TÜRK
JİNEKOLOJİK ONKOLOJİ DERGİSİ
The Turkish Journal of Gynecologic Oncology

Baskı *(Printing)*
Ayrıntı Basımevi - İvedik Organize
Sanayi Bölgesi 28. Cad. 770 Sok. No: 105-A
Ostim/ANKARA
Telefon: (0312) 394 55 90 - 91 - 92
Faks: (0312) 394 55 94 • Sertifika No: 13987

Teknik Hazırlık *(Technical Asistance)*
İhsan AĞIN

Basım Tarihi
2023

Yönetim Yeri *(Editorial Address)*
Selami Ali Mah. Bağlarbaşı Nuh Kuyusu Cad.
Ekşioğlu İkizdere Apartmanı 251/14
Üsküdar/İSTANBUL
web: www.trsgo.org

Yılda üç kez yayınlanır
(Published three times a year)
Asitsiz kağıda basılmıştır
(Printed on acid-free paper)

Türk Jinekolojik Onkoloji Derneği'nin
Resmi Yayın Organıdır ve bölgesel süreli yayındır
(The Official publication of
Turkish Gynecologic Oncology Society)
web: www.trsgo.org

ISSN: 2148-5372

TÜRK
JİNEKOLOJİK ONKOLOJİ DERGİSİ
The Turkish Journal of Gynecologic Oncology

2023-2

TÜRK JİNEKOLOJİK ONKOLOJİ DERGİSİ

YAZIM KURALLARI

Türk Jinekolojik Onkoloji Dergisi International Committee of Medical Journal Editors-2001 (Uniform Requirements for Manuscripts Submitted to Biomedical Journals) kuralları temel alınarak hazırlanmıştır.

Türk Jinekolojik Onkoloji Dergisi yılda dört kez yayınlanır. Derginin yazı dili Türkçe olup Jinekolojik Onkoloji alanındaki klinik ve deneysel çalışmalara dayalı orijinal araştırma yazıları, derlemeler, orijinal olgu sunumları ve editöre mektuplar yayınlanır. Jinekolojik cerrahi, radyoterapi, kemoterapi, patoloji, sitoloji, endokrinoloji, genetik, moleküler biyoloji ve epidemiyoloji temelinde Jinekolojik onkoloji ile ilgili tüm branşlar tarafından hazırlanan çalışmalar kabul edilmektedir. Gönderilen yazılar adı gizli tutulan iki hakem tarafından yayınlanmaya yeterliliği yönünden değerlendirilerek kabul veya red edilmektedir. Yazılar aşağıda belirtilen kurallara göre hazırlanmalı ve

Ali Ayhan
Editör, Türk Jinekolojik Onkoloji Dergisi
Güneş Tıp Kitabevi, M. Rauf İnan Sokak No: 3/B
06410-Sıhhiye, Ankara-TURKEY
e-posta: jinekolojikonkoloji@guneskitabevi.com

Adresine gönderilmelidir. Ayrıca derginin yardımcı editörlerine veya bölgesel sorumlularına da gönderilebilir. Postadaki kayıp ve gecikmeler dergimizin sorumluluğu dışındadır.

Tüm yazılar çalışmanın ana bulgularını içeren bir üst yazı ile gönderilmelidir. Üst yazıda çalışmanın başlığı, türü, -makalenin içeriği konusunda uzlaşmak yazarların sorumluluğunda olduğundan- yazarların tümünün imzası ve daha önce başka bir yerde yayınlanmadığına veya eş zamanlı olarak başka bir dergiye gönderilmediğine dair yazarların taahhütü olmalıdır. Daha önce sunulmuş bildiriler yer ve tarih belirtmek koşulu ile yayınlanabilir. Yazı, şekil, tablo, resim ve grafikler üç kopye halinde basılı olarak ve ayrıca elektronik ortamda da (disket,CD, vb.) gönderilmelidir. Daha sonra çıkacak sorunları önlemek için yazarlara yazılarının bir kopyesini saklamaları önerilir.

Elektronik Makale Gönderimi

Çalışmalar www.jinekolojikonkoloji@guneskitabevi.com adresine e-mail eklentisi olarak da gönderilebilir. Elektronik olarak gönderilen çalışmaların ayrıca basılmış şekilde gönderilmelerine gerek yoktur. Böylece posta yolu ile doğacak gecikmelerin önüne geçilebilecektir. Yazılar ve de tablolar "Word" dosyası olarak gönderilmeli; şekil, grafik ve fotograflar ise yazının içine konulmadan "JPEG" dosyası olarak gönderilmelidir. Ayrıca, tüm yazarlarca imzalanmış üst yazı "Scan" edilerek gönderilmelidir.

Yazının Hazırlanması

Yazılar Türkçe olarak hazırlanmalıdır. Yazılar standart A4 beyaz kağıt üzerine çift aralıklı olarak, kağıdın sadece bir yüzüne, 'Times New Roman' karakteri ile yazı boyutu 12 punto ve kenarlardan 2.5 cm boşluk bırakılarak hazırlanmalıdır. Sırasıyla şu bölümlerden oluşmalıdır: Başlık sayfası, Türkçe ve İngilizce özet, anahtar sözcükler, makale, teşekkür, kaynaklar, makale özeti, tablo, grafik ve şekiller. Her bir sayfa başlık sayfasından başlanarak numaralanmalı ve sayfa numaraları sağ üst köşeye yazılmalıdır.

Gözlemsel ve deneysel çalışmalarla ilgili araştırma yazıları şu başlıkları içeren alt bölümlere ayrılmalıdır: Giriş, Materyal ve Metod, Sonuçlar ve Tartışma. Materyal-metod ve sonuçlar bölümleri açıklamaya yardımcı olmak üzere ilave alt başlıklar kullanılarak hazırlanabilir. Olgu sunumlarında giriş, olgu sunumu ve tartışma bölümleri bulunmalıdır. Derleme yazılar ve editöre mektuplar kendine özgü alt başlıklardan oluşabilirler.Derleme türündeki yazılar editörler kurulu tarafından önceden planlandığı için bu tür çalışmalar gönderilmeden önce kurul onayı alınmalıdır.

Başlık Sayfası

Bu sayfa şu bilgileri içermelidir: 1) Yazının Türkçe ve İngilizce başlığı, 2) Yazarların açık ad ve soyadları, ünvanları, 3) Dergide sayfa üstlerine yazılmak üzere 60 karakteri geçmeyecek şekilde kısa başlık, 5)Çalışmanın türü, 6) Çalışmanın yapıldığı klinik, bölüm ve enstitülerin isimleri, 7) Sorumlu yazarın telefon, faks ve e-posta da dahil olmak üzere ayrıntılı yazışma adresi. Yazar sayısı araştırma makalelerinde 7'yi, olgu sunumlarında 5'i, derleme ve editöre mektuplarda 5'i geçmemelidir. Ancak çok merkezli çalışmalarda en fazla 12 yazara izin verilmektedir.

Özet

Yurt dışından gelen makalelerde Türkçe özet ve anahtar sözcük zorunluluğu olmasa da her yazıda her biri 250 kelimeyi aşmayacak şekilde İngilizce ve Türkçe özet bulunmalıdır. Bu bölümde amaç, metaryal ve metod, sonuçlar ve tartışma altbaşlıkları olmalıdır. Olgu sunumlarında amaç, olgu sunumu ve tartışma bölümleri olmalıdır. Derleme yazıların özetleri, derlemenin önemli noktalarının kısa bir değerlendirmesi olmalıdır. Editöre mektuplarda özet yazılmamalıdır.

Anahtar Sözcükler

Araştırma yapan araştırıcılarca kullanılmak üzere en fazla 6(altı) adet anahtar sözcük verilmelidir. Index Medicus'taki Medical Subjects Headings listesine uygun sözcükler kullanmaya özen gösterilmelidir.

Giriş

Okuyucuyu problem ve diğer yazarların bu konudaki bulguları hakkında bilgilendirmek amaçlanmalıdır. Çok önemli makaleler referans olarak kullanılmalı ve çalışmanın amacı hakkında açık ve ayrıntılı bilgi verilmelidir.

Materyal ve Metod

Çalışmanın tüm ayrıntıları açıkça belirtilmeli ve klinik, teknik veya deneysel yöntemler tekrarlanabilecek şekilde tüm ayrıntıları ile açıklanmalıdır. Yöntemle ilgili daha önce yayınlanmış olan yazılar kaynak gösterilmelidir.

Sonuçlar

Bulgular hiçbir yorum katılmadan belirtilmelidir. Tablo, şekil veya grafiklerdeki verilerin tekrarı olmamalıdır.

Tartışma

Bulgular, diğer yazarların önceki çalışmalarındaki bulgularla ilişkilendirilir ve bu veriler üzerine yorum yapılır. Bu bulguların deneysel araştırma veya klinik uygulama alanına katkıları da açıklanmalıdır.

Teşekkür

Kısaca verilmelidir.

Kaynaklar

Yazı içinde ilgili yerde parantez içinde kullanılmalı ve bu sıraya göre numaralandırılarak dizilmelidir. Yazarlar kaynakların doğruluğundan kendileri sorumludur. Altı yazara kadar olan yazılarda yazarların tamamı yazılmalı daha fazla ise ilk üçü yazılarak İngilizce yazılarda 'et al.'; Türkçe yazılarda 'et al.' şeklinde kısaltılmalıdır. Dergi kısaltmaları Index Medicus'a uygun olmalıdır. Olgu sunumlarında en fazla sekiz kaynak gösterilmelidir. Kaynaklar aşağıda açıklanan formatta düzenlenmelidir.

a. Kaynak bir dergi ise:

Sloan AER, Powers ME. A perspective on popular perceptions of adverse reactions to foods. J Allergy Clin Immunol 1986;78:127-132.

b. Kaynak bir kitap ise:

DiSaia PJ, Creasman WT: Clinical Gynecologic Oncology, 5. ed.,Baltimore, Mosby-Year Book Inc., 1997.

c. Kitaptan bir bölüm ise:

Clague JE, Horan MA. Injury in old age. In: Evans JG, Williams TF, Beattie BL, Michel JP, Wilcock GK (eds). Oxford Textbook of Geriatric Medicine. Oxford University Press. NY, USA, 2000; 98-102.

Makale Özeti

İçindekiler bölümünde başlığın altında kullanılmak üzere çalışma en fazla 25 kelimeyle özetlenmelidir.

Tablolar

Tablolar yazıyı tamamlamalı, yazıdaki verilerin tekrarı olmamalıdır. Her tablo ayrı bir sayfada olmalı ve ayrı ayrı 'Roman rakamları ile' numaralandırılmalıdır. Açıklayıcı bilgiler 'dipnot' şeklinde verilmeli ve dipnot üst simge şeklindeki harflerle belirtilmelidir. Tablolar yazıdaki sıraya göre numaralandırılmalıdır.

Şekil, Grafik ve Fotoğraflar

Aynı sonuçlar ya tablo ya da grafik olarak verilmeli ikisi birden olmamalıdır. Bütün şekiller, ayrı ayrı 'Arabic' olarak numaralanmalı ve yazıdan ayrı olarak sunulmalıdır. Yayıncının bu materyalleri küçültme veya büyültme hakkı saklıdır. Ok işaretleri, harfler ve numaralar profesyonelce yerleştirilmeli eğer yapılamazsa, gerçek şekil veya fotoğraf üzerine değil, yapıştırılan bir materyal üzerine yazılmalıdır. şekil altı açıklamalar kısa olmalı dört veya beş satırı geçmemelidir. 'Açıklama için makaleye bakınız' şeklindeki yazımlardan kaçınılmalıdır. Tablo, şekil ve grafiklerin listesi ayrı bir sayfada verilmelidir.

Proof

Sadece sorumlu yazara gönderilecek olup sadece gerekli değişiklikler yapılarak en kısa sürede geri gönderilmelidir. Yeni eklemeler yapılmamalıdır.

Haklar

Dergide yayınlanan yazıların yayın hakkı yayınlanmaya kabul'den itibaren Güneş Tıp Kitabevi'ne aittir. Yazıların etik ve bilimsel sorumluluğu yazarlara aittir. Yazarlara telif ücreti ödenmemektedir.

Yukarıda belirtilen şartları sağlamayan makaleler, ilgili şartların tamamlanması için yazarlarına iade edilecektir.

THE TURKISH JOURNAL OF GYNECOLOGIC ONCOLOGY

INSTRUCTIONS TO AUTHORS

- Original research papers and case reports about women's health, reproductive physiology and health are considered to be published in this journal. The reviews of the authors who are invited by the editorial board are to be considered.
- Languages of the journal are Turkish and English.
- Uploading the articles via the internet (http://trsgo.dergisi.org/submit) is suggested in order to assess articles faster.
- The editor get the articles which are stylistically appropriate analysed by advisors. When deemed necessary, they are sent to other advisors or published after the necessary changes are carried out by authors.
- Any of the authors can not be removed from the author's list without a written consent of all the authors. No person can be added to the list as the author or the order of authors cited in the list cannot be changed.
- All authors should indicate that they contribute to this journal academically and scientifically and they share the scientific and ethical responsibility of the journal in a cover letter.

Thereafter, a form will be sent to authors and the authors will be requested to fax or send this form upon signing it.

Scientific Responsibility

- Authors should plan or perform the work of their article themselves. They should write the article or revise it, make a statistical assessment or approve its final state to be sent to the publisher. The convenience of the articles to scientific rules is under the responsibility of the authors.
- The analysis of a hypothesis in research papers is performed with the statistical assessment of the data. Before articles are sent, they should be evaluated by a biostatistical expert. If biostatistical expert is not among the listed authors, then s/he should be cited in the acknowledgement part of the article. In a statistical assessment, the quantity of the findings should be indicated and measurement errors or confidence interval should be shown with coherent rates when possible. Statistical concepts, abbreviations and symbols should be described. The statistical appropriateness for the journal could be found on-line at www.acponline.org/journals/resource/unifreqr.htm

Ethical Responsibility

- Before the article is published, authors should sign and notify the form of "copyright and financial support agreement". The written form showing that the consent and support of supervisory and ethical board are provided or the principles about human experimentations laid down in Helsinki Agreement (which was adopted in 1975) (http://www.wma.net/e/policy/b3.htm) are complied with or not and the consent is obtained from people participated in the research after they are instructed should be affixed in the MATERIALS AND METHODS section.
- If animals are used in researches, then the authors should notify that they protect animals' rights and they are given approval from ethics comittee of their institutions.
- If there is a direct or indirect commercial link in the article or an institution/a firm that gives financial support for the research, the authors should describe this commercial relationship (consultation or other agreements) with this commercial product, drug or firm that is benefited from on the front page.

Evaluation of the Article In Terms of the Language It Is Written

- Turkish articles should be based on Turkish dictionary and medical terms dictionary of The Turkish Linguistic Society. English abstracts should be evaluated by linguistic experts and the expert's consent should be particularly indicated to the editor on the presentation page.
- When the written text (after approved for publishing) is published, it is accepted that it belongs to the journal and its copyright (The Turkish Society of Gynecologic Oncology) is transferred to the publisher.
- The editor does not accept the responsibility of any injury or loss to any commodity or people which can be caused by The Turkish Society of Gynecologic Oncology and the publisher.

Preparation of the Text

"The journal" uses a sample pattern for the articles sent to medical journals. The text should be written on a compatible Microsoft Word file in double space and boldface, a white and A4 paper with at least 25 mm margin on one side. The extension of the file should be *.doc.

The following article components should be written in a new blank page:

Page 1, General Heading, maximum 40 characters including spaces.

Page 2, Heading, Complete Heading, full names of authors and their academic status, addressees, approved financial support (fund)

Page 3, Abstract, Key Words, Abstract should include the target, planning, establishment of the experiment, patients, results and discussion. It should not exceed 250 words. 3 to 10 key words should be defined below the abstract. The abstract should include structural features. (It should be a structured abstract)

- Aim:
- Material &methods
- Results
- Conclusions

The following sections should be included to the article below the abstracts.

- Introduction
- Materials and Methods
- Results
- Discussion
- Acknowledgement
- Bibliography
- Tables and explanations

All individuals that are presented as authors should be qualified in authoring. Each author should contribute to the research sufficiently. Generally more than six authors are not deemed convenient.

Page 4, Heading, abstract and key words should be prepared in English. This page shall include the features of the third page. The page written in English shall be reviewed by a professional linguistic expert, if deemed necessary. This page shall be used by foreign indexes.

Acknowledgements

The people who contribute to the research not as an author but as an intellectual can be written here with their functions. Example: "Scientific Adviser", "Data Collector" or "Clinician". To write down these people's name, their consent is required. The authors are responsible for providing the written consents.

References

References should be numbered as in the order they are cited in the article. The references cited in tables and figures for the first time should be stated in the text, where the tables and figures are explained, as well. References should be written in arabic letters within brackets.

