabial ultrasound, the mass appeared more consistent with a myoma-like structure rather than a cystic lesion. Subsequently, contrast-enhanced pelvic MRI was performed. It revealed a solid mass with significant contrast enhancement, extending superiorly toward the bladder base, laterally to the left vaginal wall, and inferiorly toward the rectum. No lymphadenopathy was identified in the pelvic or inguinal regions.

Symptomatic treatment with a cephalosporin-group antibiotic and an anti-inflammatory agent was administered for one week. With this treatment, the edema and tenderness subsided. However, the patient continued to experience discomfort while sitting, so local excision was planned.

The surgery was performed under spinal anesthesia. A vertical skin incision was made

over the mass, followed by sharp and blunt dissection. Intraoperatively, the vulvar skin and subepithelial layer appeared unremarkable. A solid, well-defined mass was located in the subcutaneous tissue, in the region of the left Bartholin's gland **(Figure 1)**. Rectal examination confirmed that the rectum and anal canal were free of involvement. Vaginal examination could not be performed due to the patient's virgin status.

The mass was completely excised from the surrounding tissues in a manner similar to a myomectomy. It did not resemble an abscess. As frozen section analysis was not available, the final diagnosis was deferred until the permanent pathology results were obtained. The skin was then closed subcutaneously using 3-0 Monocryl absorbable sutures.

The patient's postoperative period was uneventful, and she was discharged 24 hours later. Final pathology revealed a vaginal leiomyosarcoma (VLMS) measuring 6×7×7 cm with positive surgical margins. Immunohistochemical staining showed focal positivity for Caldesmon, Actin, CD99, BCL-2, Desmin, Pancytokeratin (PSK), CD10, and p63. Stains for HMWCK, CK-7, CK-20, HMB-45, CD34, S-100, and CD68 were negative. The Ki-67 proliferation index was 70%. Due to the malignant pathology findings, a whole-body PET-CT scan was performed. The imaging showed no evidence of metastatic disease; however, a residual mass with high uptake measuring 10×7 mm was detected at the corner edge of the left vaginal canal. The case was discussed at an interdisciplinary tumor board.

The patient was informed that there is no established standard guideline for the management of VLMS. She declined both radiotherapy (RT) and hemi-vulvectomy. Ultimately, re-excision of the surgical margin was decided. The residual disease was removed with a minimum of 5 mm tumor-free resection margins. The tumor cells were positive for SMA, Desmin, and Caldesmon. The Ki-67 proliferation index remained at 70%, and the mitotic index was 16 mitoses per 10 high-power fields (HPF). The resection margin was confirmed to be tumor-free. Final tumor staging was pT2 pNX L0 V0 R0 G2. The patient was discharged four days later. Adjuvant external beam radiation therapy (EBRT) was planned. She underwent the recommended regimen of 25 fractions of 2 Gy (total 50 Gy), with a boost of 2 Gy × 5 fractions (total 10 Gy) to the former tumor bed, bringing the total to 60 Gy. The patient was followed up with pelvic MRI and thoracic CT every three months. No recurrence was observed during the 12-month follow-up period.

Written informed consent was obtained from the patient for publication of this case report and related images.

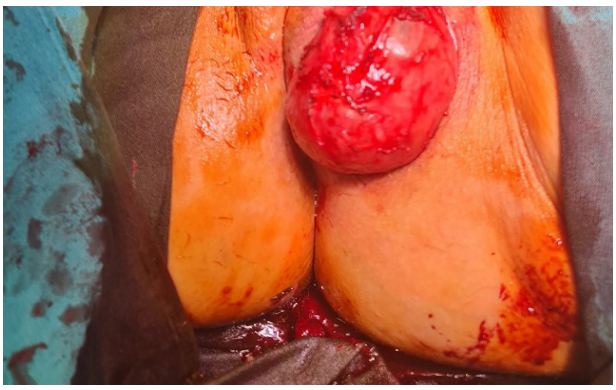

***Figure 1**: External view of leiomyosarcoma during excision*

DISCUSSION

The risk of any vulvar lesion being malignant is very low, as 98% of vulvar lesions are benign and only 2% are malignant. The most common vulvar malignancy is squamous cell carcinoma, while vulvar sarcomas are