Presentations, unpublished observations and self-assessments should not be used as references. Non-verbal references can be written in brackets. The original journal should be indicated and the expression of "to be published" should be affiliated to articles which are not published but accepted as references. References should be verified with the original documents of the authors.

The titles of journals should be in accordance with abbreviations determined in IndexMedicus. All the authors of the article should be cited. If the number of the authors are over six, "et al." should be used for the seventh author.

Examples

Article in a journal

1. Takihara H, Sakatoku J, Cockett ATK. The pathophysiology of varicocele in male infertility. Fertil Steril 1991; 55: 861- 8.

Books

2. Colson JH, Armour WJ. Sports injuries and their treatment. 2nd rev. ed. London: S. Paul, 1986. 3. Diener HC, Wilkinson M, eds. Drug-induced headache. New York: Springer-Verlag, 1988. 4. Weinstein L, Swartz MN. Pathologic properties of invading microorganisms. In: Sodeman WA Jr, Sodeman WA, eds. Pathologic physiology: mechanisms of disease. Vol. 1. Philadelphia: WB Saunders, 1974: 457-72.

Abstract

5. O'Hanley P, Sukri N, Intan N. Morbidity and mortality trends of typhoid fever due to Salmonella typhi at the Infectious Disease Hospital (IDH) in North Jakarta from 1984 to 1991 [abstract no. 945]. In: Program and abstracts of the 32nd Interscience Conference on Antimicrobial Agents and Chemotherapy. Washington, DC: American Society for Microbiology, 1992: 268.

Letter

6. Kremer J. Yardsticks for successful donor insemination [mektup]. Fertil Steril 1991; 55: 1023- 4.

"To be published"

7. Lillywhite HB, Donald JA. Pulmonary blood flow regulation in an aquatic snake. Science. "To be published"

Tables, Figures, Abbreviations, Descriptive Information and Permissions

Tables: Tables should be written to seperate pages with double spaced. They should be titled and numbered with arabic numerals as in the order they are cited in the text. Tables should not be presented as photographs. Compact titles should be given to every coloumn. Descriptive information should be provided in footnotes, not in titles. The letters of a,b,c,d,e,f. should be used in footnotes and as in the order stated hereinbefore.

Figures: Figures should be professionally drawn and photographed. Hand-drawings or typescripts are not accepted. Letters or markers should be legible and font size should be fixed for every figure. Capital letters should be used for the explanations in figures. Symbols, writings and numbers should be considerably clear in order to be legible even when they are minified for publishing. Titles and detailed explanations should be within the writings belonging to the figure not inside the drawings. Figures should be 304 dpi gray scale at least and scanned in color.

Abbreviations: An abbreviation should be stated along with the word within its first appearance in the text. Afterwards, same abbreviation should be used constantly.

Descriptive Information: Descriptive information should be written consecutively in a seperate page with double spaced.

Permissions: Materials provided from other resources should be well documented with a written statement of the copyright owner.

Case Reports

Case Reports should be brief, informative and comprised of 7 pages double spaced with a table or figure. The technique or method used is limited with 10 pages double spaced and 3 graphics.

Letter to Editor

This part is constituted of the critics about the articles that have been published in the journal recently. Letter should be brief (400 words), double spaced and comprised of 5 quotations at most. Letters and replies should be in accordance with the format of the journal. Address, phone and fax number and e-mail address should be indicated alongside the corrospondance.

Editor has a right to shorten the letter and make other modifications necessary to provide convenience with the format of the journal.

Proofreading

If there is no other directives, proofreadings will be sent to the author. When necessary corrections are carried out, the article will be resent to journal as soon as possible. A letter will be sent to the author, the acceptance of whose article is final. Changes carried out in proofreadings are within the responsibility of the author except for typos.

Note: It is very important for our publishings to be given as references in terms of fostering our national publishing

İÇİNDEKİLER / *CONTENTS*

TÜRK JİNEKOLOJİK ONKOLOJİ DERGİSİ
2023-2, Sayfa 1-8
Original Article

Analysis of Prognostic Factors in Malignancies of Gynecological Origin with Brain Metastases

Tahir Eryılmaz[1], Hüseyin Akıllı[1], Ali Ayhan[1], Ahmet Muhteşem Ağıldere[1]

ABSTRACT

Objective: We aimed to evaluate the demographic and clinical characteristics of patients diagnosed with brain metastases of gynecological origin and to analyze the factors affecting prognosis after the diagnosis of brain metastases.

Material and Methods: Forty-eight patients with brain metastases who were followed for gynecological cancer in Başkent University's Department of Gynecological Oncology between 2008 and 2021 were evaluated retrospectively. Demographic, clinical, and pathological characteristics of the patients and the distribution of treatments according to gynecological cancers since the time of primary diagnosis were noted. Median survival times after the diagnosis of brain metastasis were evaluated statistically. Prognostic factors affecting the process of brain metastasis and survival after diagnosis were statistically analyzed.

Results: The median survival time after the diagnosis of brain metastasis was 8 months. It was 12 months in cases of ovarian cancer, 4 months for endometrial cancer, 8 months for cervical cancer, 3 months for vulvar cancer, and 4 months for uterine sarcomas. In univariate analysis, lesion number, localization, extracranial metastasis status, and treatment method were found to be associated with survival after brain metastasis, while lesion localization and treatment method were independent variables affecting prognosis in multivariate analysis.

Conclusion: Patients with the best prognosis after brain metastasis were treated with combined therapy. However, stereotactic brain radiotherapy alone had a better prognosis compared to patients who received whole brain radiotherapy alone.

Keywords: Gynecologic malignancy, Brain metastasis, Prognostic Factor, Radiotherapy

ÖZET

Amaç: Jinekolojik kökenli beyin metastazı tanısı alan hastaların demografik ve klinik özelliklerini değerlendirmeyi ve beyin metastazı tanısından sonra prognozu etkileyen faktörleri incelemeyi amaçladık.

Materyal ve Metod: Başkent Üniversitesi Jinekolojik Onkoloji Anabilim Dalı'nda 2008-2021 yılları arasında jinekolojik kanser nedeniyle takip edilen ve beyin metastazı tanısı alan 48 hasta retrospektif olarak değerlendirildi. Hastaların demografik, klinik ve patolojik özellikleri ile ilk tanı anından itibaren uygulanan tedavilerin jinekolojik kanserlere göre dağılımı tespit edildi. Beyin metastazı teşhisi konulduktan sonra medyan sağkalım süreleri istatistiksel olarak değerlendirildi. Tanı sonrası beyin metastazı sonrası sağkalımı etkileyen prognostik faktörler istatistiksel olarak analiz edildi.

Bulgular: Beyin metastazı teşhisi konulduktan sonra medyan sağkalım süresi 8 aydı. Over kanserinde 12 ay, endometrial kanserde 4 ay, rahim ağzı kanserinde 8 ay, vulva kanserinde 3 ay, rahim sarkomlarında 4 aydı. Univaryant analizde lezyon sayısı, lokalizasyonu, ekstrakraniyal metastaz durumu ve tedavi yöntemi beyin metastazı sonrası sağkalım ile ilişkili bulunurken, multivaryant analizde lezyon lokalizasyonu ve tedavi yöntemi prognozu etkileyen bağımsız değişkenler olarak bulundu.

Sonuç: Beyin metastazından sonra prognozun en iyi kombine tedavi sonrasında elde edildiği görüldü. Bununla birlikte, tek başına stereotaktik beyin radyoterapisi, tek başına tüm beyin radyoterapisi alan hastalara kıyasla daha iyi bir prognoza sahipti.

Anahtar kelimeler: Jinekolojik malignite, Beyin metastazı, Prognostik faktör, Radyoterapi

Received Date: 20/06/2023 Accepted Date: 16/07/2023

[1]Başkent University Ankara Hospital, Departments of Obstetric and Gynecology, Gynecologic Oncology Clinic

Corresponding Author: Tahir Eryılmaz
Başkent University Ankara Hospital, Departments of Obstetric and Gynecology, Gynecologic Oncology Clinic

Tel: +90 536 546 32 33
E-mail: tahir_eryilmaz@hotmail.com

It was presented at 20-22 congress of 'Ulusal Jinekolojik Onkoloji Kongresi & Ulusal Servikal Patolojiler ve Kolposkopi'

Introduction

Brain metastasis (BM) is an important condition associated with serious morbidity and mortality in cancer patients (1). While it is more common in cases of breast cancer, lung cancer, and malignant melanoma, it is rarely seen in gynecological cancers (2). It was reported to occur at rates of 0.3% to 12% in cases of ovarian cancer, 0.2% to 2% in endometrial cancer, and 0.2% to 2.1% in cervical cancer (3-7). There is not enough knowledge about the incidence of BM in cases of vulvar cancer or uterine sarcoma (8, 9).

In cases of gynecological cancer with BM, the prognosis is very poor and survival is unfortunately still expressed in months. The median survival time after BM was reported as 6 months in cases of gynecological cancer in general and as 10.1, 7.5, and 5 months in ovarian, endometrial, and cervical cancers according to gynecological origin, respectively (3, 10).

In recent years, it has been reported that the survival rates of patients with BM have increased with developments in surgical techniques and radiotherapy technology. Whole brain radiotherapy (WBRT) has been used for many years to treat BM and it is applied as irradiation to the whole brain. Stereotactic brain radiotherapy (SBRT), on the other hand, involves the application of a high-dose gamma knife beam specifically to the lesion. Its use is becoming more common due to the high efficacy of the treatment and fewer side effects (11, 12).

It has been reported that patients with younger ages, high performance status, and no extracranial metastases have better prognosis after the diagnosis of BM (13). The morphological features of the tumor are thought to be important factors in determining both the prognosis and the appropriate treatment (14).

The current study aimed to evaluate the demographic and clinical characteristics of patients diagnosed with BM of gynecological origin and to analyze the factors affecting prognosis after the diagnosis of BM.

Material and Methods

A retrospective analysis of the data of patients followed in Başkent University's Gynecological Oncology Department between January 2008 and December 2021 was performed. Patients with clinical suspicion of BM underwent surgical confirmation with imaging modalities as appropriate for each case **(Figure 1)**. The inclusion criteria of the study included pathological diagnosis of primary gynecological malignancies, diagnosis of BM by computed tomography and/or magnetic resonance imaging, and no prior BM. Exclusion criteria were a history of malignancy other than gynecological cancer and the presence of neuromuscular disease unrelated to central nervous system disease and/or BM. The follow-up data and treatment information of patients who received part of their treatment in another center due to gynecological malignancy and/or BM were included in the study after their eligibility for the

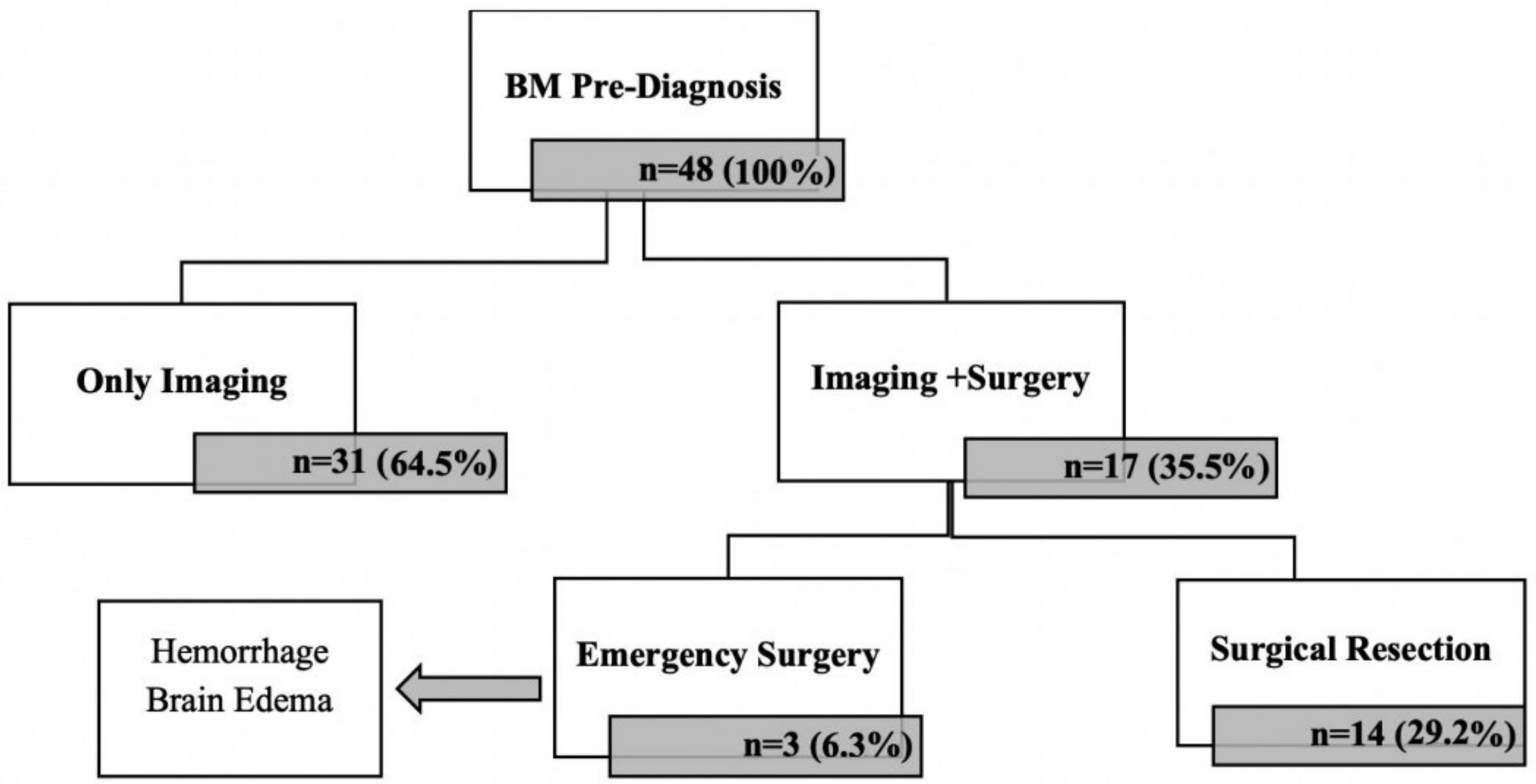

Figure 1: Distribution of brain metastasis diagnosis methods according to patients

study was confirmed. From the time of diagnosis of the primary malignancy, all treatments applied for the patients were determined by the gynecological oncology board.

BMs were detected in 48 patients followed for gynecological malignancies. Stage, tumor grade, and initial treatments applied were noted according to the origin of the gynecological malignancy. The origin and grade of the tumors were determined by pathologists experienced in gynecological cancers and subsequently re-evaluated and revised by a different pathologist according to the 2020 classification of the World Health Organization (WHO). The current International Federation of Gynecology and Obstetrics (FIGO) classification was used for staging. Initial treatments for gynecological malignancies included neoadjuvant chemotherapy, chemotherapy and radiotherapy, surgery (primary staging or primary cytoreduction) followed by chemotherapy, and surgery followed by chemotherapy and radiotherapy. The age, Karnofsky performance status (KPS) score, diagnostic method, extracranial metastasis status, morphological features of the lesion, and treatment modality of the patients diagnosed with BM were specified. The number of lesions was evaluated as single or multiple (≥2). Lesion localization was evaluated as supratentorial (brain parenchyma tissue), infratentorial (cerebellum, brain stem), or both infratentorial and supratentorial, and lesion sizes were recorded as <3 cm or ≥3 cm. Treatment modalities for BM were evaluated in 4 main groups that included patients who underwent palliative treatment, surgery, radiotherapy (WBRT/SBRT), and combined treatment (postsurgical radiotherapy).

IBM SPSS Statistics 23.0 (IBM Corp., Armonk, NY, USA) was used for statistical analysis. Data were reported as medians and ranges for continuous variables, while binary variables were reported as numbers and percentages. Chi-square tests, ANOVA, and t-tests were used as appropriate for comparisons between variables. Kaplan-Meier and log-rank tests were used to analyze survival. Factors affecting survival were evaluated with multivariate Cox regression analysis ($p<0.05$). Hazard ratios (HRs) were stated at 95% confidence intervals (95% CIs).

Results

The median follow-up time of the patients was 37.5 (1-161) months. According to cancer type, the follow-up duration was 42 (1-161) months for ovarian cancer, 28 (5-115) months for endometrial cancer, 25 (5-93) months for cervical cancer, 49.5 (37-62) months for vulvar cancer, and 35 (5-116) months for sarcoma. Twenty-seven (56.3%) patients had ovarian cancer, 8 (16.8%) had endometrial cancer, 7 (14.6%) had cervical cancer, 2 (4.2%) had vulvar cancer, and 4 (8.4%) had sarcoma. The demographic and clinical characteristics of patients diagnosed with BM are provided in **Table 1** according to the diagnosis of the primary malignancy

Table 1 • Demographic and Clinical Characteristics

	Gynecologic Cancer n=48 (100%)	Ovary n=27 (56.3%)	Endometrium n=8 (16.8%)	Cervix n=7 (14.6%)
Follow-up period after BM diagnosis (months)	20.5 (1-147)	27 (1-147)	12.5 (1-111)	14 (2-85)
Median Age at Diagnosis of BM	59.5 (29-81.5)	56 (27-80)	64 (53-70)	55 (47-67)
Stage				
I	3 (6.3%)	-	1 (12,5%)	1 (14.2%)
II	6 (12.6%)	1 (3.8%)	1 (12,5%)	3 (43.2%)
III	33 (74.3%)	22 (81.4%)	4 (50%)	2 (28.4%)
IV	8 (16.8%)	4 (14.8%)	2 (25%)	1 (14.2%)
Grade				
Low	-	-	-	-
Modarate	6 (14,3%)	-	2 (25%)	3 (50%)
High	36 (85,75)	27 (100%)	6 (%75)	3 (50%)

Devam ediyor

Table 1 • Demographic and Clinical Characteristics (Devamı)

	Gynecologic Cancer n=48 (100%)	Ovary n=27 (56.3%)	Endometrium n=8 (16.8%)	Cervix n=7 (14.6%)
Initial Treatment				
Neodjuvant Chemotherapy	3 (6.3%)	1 (3.8%)	1 (12.5%)	1 (14.3%)
Chemotherapy + Radiotherapy	2 (4.2%)	-	-	1 (14.3%)
Surgery + Chemotherapy	35 (79%)	26 (96.2%)	6 (75%)	1 (14.3%)
Surgery + Chemotherapy + Radiotherapy	5 (10,5%)	-	1 (12.5%)	4 (57.1%)
KPS Score				
≤ 30	28 (58.3%)	14 (51.9%)	6 (75%)	4 (57.1%)
> 30	20(41.7%)	12(48.1%)	2 (25%)	3 (42.9%)
Extracranial Metastases				
Absent	14 (29.2%)	11 (68.7%)	1 (6.25%)	2 (13.5%)
Present	34 (70.85%)	16 (50.5%)	7 (21.8%)	5 (15.6%)

BM: Brain Metastasis; KPS: Karnofsky Performans Scale

as ovarian, endometrial, or cervical cancer. The median time between cancer diagnosis and BM was 20.5 months. According to the gynecological origin, it was 27 (1-147), 12.5 (1-111), and 14 (2-85) months for ovarian, endometrial, and cervical cancers, respectively. The median age at the time of diagnosis of BM was 59.5 (29-81.5) years. For ovarian, endometrial, and cervical cancers it was 56 (27-80), 64 (53-70), and 55 (47-67) years, respectively. Forty-two (73.2%) cases were stage III-IV and 6 (16.8%) cases were stage I-II, while 36 (85.7%) patients had grade 3 tumors and 6 (14.3%) had grade 2 tumors. The initial treatment for the primary malignancy was surgery followed by chemotherapy for 35 (79%) patients, chemotherapy and radiotherapy for 5 (10.5%), chemotherapy and radiotherapy for 2 (4.2%), and neoadjuvant chemotherapy for 3 (6.3%).

At the time of BM diagnosis, the KPS score of 28 (58.3%) patients was ≤30 and 20 (41.7%) patients had KPS scores of >30. The diagnosis of BM was made by imaging after clinical preliminary diagnosis for 31 (61.5%) patients, while both imaging and surgical biopsy were performed for 17 (30.5%) patients. Thirty-four (70.8%) patients had extracranial metastases and 14 (29.2%) patients had isolated BMs, and 28 (58.7%) patients had multiple BM lesions and 20 (41.3%) had a single lesion. Tumor size was <3 cm in 24 (50%) cases and ≥3 cm in 24 (50%) cases. Tumors were present in 22 (45.8%) cases in a supratentorial location, in 7 (14.6%) cases in an infratentorial location, and in 19 (39.6%) cases in both locations **(Table 2).**

Considering the treatments for BM, 11(22.9%) patients underwent palliative treatment and 1 (2.1%) patient underwent surgical resection alone. There were 23 (48%) patients in the radiotherapy-only group, and 17 (35.5%) of those patients received WBRT while 6 (12.5%) underwent SBRT. Combined therapy was applied for 13 (27 %) patients, and after surgical resection, 9 (18.7%) patients received WBRT while 4 (8.3%) patients received SBRT.

The median survival time after BM was 8 months. It was 12 months for patients with ovarian cancer, 4 months for endometrial cancer, 8 months for cervical cancer, 3 months for vulvar cancer, and 4 months for sarcoma (p=0.41) **(Figure 2).**

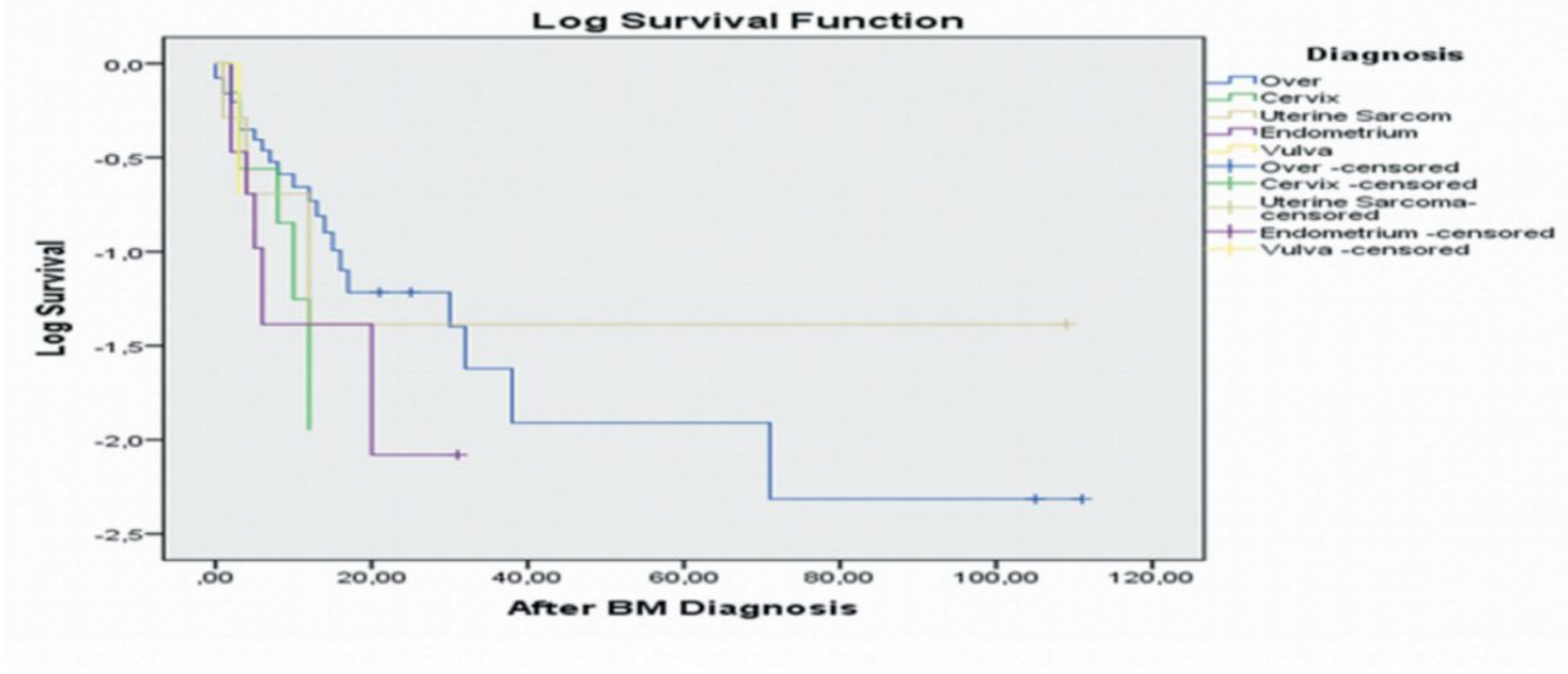

Figure 2: Median survival times after brain metastasis (months)

Table 2 • Morphological Features of BM Lesion

	Gynecologic Cancer (n=48, %100)	Ovary (n=27, 56.3%)	Endometrium (n=8, 16.8%)	Cervix (n=7, 14,6%)
Number of BM				
Single	20 (41.7%)	11 (55%)	3 (15%)	4 (20%)
Multiple	28 (58.3%)	16 (57.1%)	5 (17.8%)	3 (10.7%)
Location of BM				
Supratentorial	22 (45.8%)	10 (20.8%)	6 (12.5%)	3 (6.25%)
Infratentorial	7 (14.6%)	5 (10.4%)	-	1 (2.1%)
Supratentorial + Infratentorial	19 (39.6%)	12 (25.0%)	2 (4.2%)	3 (6.2%)
Maximum Diameter of BM				
< 3 cm	24 (50%)	17 (53.0%)	5 (62.5%)	3 (42.8%)
≥ 3cm	24 (50%)	10 (37.0%)	3 (37.5%)	4 (57.2%)
Treatment Modality				
Paliative	11 (22.9%)	6 (12.5%)	2 (4.2%)	2 (4.2%)
Surgical Resection	1 (2,1%)	–	1 (2.1%)	–
WBRT	17 (35.5%)	9 (18.7%)	2 (4,2%)	4 (83.0%)
SBRT	6 (12.5%)	4 (8.3%)	1 (2,1%)	–
Surgical Resection + WBRT	9 (18.7%)	6 (12.5%)	1 (2.1%)	1 (2.1%)
Surgical Resection + SBRT	4 (8.3%)	2 (4.2%)	1 (2.1%)	–

BM: Brain Metastasis; WBRT: Whole Brain Treatment; SBRT: Stereotactic Brain Radiotherapy

Table 3 • Univariate and Multivariate Analysis of Prognostic Factors in Patients with BM*

	Univariate Analysis			Multivariate Analysis		
Initial	**HR**	**CI 95%**	**p values**	**HR**	**CI 95%**	**p values**
Number of BM	3.26	0.31-8.92	0.02	2.13	0.38-13.09	0.41
Location of BM	0.43	0.02-0.67	0.01	0.22	0.06-0.78	0.02
Extracranial Metastases	2.85	0.34-11.82	0.01	2.20	0.57-8.48	0.25
Treatment Modality	7.45	1.37-8.54	0.001	3.71	1.44-9.57	0.007

BM; brain metastases

The effects of prognostic factors in gynecological cancers after the diagnosis of BM are summarized in **Table 3**. In univariate analysis, extracranial metastasis status (p=0.01), tumor localization (p=0.01), tumor number (p=0.02), and treatment type (p=0.00) affected prognosis. In addition, lesion localization (p=0.007; HR: 0.22; 95% CI: 0.06-0.78) and treatment modality (p=0.02; HR: 3.71; 95% CI: 1.44-9.57) were independent factors affecting survival after BM diagnosis in multivariate regression analysis.

Discussion

In the present study, we found that the incidence of BM among patients with gynecological malignancies was 0.6%. According to cancer type, the rates were 0.85%, 0.31%, 0.39%, 1.1%, and 1% for ovarian, endometrial, cervical, vulvar, and uterine sarcoma, respectively. In multivariate analysis, patients with supratentorial tumors and combined therapy had a better prognosis after the diagnosis of BM.

In an Italian multicentric study (MITO-19) of patients with ovarian cancer, the median survival time after BM was 12 months (15). In the review of endometrial cancer patients performed by Ucella et al., the median survival after the development of BM was reported as 5 months (16). Curo et al. reported survival of 2.3 months in their study of cervical cancer patients (17). These survival outcomes for ovarian and endometrial cancer are similar to our findings, but we have reported longer survival times for patients with cervical cancer. The survival times of patients with vulvar cancer and uterine sarcoma have also been presented here, but more studies are needed to draw appropriate comparisons (9, 18, 19).

Combined treatment had the best prognosis among the treatment groups. In the group of patients receiving radiotherapy alone, better survival outcomes were obtained with SBRT. Moreover, patients treated for BM had a better prognosis than untreated patients. Mahmoud-Ahmed et al. reported that the median survival time of patients who received radiotherapy after surgery was 15 months and the median survival of patients who received only radiotherapy was 2.4 months (20). In another study, Gressel et al. reported that the median survival time of patients who received radiotherapy after surgery was 10.5 months, while it was 4 months for patients who received radiotherapy alone (14). Recent studies have shown that better results can be obtained with SBRT treatment compared to WBRT because SBRT has fewer side effects and can be used more effectively for the lesion (21, 22). Meixner et al. reported that patients who received only SBRT had a median survival time of 10.7 months and had better prognosis than patients who received WBRT (23).

Patients with no extracranial metastases, supratentorial localization, and a single lesion may have much better survival with optimal treatment. However, the correlation with lesion size was not found to be statistically significant. In previous reports, it was underlined that the number of lesions and extracranial metastases are the two most important prognostic factors (12, 23). In this study, although it was found to be significant in univariate analysis, its statistical significance could not be shown in multivariate analysis.

The reported incidence of BM in cases of gynecological cancers is similar across studies conducted in the last 50 years and remains lower than 1% (24). At present, routine screening is not recommended due to the rarity of BM among patients with gynecological cancers (25). These recommendations may change with early predictions of the diagnosis of BM and the development of treatment methods (26).

Due to the general rarity of BM in cases of cancers of gynecological origin, the low number of cases included in the present study, and the fact that this was a single-center study, the frequency of BM in this patient population may not have been fully expressed. Additionally, the retrospective nature of the study may have caused misrepresentation in patient selection.

In most studies performed to date, survival outcomes after BM were found to be very poor. We suggest that the extracranial metastasis status and morphological characteristics of the lesion (lesion location, number of lesions, and size of lesions) should be considered in the selection of the most appropriate treatment method. We recommend combined therapy as the best approach in suitable cases. The more effective use of SBRT applications rather than WBRT may increase survival times, but more studies are needed in this regard.

References

1. Al-Shamy G, Sawaya R. Management of brain metastases: the indispensable role of surgery. Journal of neuro-oncology. 2009;92:275-82.
2. Nayak L, Lee EQ, Wen PY. Epidemiology of brain metastases. Current oncology reports. 2012;14:48-54.
3. Kato MK, Tanase Y, Uno M, Ishikawa M, Kato T. Brain metastases from uterine cervical and endometrial cancer. Cancers. 2021;13(3):519.
4. Gien LT, Kwon JS, D'Souza DP, Radwan JS, Hammond JA, Sugimoto AK, et al. Brain metastases from endometrial carcinoma: a retrospective study. Gynecologic Oncology. 2004;93(2):524-8.
5. Ogawa K, Yoshii Y, Aoki Y, Nagai Y, Tsuchida Y, Toita T, et al. Treatment and prognosis of brain metastases from gynecological cancers. Neurologia medico-chirurgica. 2008;48(2):57-63.
6. Pakneshan S, Safarpour D, Tavassoli F, Jabbari B. Brain metastasis from ovarian cancer: a systematic review. Journal of neuro-oncology. 2014;119:1-6.
7. Ratner ES, Toy E, O'Malley DM, Mcalpine J, Rutherford TJ, Azodi M, et al. Brain metastases in epithelial ovarian and primary peritoneal carcinoma. International Journal of Gynecologic Cancer. 2009;19(5). :856-9
8. Melone GA, D'Elia A, Brogna C, Salvati M. Uterine leiomyosarcoma metastatic to the brain: case report. Tumori Journal. 2008;94(6):856-60.
9. Yamada S, Yamada SM, Nakaguchi H, Murakami M, Hoya K, Matsuno A. A case of multiple brain metastases of uterine leiomyosarcoma with a literature review. Surgical oncology. 2011;20(4):e127-e31.
10. Borella F, Bertero L, Morrone A, Gambella A, Bovetti M, Cosma S, et al. Brain metastases from ovarian cancer: current evidence in diagnosis, treatment, and prognosis. Cancers. 2020;12(8):2156.
11. Chang EL, Wefel JS, Hess KR, Allen PK, Lang FF, Kornguth DG, et al. Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial. The lancet oncology. 2009;10(11):1037-44.
12. Monaco III E, Kondziolka D, Mongia S, Niranjan A, Flickinger JC, Lunsford LD. Management of brain metastases from ovarian and endometrial carcinoma with stereotactic radiosurgery. Cancer. 2008;113(9):2610-4.
13. Cormio G, Maneo A, Colamaria A, Loverro G, Lissoni A, Selvaggi L. Surgical resection of solitary brain metastasis from ovarian carcinoma: an analysis of 22 cases. Gynecologic oncology. 2003;89(1):116-9.
14. Gressel GM, Lundsberg LS, Altwerger G, Katchi T, Azodi M, Schwartz PE, et al. Factors predictive of improved survival in patients with brain metastases from gynecologic cancer: a single institution retrospective study of 47 cases and review of the literature. International Journal of Gynecologic Cancer. 2015;25(9).
15. Marchetti C, Ferrandina G, Cormio G, Gambino A, Cecere S, Lorusso D, et al. Brain metastases in patients with EOC: Clinico-pathological and prognostic factors. A multicentric retrospective analysis from the MITO group (MITO 19). Gynecologic oncology. 2016;143(3):532-8.
16. Uccella S, Morris JM, Multinu F, Cliby WA, Podratz KC, Gostout BS, et al. Primary brain metastases of endometrial cancer: A report of 18 cases and review of the literature. Gynecologic oncology. 2016;142(1):70-5:141-6.
17. Chura J, Shukla K, Argenta P. Brain metastasis from cervical carcinoma. International Journal of Gynecologic Cancer. 2007;17(1).
18. Dursun P, Ayhan A, Tarhan NC, Coban G, Kuscu E. Cerebellar metastasis in squamous cell vulvar carcinoma. Archives of gynecology and obstetrics. 2009;279:69-71.
19. Jaeger A, Biermann M, Prieske K, Grimm D, Grottke A, Salamon J, et al. Cerebral metastasis in recurrent squamous cell carcinoma of the vulva: case report and review of the literature. Archives of Gynecology and Obstetrics. 2020;301:327-32.
20. Mahmoud-Ahmed AS, Suh JH, Barnett GH, Webster KD, Belinson JL, Kennedy AW. The effect of radiation therapy on brain metastases from endometrial carcinoma: a retrospective study. Gynecologic oncology. 2001;83(2):305-9.