extremely rare.[2] Approximately 80 subtypes of soft tissue sarcomas are recognized.[6] Well-defined subtypes of vulvar sarcomas include malignant fibrous histiocytomas, dermatofibrosarcomas, leiomyosarcomas, angiosarcomas, angiomyxomas, liposarcomas, chondrosarcomas, rhabdomyosarcomas, and epithelioid sarcomas.[7] The rarity and heterogeneity of these tumors often lead to delays in diagnosis and treatment. Mortality rates have reportedly increased in Europe due to limited progress in prevention, diagnosis, and therapy.[8]

Vulvar leiomyosarcomas (VLMS) present with nonspecific clinical features and are frequently misdiagnosed as Bartholin cysts or abscesses.[5] VLMS typically causes discomfort due to pressure exerted by the growing mass, although it may be painless in the early stages. As the tumor enlarges, pain may develop. Since VLMS originates in the subcutaneous tissue of the vulva, a solitary fibrous nodule is often palpable upon examination.[5]

The non-cystic, solid nature of the mass and the absence of inflammatory signs should prompt clinicians to consider a potential vulvar malignancy rather than a benign Bartholin cyst in the differential diagnosis. In this case, perineal ultrasonography initially raised suspicion of a tumor. This is a non-invasive, simple, and cost-effective method that should be utilized in initial evaluations. In the second stage, contrast-enhanced pelvic MRI findings further supported the possibility of a malignant vulvar tumor. The relationship between MRI features and tumor grade is well established: irregular, multilobulated tumor shapes, intertumoral heterogeneity, and peritumoral contrast enhancement are commonly associated with high-grade soft tissue sarcomas.[9]

In the preoperative work-up, percutaneous biopsy is often not effective for diagnosing vulvar leiomyosarcoma (VLMS), as it may yield benign cytological findings. This can result in delayed or inappropriate treatment and a poorer prognosis. For an accurate diagnosis of VLMS, total excision of the nodule followed by pathological examination and immunohistochemical (IHC) staining is essential.[10] Pancytokeratin, desmin, smooth muscle actin, and caldesmon are frequently positive markers in VLMS. [11] Percutaneous biopsy may be considered when rapid initiation of treatment is necessary, particularly in cases involving metastatic disease where neoadjuvant therapy is planned.[11] Given the rarity of vulvar leiomyosarcoma, there is no universally accepted treatment protocol.[12] Classification and staging of VLMS are based on the guidelines for soft tissue sarcomas. Therapeutic recommendations follow the management protocols outlined by the European Society for Medical Oncology (ESMO) and the National Comprehensive Cancer Network (NCCN).[12]

The primary treatment for vulvar leiomyosarcoma (VLMS) involves wide local excision of the tumor with negative resection margins. In extensive or invasive cases, radical hemivulvectomy may be required.[12] Routine inguinal or pelvic lymph node dissection is not recommended.[12] There is no universally defined minimal surgical margin for VLMS. Since these tumors are often attached to adjacent organs such as the bladder, vagina, rectum, or anus—as in our case— “only” clean margins may be considered acceptable in certain situations.[13]

If pathology reveals high-grade VLMS, radiation therapy may be indicated. However, it is generally not necessary for low-grade VLMS.[12] In cases with positive surgical margins, re-

excision aiming for a 2 cm clear margin or hemivulvectomy can be performed.[12] If negative margins are successfully achieved, three additional cycles of adjuvant chemotherapy and radiation therapy may be administered. [12] The administration of chemo therapy is considered to prevent the risk of recurrence or metastasis .[12]