21. Lee Y-K, Park N-H, Kim JW, Song Y-S, Kang S-B, Lee H-P. Gamma-knife radiosurgery as an optimal treatment modality for brain metastases from epithelial ovarian cancer. Gynecologic oncology. 2008;108(3):505-9.
22. Nasioudis D, Persaud A, Taunk NK, Latif NA. Brain metastases from gynecologic malignancies: prevalence and management. American Journal of Clinical Oncology. 2020;43(6):418-21.
23. Meixner E, Eichkorn T, Erdem S, König L, Lang K, Lischalk JW, et al. Stereotactic radiosurgery for brain metastases from pelvic gynecological malignancies: oncologic outcomes, validation of prognostic scores, and dosimetric evaluation. International Journal of Gynecologic Cancer. 2022;32(2):172-180.
24. Deng K, Yang C, Tan Q, Song W, Lu M, Zhao W, et al. Sites of distant metastases and overall survival in ovarian cancer: a study of 1481 patients. Gynecologic oncology. 2018;150(3):460-5.
25. Ewend MG, Morris DE, Carey LA, Ladha AM, Brem S. Guidelines for the initial management of metastatic brain tumors: role of surgery, radiosurgery, and radiation therapy. Journal of the National Comprehensive Cancer Network. 2008;6(5):505-14.
26. Divine LM, Kizer NT, Hagemann AR, Pittman ME, Chen L, Powell MA, et al. Clinicopathologic characteristics and survival of patients with gynecologic malignancies metastatic to the brain. Gynecologic oncology. 2016;142(1):76-82.

TÜRK JİNEKOLOJİK ONKOLOJİ DERGİSİ
2023-2, Sayfa 9-14
Original Article

Diagnosis Accuracy with Frozen Section at Borderline Ovarian Tumors

Ozbilgec S[1], Akkus F[1], Demir ET[1], Yilmaz O[2], Oltulu P[2], Acar A[1]

ABSTRACT

Objective: This study examined patients diagnosed with borderline ovarian tumors by frozen section. Some of these patients' final pathologies differed from the diagnosis of borderline ovarian tumors with frozen sections. The situations that cause this difference are the subject of this study.

Material and Methods: This research investigated 68 patients who had adnexal mass surgery at the Necmettin Erbakan University Meram Faculty of Medicine Hospital between 2010 and 2022 and whose frozen section diagnosis results were recorded as borderline ovarian tumors. The diagnostic accuracy of the frozen section approach was determined using univariate and multivariate analyses.

Results: Unlike the frozen diagnosis, the features of the patients diagnosed with malignancy through definitive pathology were investigated. In these instances, the preoperative cutoff value for carcinoembryonic antigen was 1.16 ng/ml and 43 years of age.

Results and conclusion: Unlike the frozen diagnosis, the features of the patients diagnosed with malignancy through definitive pathology were investigated. In these instances, the preoperative cutoff value for carcinoembryonic antigen was 1.16 ng/ml and 43 years of age.

Keywords: Frozen section, Borderline ovarian tumors, Malignant, Carcinoembryonic antigen, Age

ÖZET

Amaç: Bu çalışmada adneksiyal kitle nedeniyle opere edilen ve frozen section ile borderline over tümörü (BOT) tanısı konulan olguların son patolojileri ile arasındaki ilişki araştırıldı.

Gereç ve Yöntem: Bu araştırma, 2010-2022 yılları arasında Necmettin Erbakan Üniversitesi Meram Tıp Fakültesi Hastanesi'nde adneksiyal kitle cerrahisi geçiren ve frozen section tanısı BOT olarak kaydedilen 68 hasta incelendi. Frozen section yaklaşımının tanısal doğruluğu, tek değişkenli ve çok değişkenli analizler kullanılarak belirlendi.

Bulgular ve Sonuç: Frozen sectiondan farklı olarak kesin patoloji ile malign tanısı konulan hastaların özellikleri araştırıldı. Bu durumlarda ameliyat öncesi CEA eşik değerinin 1,16 ng/ml olduğu ve bu olguların 43 yaşından büyük olduğu belirlendi.

Anahtar kelimeler: Frozen section, Borderline over tümörü, Malignite, CEA, Yaş

Received Date: 05/07/2023 Accepted Date: 15/08/2023

[1]Department of Obstetrics and Gynecology, Necmettin Erbakan University School of Medicine, Konya, Turkey
[2]Department of Pathology, Necmettin Erbakan University School of Medicine, Konya, Turkey

Corresponding Author: Sıtkı Özbilgeç
[1]Department of Obstetrics and Gynecology, Necmettin Erbakan University School of Medicine, Konya, Turkey

Tel: +90 505 345 12 07
E-mail: sozbilgec@yahoo.coom

Introduction

Borderline ovarian tumors (BOTs) are a diverse group of lesions known as tumors with limited malignant potential. These lesions are histologically characterized by atypical epithelial proliferation that does not include stromal invasion (1). BOTs are noninvasive tumors that sometimes spread to the peritoneum (2). These neoplasms are midway between benign cystadenomas and invasive carcinomas. They are also known as borderline, atypical, and low-risk tumors. Most pathologists, gynecologists, and oncologists use the term "borderline neoplasm," endorsed by the World Health Organization WHO. (3). Approximately 14-15% of initial ovarian tumors are borderline (4). There are several histologies for borderline tumors, such as epithelial ovarian cancer (5, 6). Among these, serous or mucinous instances are the most common. However, endometrioid, clear-cell, and Brenner borderline cancers are rare. Approximately 15 to 20% of all ovarian serous neoplasms are borderline tumors. Approximately 65 to 70% of ovarian borderline tumors have histology classified as serous (6-8). Mucinous tumors make up 11% of borderline ovarian neoplasms (9). The incidence of these tumors varies from 1.8 to 5.5 per 100,000 women per year in the US, Denmark, and Sweden (4, 10, 11). One-third of borderline ovarian tumor patients are aged under 40 years (4, 6). This emphasizes ovarian function and fertility maintenance. BOTs have the same clinical appearance as other adnexal abnormalities. Some people present with no symptoms (12). BOTs are evaluated similarly to ovarian carcinomas, but serum cancer antigen-125 (CA 125) is not helpful. Borderline tumors may cause growth in the adnexa raising suspicions of ovarian cancer. This indication provides the basis for the decision to proceed with the surgical procedure. Intraoperative frozen section is a frequent procedure, and the information obtained helps determine the surgical treatment's scope. A meta-analysis of 18 studies on frozen section results of ovarian disease showed great sensitivity (65 to 100%) and excellent specificity (>99%) (13). Large neoplasms, mucinous tumors (which have greater histologic diversity), and borderline tumors all reduce the sensitivity of the frozen section malignancy detection method because they need more sections to remove a circumscribed zone of invasive illness.

This study aimed to explore the accuracy of frozen section BOT diagnosis and determine characteristics associated with an upgrade to a conclusive diagnosis of invasive cancer in patients with a frozen section BOT diagnosis.

Material and Methods

We analyzed the clinical, laboratory, and pathological data of patients who underwent surgery for adnexal masses in our hospital between 2010 and 2022 and were diagnosed with borderline ovarian tumors using the frozen section method. A review of electronic clinical and pathological files was performed to identify individuals diagnosed with BOTs based on a frozen section or a permanent histologic finding. In line with the purpose of the research, the computerized records of the patients were examined to obtain information on their ages, whether or not they had gone through menopause, the size of their tumors, serum tumor markers carcinoembryonic antigen (CEA) and CA-125, and permanent pathology reports.

SPSS version 22 (IBM SPSS Statistics, IBM Corporation, Armonk, NY, USA) was used for all statistical calculations. Descriptive features (mean, median, and standard deviation) were evaluated with descriptive statistical tests. The normal distribution of the variables was analyzed according to Kolmogorov Smirnov and Shapiro–Wilk tests. Comparisons of categorical parameters were analyzed with the help of the chi-square test and Fisher's exact test. Since our data were not normally distributed, the nonparametric Kruskal Wallis test was used for multiple comparisons. The Mann Whitney U test was used to compare the two groups. In addition, the operating characteristic (ROC) curve was constructed to determine the optimal threshold value of CEA level and age for an elevation in permanent pathological diagnosis. A p-value of $p<0.05$ was considered significant.

All procedures performed in the current study were approved by the institutional review board (Reference number: 3822 and Year: 2022) following the 1964 Helsinki Declaration and its later amendments.

Results

We investigated 68 women aged 23 to 85, with a median of 50 years. Table 1 shows the patients' demographic information. It includes the patient's age, menopause status, preoperative CEA and CA-125 levels, maximum tumor sizes, tumor surface area, bilaterality, and permanent pathologies.

Among the 37 cases where the final pathology report was BOTs, seven were found to have microinvasion. Two were serous, two were mucinous, and one was an endometrioid-type BOT. All three types of BOTs showed a comparable microinvasion distribution.

Table 1 • Characteristics of 68 cases whose frozen section results were reported as borderline

Charecteristics	Median (min-max)
Age (year)	50 (23-85)
Menopause status	
Premenopause	32 (47.1%)
Postmenopause	36 (52.9%)
CEA (ng/ml)	1.09 (0.28-271)
CA-125 (u/ml)	28.5 (0.66-5196)
Largest diameter of the Tumor (mm)	100 (25-300)
Bilaterality	12 (17.6%)
Final pathology	
Benign	9 (13.2%)
Borderline	37 (54.4%)
Malignant	22 (32.4%)

[CEA: Carcinoembryonic antigen (0-5.2 ng/ml), CA-125: Cancer antigen 125 (0-35 U/ml)]

Table 2 compares age, number of children, CEA and CA-125 values, and largest tumor diameter of the patient groups with final pathology reports diagnosed as benign, malignant, or borderline.

We evaluated the variables associated with a diagnostic upgrade from borderline tumor to invasive carcinoma, as given in Table 3. In final reports, there was no statistically significant correlation between the tumor histologic type, maximum tumor diameter, or serum CA-125 levels and the transition from diagnosis of BOTs to invasive carcinoma. However, factors such as age, menopause status, and a higher blood CEA level were all substantially related to an upgraded invasive cancer diagnosis.

Table 2 • Comparison of the variables according to permanent pathologies

Age (year)	50.22±20.71	55.68±11.69	43.81±16.43	0.027
Number of children	3.0±1.3	2.9±1.3	2.9±1.5	0.966
CEA (ng/ml)	0.92±0.58	3.43±5.17	1.5±2.57	0.018
CA-125 (u/ml)	38.14±56.89	144.19±209.37	252.97±901.44	0.172
Largest diameter of Tumor (mm)	82.23±60.8	131.3±72.03	135.2±85.2	0.082

Kruskal Wallis test, [CEA: Carcinoembryonic antigen (0-5.2 ng/ml), CA-125: Cancer antigen 125 (0-35 U/ml)].

Table 3 • Variables that cause invasive cancers to be diagnosed as BOTs in frozen section.

	Permanent pathology report		
Characteristics	**Borderline tumor (*n* = 37)**	**Carcinoma (*n* = 22)**	***p*-value**
Age, median (min-max)	40 (23-79)	54.50 (31-74)	**0.006**
Menopause, number (percentage)	15 (40.5%)	16 (72.7%)	**0.017**
The largest diameter of the tumor (cm)			
Median (min-max)	11 (2.5-30)	11.25 (3-30)	0.784
Serum tumor markers			
CEA, median (min-max)	0.95 (0.44-16.20)	1.27 (0.42-20.50)	0.013
CA125, median (min-max)	26.40 (5.42-5196)	62.11 (7.01-750)	0.221 0.319
Histologic cell types (number, percentage)			
Mucinous	17 (45.9%)	11 (50%)	
Serous	19 (51.4%)	8 (36.4%)	
Endometrioid	1 (2.7%)	2 (9.1%)	
Clear cell	0	1 (4.5%)	

In the ROC curve analysis, the cutoff threshold for CEA was determined to be 1.16 ng/mL using the Youden index (Figure 1). This value was 43 for the age variable.

Discussion

In this particular study, we concluded that frozen section biopsy failed to correctly identify invasive carcinomas as BOTs in 32.24% of all patients. In comparable research, this percentage was 27% (14). In a similar study, the final pathology of 6, 13.6% of 44 patients examined with the frozen section procedure was reported as malignant (15). This rate is much lower than the value we found in our study. In another study examining 41 patients diagnosed with BOTs with frozen sections, the final pathology of 13 patients was reported as malignant. The rate here is 31.7% (16). This result is compatible with our study.

The risk factors for a change in the final diagnosis from frozen sections include the largest diameter of the tumor size, the presence of solid components, and a multilocular appearance (17). Because intraoperative frozen sections are performed without the assistance of immunohistochemical staining and molecular studies, the accuracy of the diagnosis is largely dependent on the patient's clinical history, as well as the gross examination and microscopic interpretation of the morphologic findings (18). Misdiagnosis by frozen section biopsy has been attributed to sampling and interpretation errors.

Brun et al. determined the elements that influenced the accuracy of the diagnosis of ovarian cancers using frozen section analysis. They discovered that the expertise of pathologists might predict the incorrect diagnosis of borderline tumors (19).

According to the statistical analysis, the preoperative CEA values were significantly different between cases with benign and malignant final pathology reports. Similar to this finding, we found that this distinction was observed between the borderline and malignant subgroups. However, our investigation revealed that this distinction was not observed between the benign and BOT groups. In a similar study, preoperative CEA values did not differ between the final pathology report groups, while CA-125 values were significantly different (14). According to the permanent pathology reports, our analysis did not find a significant difference in CA-125 levels between the borderline and malignant groups.

Among the cases whose final pathologies were reported as carcinoma, endometrioid and clear cell types were at a similar rate, while the incidence of mucinous and serous types was different from these two and showed similarity to each other. The histological type of the tumor effectively upgraded the final pathology report as carcinoma in a similar study (14). Our study did not find such an effect on the histological type of the tumor.

The present study has several shortcomings due to its restrictions. It was a retrospective study performed at a single center with BOT patients. Another limitation was that different pathologists evaluated the frozen and permanent pathologies. The lack of clearly defined criteria for using the frozen section approach was another limitation of the study.

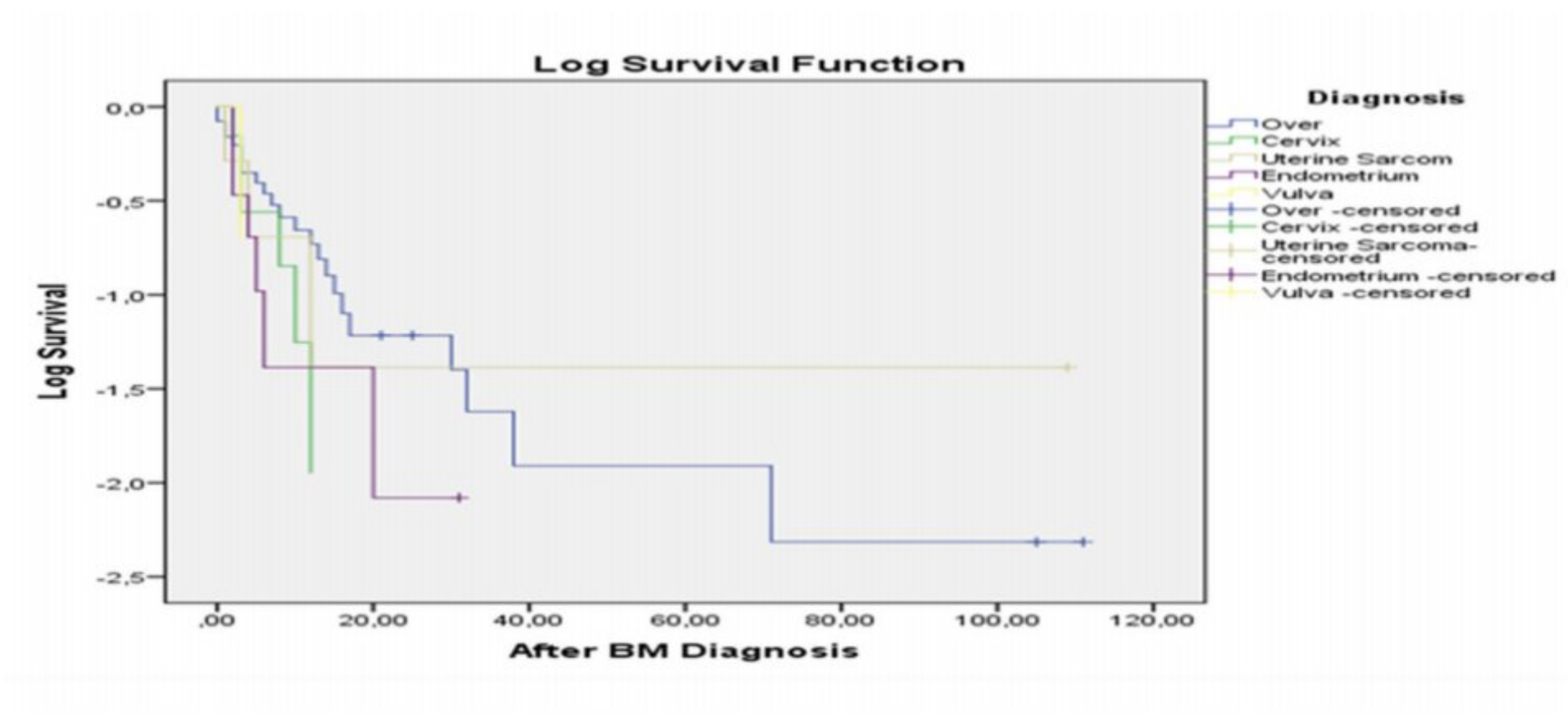

Figure 1: Upgrade to the final pathology report based on a receiver operating characteristic curve with varying CEA level and age cutoff values.

Conclusion

BOTs discovered by frozen section had an increased likelihood of being permanently diagnosed as invasive carcinoma in cases where the patient was older than 43 years and exhibited elevated levels of the tumor marker CEA (>1.16 ng/mL) in their blood. These results can be helpful inpatient counseling and surgical decision-making.

Conflict Of Interest

The authors declare no conflicts of interest.

Funding

None.

Data Availability Statement

Upon a reasonable request, the corresponding author can provide access to the data supporting the conclusions of this research.

References

1. Seidman JD, Cho KR, Ronnett BM, Kurman RJ. Surface epithelial tumors of the ovary. Blaustein's pathology of the female genital tract2002.
2. Seidman JD, Kurman RJ. Pathology of ovarian carcinoma. Hematology/oncology clinics of North America. 2003;17(4):909-25, vii.
3. Karseladze AI. [WHO histological classification of ovarian tumors. Geneva, 1999 (R.E.Scully, L.H.Sobin]. Arkhiv patologii. 2005;Suppl:1-64.
4. Skírnisdóttir I, Garmo H, Wilander E, Holmberg L. Borderline ovarian tumors in Sweden 1960-2005: trends in incidence and age at diagnosis compared to ovarian cancer. International journal of cancer. 2008;123(8):1897-901.
5. Trimble CL, Trimble EL. Ovarian tumors of low malignant potential. Oncology (Williston Park, NY). 2003;17(11):1563-7; discussion 7-70, 75.
6. Harter P, Gershenson D, Lhomme C, Lecuru F, Ledermann J, Provencher DM, et al. Gynecologic Cancer InterGroup (GCIG) consensus review for ovarian tumors of low malignant potential (borderline ovarian tumors). International journal of gynecological cancer: official journal of the International Gynecological Cancer Society. 2014;24(9 Suppl 3):S5-8.
7. Hart WR. Borderline epithelial tumors of the ovary. Modern pathology : an official journal of the United States and Canadian Academy of Pathology, Inc. 2005;18 Suppl 2:S33-50.
8. Jones MB. Borderline ovarian tumors: current concepts for prognostic factors and clinical management. Clinical obstetrics and gynecology. 2006;49(3):517-25.
9. Lazarou A, Fotopoulou C, Coumbos A, Sehouli J, Vasiljeva J, Braicu I, et al. Long-term follow-up of borderline ovarian tumors clinical outcome and prognostic factors. Anticancer research. 2014;34(11):6725-30.
10. Mink PJ, Sherman ME, Devesa SS. Incidence patterns of invasive and borderline ovarian tumors among white women and black women in the United States. The results from the SEER Program, 1978-1998. Cancer. 2002;95(11):2380-9.
11. Hannibal CG, Huusom LD, Kjaerbye-Thygesen A, Tabor A, Kjaer SK. Trends in incidence of borderline ovarian tumors in Denmark 1978-2006. Acta obstetricia et gynecologica Scandinavica. 2011;90(4):305-12.
12. Goff BA, Mandel LS, Melancon CH, Muntz HG. Frequency of symptoms of ovarian cancer in women presenting to primary care clinics. Jama. 2004;291(22):2705-12.
13. Geomini P, Bremer G, Kruitwagen R, Mol BW. Diagnostic accuracy of frozen section diagnosis of the adnexal mass: a metaanalysis. Gynecol Oncol. 2005;96(1):1-9.
14. Chen YY, Lin H, Wu CH, Lan J, Tsai CC, Fu HC, et al. Factors associated with the inconsistent diagnosis between frozen section and permanent pathologic examination in borderline ovarian tumors. Journal of Obstetrics and Gynecology Research. 2021;47(8):2729-36.
15. Basaran D, Salman MC, Calis P, Ozek A, Ozgul N, Usubütün A, et al. Diagnostic accuracy of intraoperative consultation (frozen section) in borderline ovarian tumors and factors associated with misdiagnosis. Journal of obstetrics and gynecology : the journal of the Institute of Obstetrics and Gynecology. 2014;34(5):429-34.
16. De Decker K, Jaroch KH, Bart J, Kooreman LF, Kruitwagen RF, Nijman HW, et al. Borderline ovarian tumor frozen section diagnoses with features suspicious of invasive cancer: a retrospective study. Journal of ovarian research. 2021;14(1):1-6.
17. Park JY, Lee SH, Kim KR, Kim YT, Nam JH. Accuracy of frozen section diagnosis and factors

associated with final pathological diagnosis upgrade of mucinous ovarian tumors. J Gynecol Oncol. 2019;30(6):e95.

18. Buza N. Frozen Section Diagnosis of Ovarian Epithelial Tumors: Diagnostic Pearls and Pitfalls. Archives of pathology & laboratory medicine. 2019;143(1):47-64.

19. Brun JL, Cortez A, Rouzier R, Callard P, Bazot M, Uzan S, et al. Factors influencing the use and accuracy of frozen section diagnosis of epithelial ovarian tumors. American journal of obstetrics and gynecology. 2008;199(3):244.e1-7.

TÜRK JİNEKOLOJİK ONKOLOJİ DERGİSİ
2023-2, Sayfa 15-18
Original Article

HPV burden and risk of CIN II or worse pathology in patients with atypical squamous cell of undetermined significance (ASCUS) cytology

Ata Erdem Turk[1], Bahar Nur Sahin[1], Deniz Gokce Yıldız[1], Ada Aray[1], Berkay Aksoyak[1], Zeynep Berra Şimsek[1], Tuğba Tekelioglu[2], Huseyin Akıllı[2], Esra Kuşçu[2], Ali Ayhan[2]

ABSTRACT

Objective: The aim of the study was to evaluate the Human Papillomavirus (HPV) burden and the risk of Cervical Intraepithelial Lesion grade II(CIN-II) or worse pathology in patients with Atypical Squamous Cell of Undetermined Significance (ASCUS) cytology at the time of diagnosis.

Material and Methods: The study included patients who have ASCUS cytology and underwent HPV testing between the years 2011-2021.Colposcopic biopsy were performed in patients with positive HPV.The patient's medical records and demographic information were evaluated retrospectively. The proportion of HPV positivity and the risk of CIN-II or worse pathology were evaluated by using SPSS package programme.

Results: Median age was 39 years (22-73y).749 patients had HPV test and 353(47.1 %) of them was HPV positive. 68(10.7 %) patients had HPV-16, 44(7%) had HPV-52, 39(6%) had HPV-18 and 32(5.1%) had HPV-31. Eighty-eigth (11.7%) patients had HPV-16/18 and 90(12 %) had more than three HPV types. 369(51%) patients underwent cervical biopsy and 236(64%) of them had cervicitis or normal pathology.52(14.1%) patients had CIN-I ,22(6%) had CIN-II, 57(15.4%) had CIN-III and 2(0.5%) had Carcinoma in Situ. HPV-16 and/or 18 was found to increase the risk of the presence of CIN-II+ lesions in multivariate analysis(OR: 6.2, 95%CI 3.3-11.9, P=0.00).Sensitivity and specifity of HPV-16/18 for detecting CIN-II+ lesion was 54.7% and 83% respectively and the Negative Predictive Value(NPV) was 89% and Positive Predictive Value(PPV) was 56.7%.

Results and conclusion: HPV positivity in the ASCUS population is relatively high in our institution and risk of CIN-II+ lesions sixfold increased with the presence of HPV-16/18. Moreover,HPV-16/18 testing has low PPV and high NPV in detecting CIN-II plus lesions.

Keywords: Atypical Squamous Cells of Undetermined Significance (ASCUS), Human Papillomavirus (HPV), Cervical Intraepithelial Neoplasia II plus(CIN-II+), Cervical Cancer

ÖZET

Amaç: Önemi belirsiz atipik skuamöz hücre(ASCUS) sitolojisi olan hastalarda tanı anında HPV yükü ve servikal intraepitelyal lezyon grad II(CIN II) veya üstü patoloji riskini değerlendirmektir.

Gereç ve Yöntem: Çalışmaya 2011-2021 yılları arasında ASCUS sitolojisi olan ve Human Papillomavirus(HPV) testi yapılan hastalar dahil edildi. HPV testi pozitif olan hastalara kolposkopik biyopsi yapıldı. Hastanın tıbbi kayıtları ve demografik bilgileri geriye dönük olarak değerlendirildi. HPV pozitiflik oranı ve CIN II veya daha kötü patoloji riski SPSS paket programı kullanılarak değerlendirildi.

Bulgular ve Sonuç: Ortanca yaş 39(22-73) idi. 749 hastaya HPV testi uygulandı, 353'ünde(%47,1) HPV pozitifti. 68 hastada HPV-16(%10,7), 44(%7) hastada HPV-52, 39(%6) hastada HPV-18 ve 32(%5,1) hastada HPV-31 pozitifti. Seksen sekiz hastada (%11.7) HPV-16 /18 ve 90(%12) hastada üçten fazla HPV tipi pozitifti. 369(%51) hastaya servikal biyopsi yapıldı ve bunların 236(%64)'sında servisit veya normal patoloji vardı.52(%14,1) hastada CIN-I, 22(%6)'de CIN-II, 57(%15,4)'de CIN-III ve 2(%0,05) hastada carcinoma in situ saptandı. HPV Tip-16 ve/veya 18'in multivaryant analizde CIN-2+ lezyonlarının varlığı riskini artırdığı bulunmuştur (OR:6,2, %95 GA: 3,3-11,9, P=0,00). HPV-16/18 testinin CIN-2 + lezyonunu saptamada duyarlılık ve özgüllüğü sırasıyla %54,7 ve %83 olarak bulundu ve aynı test için Negatif Öngörü Değeri (NPV) %89 ve Pozitif Öngörü Değeri(PPV) %56,7 idi.

Anahtar Kelimeler: Önemi Belirsiz Atipik Skuamoz Hücre (ASCUS), Human Papillomavirus(HPV), Servikal İntraepitelyal Neoplazi II plus(CIN-II+) , Serviks Kanseri

Received Date: 06/07/2023 Accepted Date: 15/08/2023

[1]Başkent University School of Medicine
[2]Başkent University School of Medicine, Department of Gynecology And Obstetrics

Corresponding Author: Ata Erdem Turk
Başkent University School of Medicine, Ankara

Tel: +90 553 203 52 40
E-mail: dr.ataerdemturk@gmail.com

Introduction

Cervical cancer is the 4th most commonly diagnosed cancer in women and the 4th most common cause of death among women.(1)The development and proliferation of screening programs over the years have reduced the incidence and mortality rate.(2, 3, 4)

ASC-US (Atypical Squamous Cells of Undetermined Significance) are abnormal cell findings related to inflammation or premalignancy detected on microscopic examination. (5) The incidence of ASC-US in the normal population is 4.1-4.2%(6, 7). In Turkey prevalance of ASC-US in the normal population is 1.07% and incidence of ASC-US in the HPV positive population is approximately 6 %(8, 9). However, ASC-US alone is not sufficient for the detection and planning of further examinations of Cervical Intraepithelial Neoplasia II (CIN II) and more advanced pathologies (CIN II+).(10)Moreover, many countries, have published age-standardized cervical cancer screening guidelines in which cervical cytology and the HPV test are used together.

According to their carcinogenic properties, high-risk HPV types (HR-HPV); HPV-16, 18, 31, 33, 45, 52, and 58 are involved in more than 90% of cervical cancers.(11)However, the immune response of people infected with HPV usually clears the virus within 12-24 months and allows them to recover asymptomatically. However, a small portion may persist and contribute to the development of cervical dysplasia and cancer.(9, 12, 13, 14, 15)

The prevalence of HR-HPV in patients with ASC-US was reported as 30.2-32.6%, and according to HPV types, the prevalence was as followed; 8.2% for HPV 16 and 2.9% for HPV 18.(6, 16)However, the association of ASC-US and HPV may differ in various regions of the world. For this reason, the rate of co-occurrence is often reported differently (21.5%,(17) 30.3%,(16) 48.7%,(7)).

CIN I(LSIL) usually regresses on its own without causing malignancy, whereas CIN II- III (HSIL) is prone to malignancy and requires treatment.(4, 18) HPV positivity at the time of ASCUS is associated with a 0.4% risk of immediate development of CIN III, whereas the risk within five years is 4%.(19) Our goal in this study is to evaluate the viral load of HPV at the time of diagnosis and the risk of CIN II and more advanced pathologies in patients diagnosed with ASC-US.

Material and Methods

In this study, 1,947 patients with ASCUS cytology, were evaluated at the Başkent University Hospital between 2011-2021. 1198 of the 1947 patients who were diagnosed with CIN I+ in their previous biopsies before ASC-US, who did not have an HPV test within 3 months, and who did not have satisfactory data in the hospital's database were excluded from the study. A total of 749 patients who had ASCUS cytology as a result of the smear test and had an HPV testing within three months were included in the study.

Liquid-based conventional cervical cytology samples were obtained from each patient using an endocervical brush and plastic spatula following the manufacturer's instructions. The samples were used for the assay of cytology and HC2 hrHPV. The cytological evaluation was performed in Başkent University Laboratory, which is working according to the Bethesda criteria.

Hybrid Capture 2 (HC2) test (Qiagen, Gaithersburg, MD) used in our hospital for HPV testing, detects 13 hrHPV types (16,18,31,33,35,39,45,51,52,56,58,59 and 68). Swab samples taken from our patients were placed in 1ml phosphate buffer and HPV DNA was obtained by Qiacubeda (Qiagen). 4 different samples taken from the same patient were placed in the Rotor-Gene Q (Qiagen) to replicate and visualize the DNAs and to distinguish between positives and negatives. These samples were then analysed on the computer in 4 different channels. Samples above the threshold line were considered positive.

Colposcopic biopsies with or without endocervical curettage (ECC) were performed on patients within 6 weeks of their ASC-US and HPV diagnosis. Afterwards, the biopsy and ECC samples were evaluated by the pathology department of The Başkent University and diagnosed according to CIN terminology and standard criteria.