Tumor size and grade are important prognostic factors.[6,8,11] Neoadjuvant chemotherapy is supported on the basis that it can enable radical surgery by reducing tumor size. One published case involved a 72-year-old woman with a 12.5 cm VLMS who received three cycles of neoadjuvant chemotherapy, resulting in a partial response. This was followed by radical vulvectomy with negative surgical margins. Three additional cycles of adjuvant chemotherapy were administered, and no recurrence was observed during the follow-up period.[14] If the tumor appears infiltrative or metastases are detected, neoadjuvant chemotherapy combined with radiotherapy may be considered.[14] Due to the invasive nature of these tumors, the risk of recurrence remains high—even with negative surgical margins—ranging from 65% to 77%.[6] Additionally, local recurrence in low-grade tumors may also warrant adjuvant radiotherapy.[12]

Management of VLMS during pregnancy requires balancing the risk of tumor progression with the risk of premature delivery.[15] Tumor size has been reported to increase rapidly during pregnancy. If feasible, complete resection of the tumor is recommended at 34 weeks of gestation under spinal anesthesia. Following pathological confirmation of vulvar leiomyosarcoma, induction of labor should be planned. Vaginal delivery may be permitted if there are no obstetric contraindications. Postpartum imaging with contrast-enhanced abdominopelvic MRI and PET-CT is used to exclude local or distant metastases.[15]

The different clinical scenarios for the management of VLMS are summarized in Table 1 with relevant references.

Table 1: Clinical Scenarios and Management of Vulvar Leiomyosarcoma (VLMS)

Scenario/Case	Diagnostic Approach	Treatment Strategy	Additional Notes	Reference
Initial presentation (non-specific symptoms)	Physical exam, perineal ultrasonography	Proceed with further imaging and diagnostic evaluation	Symptoms may mimic Bartholin cyst; solid, non-cystic mass without inflammation should raise suspicion	[5]
Suspicion of malignancy	Contrast-enhanced pelvic MRI	Guides surgical planning; MRI features like multilobulation, heterogeneity indicate high-grade tumors	MRI is helpful in assessing tumor grade and extent	[9]
Preoperative work-up	Total excision with pathological and IHC analysis	Preferred over percutaneous biopsy	IHC markers (pancytokeratin, desmin, SMA, caldesmon) are frequently positive in VLMS	[10,11]

Localized or extensive VLMS	Pathology and imaging to assess tumor extent	Wide local excision with negative margins; radical hemivulvectomy for extensive cases	Clean margins acceptable in some cases involving adjacent organs	[12,13]
Cases with positive or high-risk margins	Pathological confirmation	Re-excision with 2 cm margin or hemivulvectomy; adjuvant chemotherapy and radiotherapy (3 cycles) if negative margins achieved	Adjuvant therapy aims to reduce recurrence/metastasis risk; lymph node dissection not	[12]
Large, infiltrative, or metastatic tumors	Clinical staging, biopsy if needed	Neoadjuvant chemotherapy ± radiotherapy, followed by surgery	Helps reduce tumor burden before radical surgery	[6,11,14]
Case example (72 y/o, 12.5 cm tumor)	Biopsy, followed by imaging	3 cycles neoadjuvant chemo → radical vulvectomy → 3 cycles adjuvant chemo	No recurrence observed in follow-up	[14]
Pregnancy with VLMS	Clinical evaluation + imaging	Surgical excision at 34 weeks under spinal anesthesia, followed by induction of labor	Vaginal delivery possible if no obstetric contraindications; postpartum PET-CT & MRI to rule out metastases	[15]

CONCLUSİON

This case presents the successful management of vulvar leiomyosarcoma through local re-excision and radiotherapy following a positive surgical margin after wide local excision. It highlights the diagnostic challenges and emphasizes that treatment can be individualized based on the radiologic and pathologic characteristics of the tumor.

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