IBM SPSS Statistics 23.0 was used to perform statistical analyses. Continuous variables were documented as medians and ranges, while categorical variables were reported as frequencies and percentages. The chi-square test or Fisher exact test, where appropriate, was applied for categorical data. Univariate analyses were done by using a chi-square test to the factors affecting the presence of CIN II plus lesions. The cut-off of $p < 0.05$ was chosen as the level of significance. Multivariate analysis was performed for factors affecting the Risk of CIN II Plus lesions at

the time of diagnosis and to obtain Odds ratios (ORs) by using the Cox regression model. This study was approved by Başkent University Clinical Research and Ethics Committee.

Results

Seven hundred forty-nine(749) patients were included in the study. Median age was 39 years (22-73y). 307 patients (41%) were admitted to the clinic with vaginal discharge, 101 (15%) presented abnormal bleeding, 40 (5.3%) pelvic pain, 28(4%) itching and 190 patients (25.4%) were asymptomatic. The conventional smear technique was used in 152 patients (20.3%) and the liquid-based smear technique was used in 597 patients (79.7%).

Clinicopathological and demographic characteristics are listed in Table 1. HPV test results were positive in 353(47.1%) patients and negative in 396(52.9%) patients. HPV Type-16 was detected in 68(10.7%) patients, Type-18 in 39(6%) patients, Type-52 in 44(7%) patients, Type-45 in 16(2.5%) patients, Type-31 in 32 patients (5.1%) and Type-51 in 38 patients (6%). HPV Type-16 and/or 18 was positive in 88 patients (11.7%) and 90 patients (12%) had more than 3 HPV types. Figure 1.

369(%51) patients were evaluated with a colposcopic examination and a cervical biopsy procedure. Cervicitis or normal findings were detected in 236(64%) patients, CIN I in 52(14.1%) patients, CIN II in 22(6%) patients, CIN III in 57 patients (15.4%), and carcinoma in situ (CIS) in 2(0.5%) patients. 81(%22) cases presenting CIN II or worse were analysed.

In the univariate analysis, it was observed that HPV Type-16 increased the risk of the presence of CIN II+ lesions in patients with ASC-US (OR: 5.9, 95% CI: 3.03 -11.7, P=0.00). However, HPV Types 18, 31, 45, 51, and 52 did not cause a significant increase in the risk of the presence CIN II+ lesions (p=0.3, p=0.3, p=0.055, p=0.3, and p=0.06 respectively). HPV Type 16 and/or 18 was found to increase the risk of the presence of CIN II + lesions inunivariate analysis (OR: 6.3, 95%CI 3.3-12, P=0.00) and multivariate analysis (OR: 6.2, 95%CI 3.3-11.9, P=0.00). CIN II + lesions were detected in 23(46%) of 50 HPV16 positive cases and 29(43.3%) of 67 HPV16/18 positive cases Table 2.

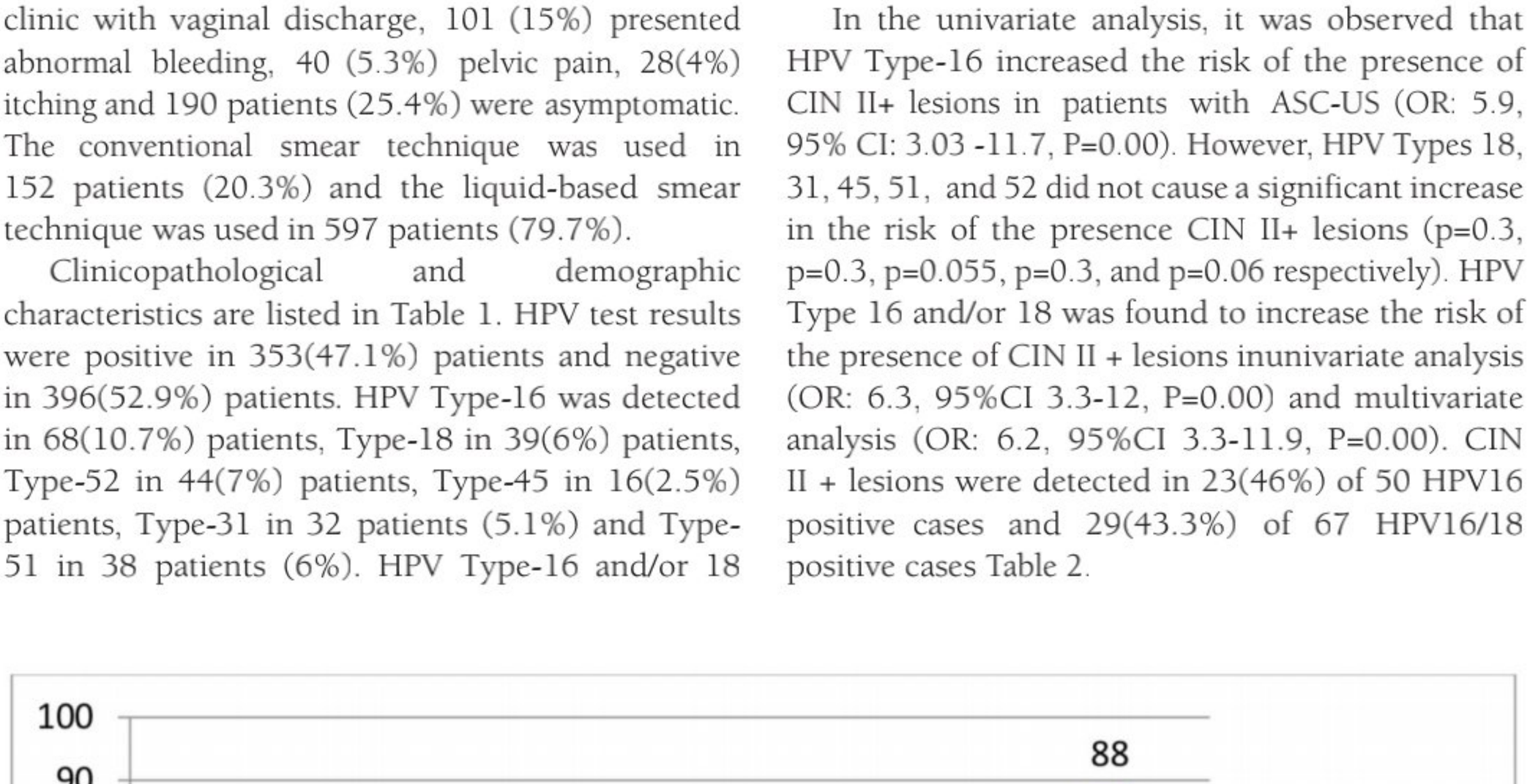

Figure 1: Distribution of HPV types
Abbreviations: HPV (Human Papilloma Virus)

Table 1 • Characteristics of patients (n=749)

Characteristics	n (%)
Median age	39 (22-73y)
Complaint	
None	190 (25.4 %)
Irreguler Bleeding	101 (15 %)
Vaginal Discharge	307 (41 %)
Itching	307 (41 %)
Pelvic Pain	28 (4%)
Unknown	73 (9.7 %)
Smoking	
Yes	172 (23 %)
No	337 (45 %)
Unknown	240 (32 %)
Oral contraceptive pills	
Yes	37 (5%)
No	415 (55 %)
Unknown	297 (40 %)
Menopausal status	
Premenopause	515 (68 %)
Postmenopause	115 (15 %)
Parity	
Nullipar	212 (29 %)
Multipar	408 (55 %)
Unknown	127 (16 %)
Smear technique	
Conventional	152 (20.3%)
Liquid base	597(79.7 %)
HPV test	
Negative	396 (52.9%)
Positive	353 (47.1 %)
Cervical Biopsy	369 (51 %)
Pathology	
Normal/ Inflamation	236 (64.0 %)
CIN I	52 (14.1%)
CIN II	22 (6.0 %)
CIN III	57 (15.4 %)
Carcinoma in-situ	2 (0.5 %)

The sensitivity of the HPV testing in detecting CIN II + lesions in patients diagnosed with ASC-US was 87%, with a specificity of 40%, Positive Predictive Value (PPV) was 92%, and Negative Predictive Value (NPV) was 29.2%. The sensitivity and specificity of HPV 16/18 genotyping was 54.7% and 83% respectively. PPV and NPV with sensitivity and specifity were given in Table 3.

Discussion

In this study, 47.1% of patients with ASC-US had positive HPV test results. When these patients were evaluated with cervical biopsy, 29.5% had CIN II+ lesions. It was found that HPV 16-18 genotypes 6.2 times increased the risk of the presence of CIN II+ lesions. In addition, it has also been observed that the HPV16/18 genotyping had low sensitivity and high specificity in detecting CIN II+ lesions in patients with ASC-US.

In the study in which more than 4 million patients were screened in Turkey, the most common HPV genotype was found to be Type-16, and the second most common genotype was Type-51.(20) Compared to that study, we have found that the most common HPV genotype was Type-16 followed by Type-52 in our study cohort.

Table 2 • Risk of CIN II or worse pathology at the time of ASCUS according to HPV types

	Univariant Analyses			Multivariant cox-regression analyses		
HPV Type	**OR**	**95 % CI (lower-higher)**	**P value**	**OR**	**95 % CI (lower-higher)**	**P value**
16	5.9	3.03-11.7	0.00	1.3	0.8-1.2	0.12
18	1.4	0.4-3.6	0.3			
31	1.7	0.5-6.2	0.3			
51	1.6	0.6-4.4	0.3			
52	0.4	0.01-1.12	0.06	1.8	0.7-2.14	0.3
45	0.2	0.06-1.01	0.055	1.4	0.9-1.7	0.4
16-45	5.9	3.03-11.7	0.00	1.2	0.2-5.4	0.7
16-52	4.9	2.5-8.9	0.00	2.1	0.7-6.3	0.1
16-18	6.3	3.3-12	0.00	6.2	3.3-11.9	0.00

HPV(Human Papilloma Virus), OR(Odds Ratio), CI(Confidence Interval)

Table 3 • The sensitivity and spesificity of HPV testing and HPV 16/18 genotyping testing

	Sensitivity	**Specificity**	**PPV**	**NPV**
HPV	87 %	40 %	92 %	29.2 %
HPV 16/18	54.7 %	83 %	56.7 %	89 %

HPV(Human Papilloma Virus), PPV(Positive Predictive Value), NPV(Negative Predictive Value)

In another study, where 697 patients had an ASC-US or LSIL cervical cytology, high-risk HPV was found in 62.8% of them, again, with Type-16 being the most common HPV genotype.(21) In the ATHENA study, in which 40,901 patients were screened, HPV+ was seen in 29.7% of 2,617 patients with abnormal cytology. While HPV16 positivity was seen in 0.7% of patients with normal cytology, this rate increased 9-fold to 6.3% in patients with abnormal cytology.(22) Since our study was hospital-based, HPV genotyping was found to be higher than in other studies. We ascertained the HPV16/18 association as 13.9% and found that the incidence of CIN II+ lesions in HPV 16/18 positive patients was lower than in patients with only the HPV Type-16 genotype. In the ATHENA study, HPV positivity was 32.6%-31.5%, Type-16 positivity was 8.2% and Type-18 positivity was 2.9% in 1578 patients diagnosed with ASC-US. HPV 16/18 was observed in 44% of patients with CIN II and 61% of patients with CIN III+.(22)

In another study, where 1089 HPV+ patients were analysed, abnormal cervical cytology was observed in approximately 40% of patients and HSIL was observed in 14.65% of these patients. When all HPV-positive patients were examined, the percentage of HSIL was 5.79. (11)

In another study conducted in Turkey, which included patients with ASCUS cytology, the prevalence of HPV-16 positivity was found to be 36%, HPV-18 positivity was 5%, HPV-31 positivity was 8%, HPV-45 positivity was 4%, and HPV-52 positivity was 4%. When these patients were examined through colposcopic biopsy procedures, it was found that among those with a co-occurrence of ASCUS and HPV, CIN2+ pathologies were detected at a rate of 24.3%, and among patients with a co-occurrence of HPV 16 and/or 18, CIN2+ pathologies were detected at a rate of 41.7%.(23) These data substantiate our findings.

In our study, HPV positivity and the risk of CIN II+ lesions were found to be higher than in other studies because most of the patients presented with complaints.

In another hospital-based study, when 50,943 patients were screened, HPV negativity was observed in 26,291 patients, and CIN II+ lesions were detected in 1.38% of these patients. Whereas in HPV-positive patients, CIN II+ was detected in 19.95% of patients, so approximately 15 times higher.(24)

Comparable to current study a study from japan analysed the incidence of CINII+ lesions in ASCUS population according to HPV status and they showed that the incidence in HPV positive patients was 35.4%. (25)

In a study conducted on colposcopy, cytology, HPV, and ASC-US, 889 out of 2661 patients were evaluated on HPV, while the remaining patients were evaluated on colposcopy and repeated cytology. The patients evaluated with HPV were mostly women between the ages of 20 and 30; 82.1% were multiparous, 22.7% have never used contraceptives and 77.7% had never smoked before.(26) 41% of the patients who were examined under the HPV section had high-risk HPV,(26) the average age of patients who consulted was 30. In our study, most of the women were non-smokers, 55% were multiparous, 68% were premenopausal, oral contraceptive use was 5%, and the most common complaint was about vaginal discharge.

The fact that our study had some limitations, which were: its retrospective design, being a monocentric study, a relatively small number of patients who mostly applied due to pre-existing complaints, and lack of colposcopic findings.

It has also been shown in that HPV negative patients with Ascus and patients who do not have any intraepithelial lesion or malignancy in their cytology have similar risk of developing CIN III or CIN II lesions which is very low. Therefore, HPV positivity has a great importance in terms of lesions.(25)

In conclusion, we have found that the HPV viral load can reach up to 50% in patients presenting within the ASCUS population. Moreover, HPV genotyping should be performed to assess the risk of CIN II+ lesions in these patients.

References

1. Sung, Hyuna, et al. "Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries." CA: a cancer journal for clinicians 71.3 (2021): 209-249.
2. Kuo DY, Goldberg GL. Screening of cervical cancer: where do we go from here? Cancer Invest. 2003;21(1):157-61.
3. Musa J, Achenbach CJ, O'Dwyer LC, Evans CT, McHugh M, Hou L, et al. Effect of cervical cancer education and provider recommendation for screening on screening rates: A systematic review and meta-analysis. PLoS One. 2017;12(9):e0183924.
4. McCredie MR, Sharples KJ, Paul C, Baranyai J, Medley G, Jones RW, Skegg DC. Natural history of cervical neoplasia and risk of invasive cancer in women with cervical intraepithelial neoplasia 3: a retrospective cohort study. Lancet Oncol. 2008 May;9(5):425-34. doi: 10.1016/S1470-2045(08)70103-7. Epub 2008 Apr 11. PMID: 18407790.
5. The 1988 Bethesda System for Reporting Cervical/Vaginal Cytological Diagnoses. *JAMA*. 1989;262(7):931–934. doi:10.1001/jama.1989.03430070079034
6. Stoler, Mark H., et al. "High-risk human papillomavirus testing in women with ASC-US cytology: results from the ATHENA HPV study." American journal of clinical pathology 135.3 (2011): 468-475.
7. Tao, Xiang, et al. "Atypical squamous cells of undetermined significance cervical cytology in the Chinese population: Age stratified reporting rates, high risk HPV testing, and immediate histologic correlation results." Cancer Cytopathology 129.1 (2021): 24-32.
8. Turkish Cervical Cancer And Cervical Cytology Research Group. Prevalence of cervical cytological abnormalities in Turkey. Int J Gynaecol Obstet. 2009 Sep;106(3):206-9. doi: 10.1016/j.ijgo.2009.04.003. Epub 2009 Jun 21. PMID: 19541303.
9. Gultekin, Murat, et al. "Initial results of population based cervical cancer screening program using HPV testing in one million T urkish women." International journal of cancer 142.9 (2018): 1952-1958.
10. Carozzi, Francesca Maria, et al. "Triage with human papillomavirus testing of women with cytologic abnormalities prompting referral for colposcopy assessment." Cancer Cytopathology: Interdisciplinary International Journal of the American Cancer Society 105.1 (2005): 2-7.
11. Liu, Fang, et al. "Association of human papillomavirus genotype distribution and cervical cytology: a cross-sectional study." Epidemiology & Infection 149 (2021).
12. de Sanjose, Silvia, Maria Brotons, and Miguel Angel Pavon. "The natural history of human papillomavirus infection." Best practice & research Clinical obstetrics & gynaecology 47 (2018): 2-13.
13. Avcı, Gülçin Alp, and Gülendam Bozdayı. "Human papillomavirus." Kafkas Journal of Medical Sciences 3 (2013): 136-144
14. A Phase I Study of Quadrivalent Human Papilloma Virus (HPV) (Types 6, 11, 16, 18)Recombinant Vaccine in HIV-Infected and HIV-Negative Pre-Adolescents, Adolescents and Young Adults

15. Petca, Aida, et al. "Non-sexual HPV transmission and role of vaccination for a better future." Experimental and Therapeutic Medicine 20.6 (2020): 1-1.
16. Zhang, Huina, et al. "Immediate histologic correlation in women with atypical squamous cells of undetermined significance cytology and positive high risk HPV: A retrospective review of 6000 cases in a large academic women's hospital." Cancer Cytopathology 128.11 (2020): 852-859.
17. Zhou, Feng, et al. "Prevalence of genotype-specific human papillomavirus in cytology specimens and cervical biopsies, and its implication in cervical cancer risk stratification: a retrospective study of 10647 cases." Journal of Cancer 12.23 (2021): 7167.
18. Bansal N, Wright JD, Cohen CJ, Herzog TJ. Natural history of established low grade cervical intraepithelial (CIN 1) lesions. Anticancer Res. 2008 May-Jun;28(3B):1763-6. PMID: 18630456.
19. Egemen, Didem, et al. "Risk estimates supporting the 2019 ASCCP risk-based management consensus guidelines." Journal of lower genital tract disease 24.2 (2020): 132.
20. Gultekin, Murat, et al. "How to triage HPV positive cases: Results of four million females." Gynecologic oncology 158.1 (2020): 105-111.
21. Phianpiset, Rattiya, et al. "ASCCP Risk-Based Colposcopy Recommendations Applied in Thai Women With Atypical Squamous Cells of Undetermined Significance or Low-Grade Squamous Intraepithelial Lesion Cytology." Obstetrics & Gynecology 136.3 (2020): 510-517.
22. Monsonego, Joseph, et al. "Prevalence of high-risk human papilloma virus genotypes and associated risk of cervical precancerous lesions in a large US screening population: data from the ATHENA trial." Gynecologic oncology 137.1 (2015): 47-54.
23. Yalcin, Ibrahim, et al. "Analysis of histopathology results of ASCUS and LSIL cytology in HPV DNA positive cases." *Acta Oncologica Turcica* 51.3 (2018): 306-310.
24. Demarco, Maria, et al. "Risks of CIN 2+, CIN 3+, and cancer by cytology and human papillomavirus status: the foundation of risk-based cervical screening guidelines." Journal of lower genital tract disease 21.4 (2017): 261.
25. Aoki, Eiko Saitoh, et al. "Validation of HPV triage in cytology-based cervical cancer screening for ASC-US cases using Japanese data." Journal of Gynecologic Oncology 34 (2022).
26. Baena, Armando, et al. "Comparison of immediate colposcopy, repeat conventional cytology and hrHPV testing for the clinical management of ASC-US cytology in routine health services of Medellin, Colombia: The ASCUS-COL Trial." International Journal of Cance

TÜRK JİNEKOLOJİK ONKOLOJİ DERGİSİ
2023-2, Sayfa 23-32
Original Article

Pelvic Exenteration For Primary and Recurrent Gynecologic Malignancy

Tuğçe SIRMA[1], Yunus İLHAN[1], Levent AKMAN[1], Mustafa Coşan TEREK[1], Ahmet Aydın ÖZSARAN[1], Nuri YILDIRIM[1]

ABSTRACT

Introduction: Pelvic exenteration is often the only curative treatment option for selected locally advanced tumors, and especially for recurrent cancers. The primary aim of this study is to assess the clinical features, types and frequency of operative and postoperative complications of patients who underwent pelvic exenteration operation by our clinic.

Material and Methods: Retrospectively, between 2019 and 2023, 14 patients with primary and recurrent gynecologic tumors who underwent pelvic exenteration were assessed in our clinic.

Findings: All patients treated with anterior, posterior and total exenteration. Mean age was 56 (range, 26-71 years). The most primary tumors were cervical cancer (n=5, 35.7%) and ovarian cancer (n=5, 35.7%). 28.5% of patients received neoadjuvant chemotheraphy before exenteration, 35.7% of patients were treated with primary chemo-radiotheraphy and 3 patients didn't receive preoperative treatment. Urinary diversion was ileum conduit (64.2%). Mean operation time, estimated blood loss and hospital stay were 420 minutes, 2 units and 25 days. There were no intraoperative complications. Total morbidity rate was 28.5%; 7.1% of patients had early complications (<30 days after surgery) whereas 3 patients (21.4%) had late complications. Re-operation was not required in any patients. Disease recurrence occurred in 50% patients. There were no post-operative deaths (<30 days from surgery) nor intra-operative mortality. Eight patients died from recurrent malignancy. In our study survival was not assessed because of the short follow-up time.

Results and conclusion: Pelvic exenteration is the only curative surgical method in locally invasive or recurrent gynecological tumors, with high complication rates and hospital stays.

Keywords: Pelvic exenteration, Recurrence, Gynecologic cancer, Prognosis, Cervical cancer

ÖZET

Giriş: Pelvik ekzenterasyon, seçilmiş lokal ileri ever tümörler ve özellikle tekrarlayan kanserler için genellikle tek küratif tedavi seçeneğidir. Bu çalışmanın primer amacı, kliniğimizde pelvik ekzenterasyon operasyonu geçiren hastaların klinik özelliklerini, tiplerini ve operatif ve postoperatif komplikasyon sıklığını değerlendirmektir.

Gereç ve Yöntem: Kliniğimizde 2019-2023 yılları arasında primer ve nüks jinekolojik tümör nedeniyle pelvik ekzenterasyon yapılan 14 hasta retrospektif olarak değerlendirildi.

Bulgular: Tüm hastalara anterior, posterior ve total ekzenterasyon uygulandı. Ortalama yaş 56 (26-71 yaş arası) idi. Pelvik ekzenterasyonun en sık nedenleri servikal kanser (n=5, %35,7) ve over kanseriydi (n=5, %35,7). Ekzenterasyon öncesi hastaların %28,5'ine neoadjuvan kemoterapi, %35,7'sine primer kemo-radyoterapi ve 3 hastaya preoperatif tedavi verilmemiştir. Üriner diversiyon şekli ileum konduit (%64,2) idi. Ortalama operasyon süresi, tahmini kan kaybı ve hastanede kalış süresi 420 dakika, 2 ünite ve 25 gündü. Hiçbir intraoperatif komplikasyon görülmedi. Toplam morbidite oranı %28,5; hastaların %7,1'inde erken komplikasyon (ameliyattan <30 gün sonra), 3 hastada (%21,4) geç komplikasyon görüldü. Hiçbir hastada reoperasyon gerekmedi. Hastaların %50'sinde nüks gelişti. Postoperatif (ameliyattan <30 gün sonra) veya intraoperative ölüm olmadı. Sekiz hasta maligniteden ötürü vefat etti. Çalışmamızda kısa takip süresi nedeniyle sağkalım değerlendirilemedi.

Sonuç: Lokal invaziv veya nüks jinekolojik tümörler için pelvik ekzenterasyon, yüksek komplikasyon oranları ve hastanede kalış süresi olan, tek küratif cerrahi yöntemdir.

Anahtar Kelimeler: Pelvik ekzenterasyon, Rekürrens, Jinekolojik kanser, Prognoz

Received Date: 17/05/2023 Accepted Date: 24/07/2023

[1]Ege University Faculty of Medicine, Department of Obstetrics and Gynecology, Division of Gynecological Oncology, İzmir, TURKEY

Corresponding Author: Tuğçe SIRMA
Adres: Ege University Faculty of Medicine, Department of Obstetrics and Gynecology, Division of Gynecological Oncology, İzmir, TURKEY

Tel: 0507 245 52 90
E-mail: drtugcesirma@hotmail.com

ORCID ID: 0000-0002-0098-8915

Introduction

Pelvic exenteration (PE) describes a radical surgery involving the en bloc resection of the pelvic organs, including the internal reproductive organs, bladder, and rectosigmoid.[1] Indications include advanced primary or recurrent pelvic malignancies, most commonly centrally recurrent cervical carcinoma, but also other gynecologic tumors and urologic and rectal cancers.[1]

Pelvic exenteration has been used for 60 years to treat cancers of the lower and middle female genital tract in radiated pelvis.[2] PE was first performed by the physician Alexander Brunschwig in 1948 as a palliative, radical surgical procedure for recurrent cervical carcinoma.[3] This demonstrated proof of concept for PE, with a postoperative survival of up to 8 months, and a 23% surgical mortality rate.[3] Since 1948 several developments in perioperative care and surgical technique have improved survival.[1]

PE may consist of complete PE (i.e., total exenteration) or partial PE (i.e., anterior or posterior exenteration), depending on the location and extent of the tumor. Total PE involves resection of the female reproductive organs, lower urinary tract, rectosigmoid colon, anus, and surrounding soft tissues.In anterior exenteration, the rectum and anus are spared from resection, while in posterior exenteration the urinary bladder and urethra are preserved.PE is further classified into supralevator or infralevator (translevator) resection.[1] In supralevator exenteration, pelvic viscera are divided above the pelvic floor muscles preserving the levator ani muscles, anal sphincter, and urogenital diaphragm. In infralevator exenteration these structures are resected.[1]

In highly selected patients with non-metastatic gynecological cancers who present with recurrent or persistent disease after chemoradiotherapy, PE with curative intent has a 5-year survival rate of up to 50%,whereas in patients with recurrent gynecological cancers, the 2-year survival rate is only 25–32%. Survival benefit can only be derived if there is complete surgical clearance of cancerous tissue at surgery through achieving histologically tumor-free margins (i.e. R0 resection).Besides PE with curative intent, PE can also be performed with palliative intent.[10]

The multidisciplinary decision to pursue PE is a balancing act between achieving beneficial outcomes against the risk of surgical complications affecting quality of life, in patients who have often already undergone several prior treatments.[10] PE remains a radical procedure with significant complications (31-92%).[2] To date, post-surgical complications remains as high as 50%, as the previously irradiated surgical field is prone to wound disruption and superinfection after surgery.[2,10] Apart from complications related to any major abdominopelvic surgery, common complications of PE include those of the urinary or bowel reconstruction and pelvic floor flaps; late post-operative complications may also occur, including anastomotic strictures, chronic fistula formations, and tumor recurrence.

Nonetheless, PE remains a challenging procedure requiring a highly skilled interdisciplinary surgical team. It is rarely performed across the world which is mirrored by the mostly small cohort sizes and/ or wide time frame for analysis in the data published up to date. The objective of this study was to review a single-institution experience of PE for patients with primary advanced or recurrent gynecologic malignancy, in terms of patient and surgical characteristics, complications, recurrences.

Material And Methods

Retrospectively, 14 patients underwent PE due to gynecological cancer from May 2019 to March 2023 in Ege University Medical Faculty Gynecology Oncology Clinic. All patients were evaluated with PET-CT ± low abdomen MRI before surgery. Patients underwent 4 total pelvic exenterations, 5 anterior exenterations and 5 posterior exenterations in our clinic.

The inclusion criterion was the patients who had gynecological cancer without other malignancy. In this study, which is based on retrospective data analysis, all clinical information was obtained from hospital clinical records. Patient follow-ups were completely done by our clinic, and the information was obtained from clinical patient records. All the 14 patients were followed until death or when alive until March 2023.

Parameters for analysis were evaluated and categorized in pre-, intra- and postoperative period. Demographic criteria such as age was taken into consideration as well as previous treatment in case of recurring or persistent disease along with neoadjuvant intent and need for adjuvant treatment.

Selection criteria for surgery included: age (younger than 80 years), no gross pelvic side-wall involvement (considered as a macroscopic clearly unresectable infiltration of pelvic wall likely involving the sacral nervous system), no suspect of extra-pelvic disease, willingness to receive blood transfusions if needed and good psychological balance. A biopsy confirming the diagnosis of persistent/recurrent tumor was performed in each patient prior to the definitive procedure.

Surgery always began with an exploratory laparotomy and abdomino-pelvic exploration; any suspicious lesion was submitted for frozen section and if extra-pel-

vic metastatic disease was confirmed the procedure was aborted. Surgical parameters which were evaluated for the study include: type of PE, duration of surgery, total blood loss, number of transfusions, intra-operative complications and length of hospital stay. The operations were performed under the control of a gynecologist oncologist, and some procedures were performed by a general surgeon and a urologist. The procedure was completed in case the intra-operative findings suggested a high probability to obtain clear margins on the surgical specimen.

Patients were admitted to the Intensive Care Unit for at least the first 24 post-operative hours and then transferred to the regular Gynecologic Oncology ward. Morbidity in regard to postoperative complications was assessed.

Computed Tomography (CT), Magnetic Resonance Examination (MRI) and PET-CT were applied to all patients preoperatively, and the operation decision was evaluated in the tumor board with the cooperation of radiation oncologist, medical oncologist, radiology specialist, nuclear medicine specialist and gynecologist oncologist. Complete blood count and biochemistry evaluations were performed before the operation. Pelvic exenteration was not applied to patients with distant metastases, and pelvic exenteration was planned for patients with local recurrence or primary locally invasive disease. Surgery was not recommended for patients with pelvic sidewall involvement in local recurrence.

All intraoperative and postoperative complications were recorded. All histopathological examinations were performed by gyneco-pathologists, and the results were discussed in the tumor board, and adjuvant radiotherapy and chemotherapy were applied if necessary. The patients were followed up in our clinic. After discharge, every 3 months the patients were evaluated with gynecological examination and transvaginal ultrasound, every 6 months whole body tomography and tumor markers, and PET-CT if needed.

Results

The median age of the patients was 56 (range, 26-71 years), and 78.5% of them were over 50 years of age. The primary reason for pelvic exenteration was cervical cancer (n=5, 35.7%) and ovarian cancer (n=5, 35.7%), followed by endometrial cancer (n=3, 21.4%) and uterine leiomyosarcoma (n=1, 7.1%). Histopathologically, 5 patients were diagnosed with ovarian high-grade serous carcinoma, 5 patients with cervical squamous cell carcinoma, 3 patients with endometrioid type endometrial adenocarcinoma, and 1 patient with uterine leiomyosarcoma (Figure 1).

Four (28.5%) patients underwent total pelvic exenterations, 5 (35.7%) anterior exenterations and 5 (35.7%) posterior exenterations. Five of 14 patients (35.7%) who underwent pelvic exenteration received previous treatment and developed recurrence, 3 pa-

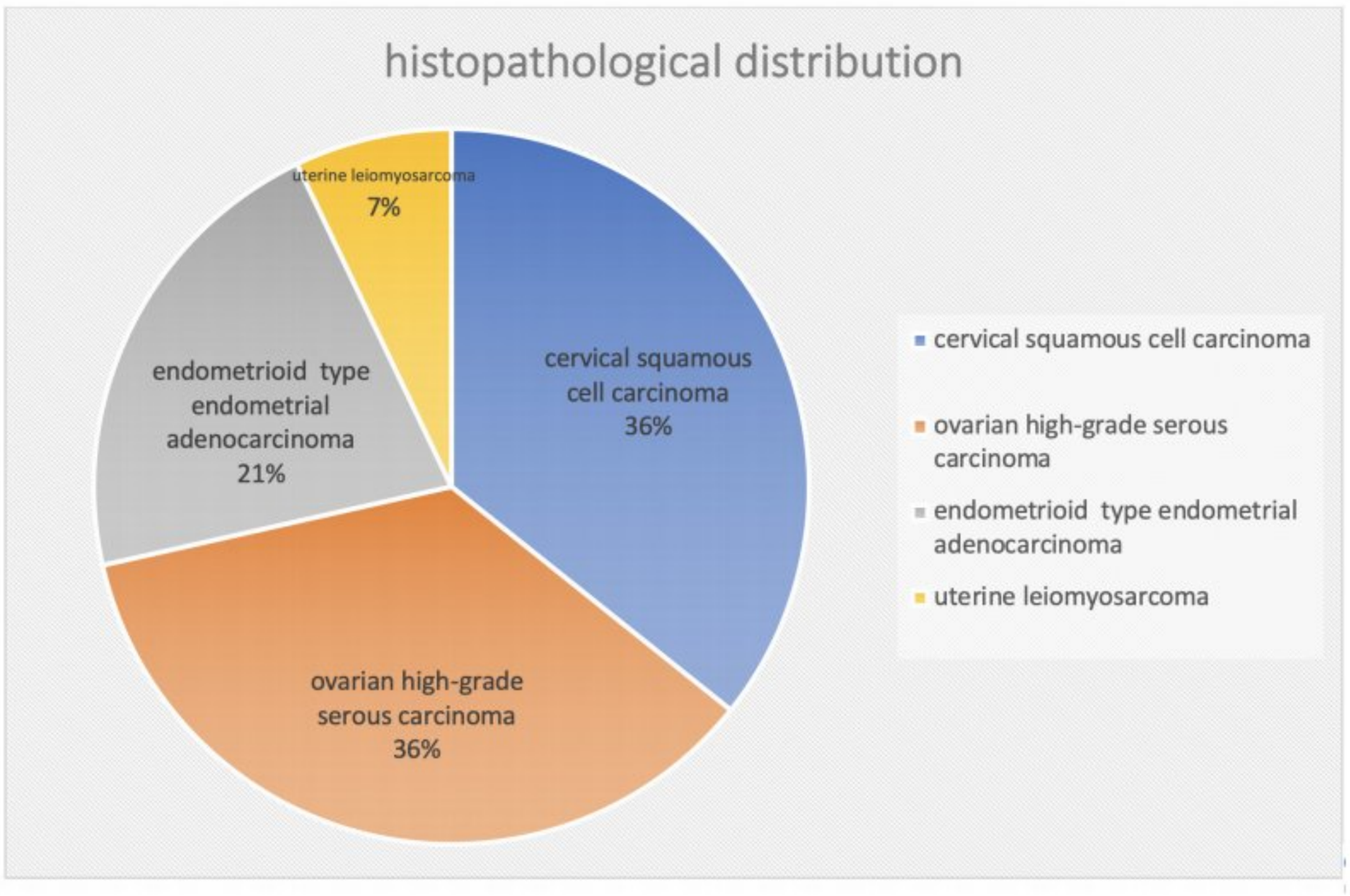

Figure 1: Histopathological distribution of patients who underwent pelvic exenteration

tients (21.4%) underwent pelvic exenteration after neoadjuvant therapy and occurred partial response, 3 patients (21.4%) underwent primary pelvic exenteration, 1 patient (7.1%) were persistent under primary treatment and 2 patients (14.2%) were progressed under primary treatment (Table 1). Four patients (28.5%) received neoadjuvant treatment prior to exenteration who were treated with neoadjuvant chemotherapy due to 2 ovarian cancer, 1 leiomyosarcoma and 1 endometrial cancer and five patients (35.7%) were treated with primary radiotherapy and chemotherapy due to 4 cervical cancer and 1 endometrial cancer.

The patient with synchronous ovarian and endometrial adenocarcinoma was treated with chemotherapy and radiotherapy after neoadjuvant chemotherapy followed by interval debulking surgery. 11 months after the end of the treatment, total pelvic exenteration was performed because of central pelvic recurrence invading the bladder and rectum mucosa. At the 4th month after exenteration, recurrence with vaginal cuff, liver and spleen parenchymal metastasis was detected, and death occurred due to covid-19 pneumonia while treatment was being planned.

Table 1 • Patient and clinical disease characteristics

Characteristics	Number (%)
Age in years	56 (range, 26-71) (78.5%)
Primary site of cancer	
Cervical canser	5 (35.7%)
Endometrial cancer	3 (21.4%)
Leiomyosarcoma	1 (7.1%)
Ovarian cancer	5 (35.7%)
Previous treatment	
None	3 (21.4%)
NACT	3 (21.4%)
Primary CRT	4 (28.5%)
Primary CRT followed by DS	1 (7.1%)
NACT followed by DS and adj CRT	1 (7.1%)
Surgery and adjuvant CRT	1 (7.1%)
Surgery and RT	1 (7.1%)
Indication for exenteration	
Primary treatment	3 (21.4%)
Persistent disease under primary treatment	1 (7.1%)
Progressive disease under primary treatment	2 (14.2%)
Recurrent disease after primary treatment	5 (35.7%)
Partial response after neoadjuvant treatment	3 (21.4%)
Types of pelvic exenteration	
Anterior	5 (35.7%)
Posterior	5 (35.7%)
Total	4 (28.5%)
Cancer	
Primary	9 (64.2%)
Relapse	5 (35.7%)

NACT: Neoadjuvant chemotherapy, CRT: chemo-radiotherapy, DS: debulking surgery RT: radiotherapy

Pelvic exenteration was performed in 5 patients with squamous cell carcinoma. Two patients were stage 2b cervical cancer and received primary chemo-radiotherapy. Due to the development of recurrence in one patient and partial response to the treatment in the other patient, total pelvic exenteration was applied to the patient with recurrence and anterior exenteration to the other patient, respectively. According to the pathology results of both patients, there was no need for adjuvant treatment. No recurrence was observed in the 18 and 5-month follow-ups of the patients. One patient with cervical squamous cell carcinoma was diagnosed incidentally after laparoscopic hysterectomy for CIN3 and adjuvant external and internal radiotherapy was applied. One year after the end of the treatment, central recurrence developed in the hysterectomy site, and anterior exenteration and then radiotherapy was applied. Recurrence was detected in the 21-month follow-up of the patient. One of the other 2 cervical cancer cases was stage 3c1 and progressed under primary chemoradiotherapy treatment and because of bladder and rectal invasion detected, underwent salvage total exenteration and then received adjuvant chemotherapy. Death occurred 5 months after the last dose of chemotherapy due to extensive intraperitoneal recurrence. The other 26-year-old case with cervical cancer was accepted as stage 3c and ovarian transposition was performed first, and after it progressed under primary chemoradiotherapy, bladder and rectum invasion were detected, and salvage total exenteration was performed. Pathology-confirmed lymph node involvement was observed in this patient. In first 30 days Whole body tomography was taken at the postoperative 3rd month showed LAP in the paraaortic, mediastinal, supraclavicular area and metastatic nodules in the lung. The patient is still receiving ongoing chemotherapy treatment.

Lung parenchymal metastasis was detected at the time of diagnosis in one of 2 patients who diagnosed with uterine endometrioid adenocarcinoma and after cytoreductive surgery adjuvant chemotherapy and radiotherapy were applied. Five years after the treatment, central pelvic recurrence developed invading the bladder floor and neck, and chemotherapy was given after anterior pelvic exenteration. At the 3rd month after chemotherapy, recurrence of vaginal cuff invading the pubic bone was detected and palliative radiotherapy was applied. The other patient was treated with primary chemotherapy and radiotherapy, since cervix and bladder invasion were present at the time of initial diagnosis. After the cytoreductive surgery, isolated vaginal cuff recurrence was detected 1 year later, and anterior pelvic exenteration was performed due to surgical difficulty because of radiotherapy fibrosis. No residual tumor/recurrence was observed in the 29-month follow-up of the patient.

In 3 of 5 patients diagnosed with ovarian high-grade serous carcinoma, rectal invasion was detected during surgery, posterior exenteration and then chemotherapy was applied. No residual tumor/recurrence was observed in the 23, 27 and 11-month follow-ups of these patients, respectively. In the other 2 patients, diffuse ascites and peritoneal carcinomatosis findings were detected at the time of diagnosis, and posterior exenteration were performed due to rectal invasion after neoadjuvant chemotherapy and received chemotherapy following surgical recovery. No residual tumor/recurrence was observed in the 25-month follow-up in one patient and in the other patient recurrence was occurred in fourth month.

One patient diagnosed with uterine leiomyosarcoma with bladder and lung metastases firstly received neoadjuvant chemotherapy then underwent anterior exenteration and received chemotherapy treatment. Lung parenchyma and thoracolumbar vertebral metastases were detected 5 months after the treatment, and she received radiotherapy and chemotherapy treatment.

An ileal conduit was performed to 9 patients who underwent anterior and total exenteration. In all 5 patients who underwent anterior exenteration, non-continent ileal conduit (bricker diversion) was performed. In two of 4 patients who underwent total exenteration, non-continent ileal conduit (bricker diversion) was performed and in the other two patients continent ileal conduit (ureterosigmoidostomy-hybrid diversion) was performed. In 5 patients who underwent posterior exenteration, one Hartmann colostomy, two transverse end colostomy and two rectosigmoid resection and end-to-end anastomosis were applied. In all 4 patients who underwent total exenteration, rectosigmoid resection and end-to-end anastomosis was performed; besides a protective ileostomy (because of the receiving chemo-radiotherapy) was made in two of them and because of the ureterosigmoidostomy, stoma was formed from the descending colon in the others.

Seven patients (50%) had a recurrence after PE of which three (42.8%) caused by cervical cancer, 2 (28.5%) endometrial cancer, 1 (14.2%) ovarian cancer and 1 (14.2%) leiomyosarcoma. The median interval from the PE to recurrence was 6.4 months (range, 3-21 months). Mortality observed in 8 patients (57.1%) mostly due to cervical (n=2) cancer which was caused by recurrence and endometrial cancer (n=2) which was caused by covid-19 pneumonia and recurrence. In our study, survival was not taken as the main outcome because the patient follow-up period was not very long.

The median operation time was 420 minutes. The average intra-operative blood transfusion requirement was 2 units. The average hospital stay were 25 days. No intraoperative complications composed. Early (< 30 days) and late complications after surgery occurred. Overall morbidity rate was 28.5% among 4 patients underwent pelvic exenteration for both recurrent and locally advanced pelvic malignancies. Prophylactic antibiotic therapy and anticoagulation therapy with fractionated heparin were started in each patient in the postoperative period. Wound infection as early complication developed in 1 patient (7.1%, grade II), and antibiotic agent replacement was required. Grade 3 ureterohydronephrosis as late complication developed in 2 (14.2%, grade IIIa) patients due to ureteroileal anastomotic stenosis after reconstructive surgery in the first month, which was treated with nephrostomy. Both urinary tract infection (7.1%, grade II) and urine leakage from ureter anastomosis (7.1%, grade IIIb) as early complications occurred in one patient. None of the patients developed ileus. No patient needed re-surgery in the first 30 days. No intraoperative or peri-operative (<30 days after surgery) death was observed (Table 2).

Adjuvant treatment was planned due to pathology results and/or recurrence after pelvic exenteration. After pelvic exenteration, chemotherapy and radiotherapy treatment were applied to one (7.1%) patient, radiotherapy only to 3 (21.4%) patients, and chemotherapy only to 8 (57.1%) patients. Radiotherapy was applied to 2 patients due to post-operative bone metastasis. Due to urinary anastomotic leakage after total exenteration in one patient, although chemotherapy was planned for the patient with metastases in the lung, abdomen and mediastinum in her tomography, it has not been started yet. Metastases were detected in the vaginal cuff, liver and spleen after total exenteration in one patient and chemotherapy was planned, but death occurred due to covid-19 pneumonia before chemotherapy had not started. 2 (14.2%) patients did not receive any adjuvant treatment and are being followed up.

Discussion

Pelvic exenteration remains the only potentially curative treatment for selected patients with advanced or persistent/recurrent gynecologic malignancies.[11] Centrally recurrent cervical cancer after radiation is the most common indication for PE. The role of PE for en-

Table 2 • Surgical outcomes and complications*

Surgical outcomes and complications	Number (%)
Lymph node involvement	1 (7.1%)
Recurrence	7 (50%)
Time of recurrence after primary treatment (months)	6.4 (range, 3-21)
Type of urinary tract reconstruction (ileal conduit)	(9)
Types of pelvic exenteration	
Non-continent (bricker diversion)	7 (77.7%)
Continent (Ureterosigmoidostomy-hybrid diversion)	2 (22.2%)
Type of bowel reconstruction (colon diversion)	9
Hartmann colostomy	1 (11.1%)
Rectosigmoid resection + end-to-end anastomosis	2 (22.2%)
Rectosigmoid resection + end-to-end anastomosis + protective ileostomy	2 (22.2%)
Rectosigmoid resection + end-to-end anastomosis + descending colon stoma	2 (22.2%)
Transverse end colostomy	2 (22.2%)
Overall morbidity	
Urine leak from ureter anastomosis (grade IIIb)	1 (7.1%)˚
Uretero-hydronephrosis (needed nephrostomy) (grade IIIa)	2 (14.2%)
Urinary tract infections (grade II)	1 (7.1%)˚
Wound infection	1 (7.1%)
Ileus	-
Thrombo-embolism	-
Fistula due to reconstruction	-

Devam ediyor

Table 2 • Surgical outcomes and complications* (Devamı)

Surgical outcomes and complications	Number (%)
Mean operation time in minutes	420
Transfusion units, median	2
Hospital-stay (days)	25
Intra- and postoperative mortality within 30 days	-
Patients requiring reoperation because of complication to pelvic exenteration	-
Adjuvant therapy	
None	2 (14.2%)
Chemotherapy and radiotherapy	1 (7.1%)
Radiotherapy only	3 (21.4%)
Chemotherapy only	8 (57.1%)
Overall mortality	8 (57.1%)

* Urinary tract infection and urine leak from ureter anastomosis occurred in only one patient.

dometrial and (even more so) for ovarian cancer, is debated because of their tendency to metastasize outside the pelvis and a good sensitivity to chemotherapy of the latter.[12] Anyhow, many studies have included patients with endometrial cancers in their series.[11] Five (41.1%) of the 14 patients included in the study consisted of patients who were operated for cervical cancer, and this rate is less than the current literature rates. Our study confirms that PE should be considered in patients with local recurrence of endometrial and ovarian cancer.

Obesity, advanced age and systemic disease may interdict an extensive surgical effort in direct relation to the severity of these factors.[13] The age of the patient is a relatively important selection criterion, with most of our successful operations being performed in patients 70 years or younger, although occasionally older patients are appropriate candidates.[1] The median age of the patients was 52 years. In most of the studies in the literature, the mean age was over 50, and the median age result in our study is consistent with the literature.[11]

The mainstay for treatment success in terms of locoregional control and long-term survival is resection of the pelvic tumour with clear margins (R0).[2] The techniques for pelvic reconstruction have evolved over the past several decades so as to include continent urinary conduits, primary re-anastomosis of the rectosigmoid colon.[1] The creation of a continent urinary conduit, and functional low colon can be performed with acceptable morbidity and gives the patient the opportunity for a better function of preserved pelvic organs following this extensive extirpative surgery.[1] Many factors influence the choice of urinary diversion from which the patient would benefit most, such as the prior treatment received (surgical, radio- and/or chemotherapy). The ileal conduit, which is applied as a urinary diversion method in our clinic, is accepted as the fastest, easiest and most reliable diversion method. In our cohort, 64.2% of the patients who underwent total and anterior PE received an ileal conduit, which is in accordance with other studies.[11] One Hartmann colostomy, two transverse end colostomy and two rectosigmoid resection and end-to-end anastomosis were applied in patients who underwent posterior exenteration. Gastrointestinal anastomotic leaks up to 40% have been found in the literature in the lower colorectal and anorectal anastomoses performed in this group of patients.[2] However, anastomotic leakage was not encountered in our study, and there was no complication related to the colostomy application in any of the patients who underwent end colostomy.

Although surgery-related mortality is now less than 5%, the rate of severe postoperative complications still exceeds 50%.[2] Therefore, careful preoperative patient evaluation is essential to select only those patients who will benefit from this operation.For this reason, patients should be evaluated with magnetic resonance to detect local spread before the operation, and PET-CT for the possibility of distant metastasis. In the literature, a wide range of complication rates is described, varying from 21.3% to 94.4%.[1,20,21] In our cohort, overall morbidity rate was 28.5% among 4 patients which is compatible with them. No intraoperative complications composed. Early (< 30 days) and late complications after surgery occurred. Pyelonephritis, ureteric obstruction, urinary stones and stomal complications are the most common complications.[22] In our patient group, postoperative urinary obstruction (grade IIIa) developed in 2 (14.2%) patients and nephrostomy was inserted which

is accordant with the literature.[23] Only in one patient, both urinary diversion anastomotic leakage (7.1%, grade IIIb) and urinary infection (7.1%, grade II) were observed in the first postoperative month which were higher in the literature.[2] Complications were observed at lower rates in the literatures.[22] In the study, wound infection (grade II) rate was 7.1% which is consistent with the literatures.[22] The quality of life was not investigated in this study.

Considering the parameters such as operation time, blood transfusion, length of stay in the intensive care unit, length of stay in the hospital, our results seem to be compatible with the results of the literature.[2] We accept it as an expected result considering the average blood transfusion, long operation times and high hospital stay, high comorbidity, high dose radiotherapy, moderate general health status, and ultraradical surgical procedures including organ excision.

It is seen that most of the patients received radiotherapy ± chemotherapy during the primary diagnosis whether or not they were operated. This rate was 78.5% in the whole cohort and 22.4% in patients who had exenteration due to cervical cancer. This may be explained by the fact that the recurrence rate is higher in patients who are started on radiotherapy and chemotherapy treatment for advanced stage compared to early-stage cancers.

After pelvic exenteration, chemotherapy and radiotherapy was applied to one (7.1%) patient, radiotherapy only to 3 (21.4%) patients, and chemotherapy only to 8 (57.1%) patients correlated with the literature.[11,23] Radiotherapy was applied to 2 patients due to post-operative bone metastasis. 2 (14.2%) patients did not receive any adjuvant treatment and are being followed up.

Mortality observed in 8 patients (57.1%) mostly due to cervical (n=2) cancer which was caused by recurrence and endometrial cancer (n=2) which was caused by covid-19 pneumonia and recurrence.

In our study, survival was not taken as the main outcome because the patient follow-up period was not very long. When we look at the literature, it is seen that the survival figures are usually given as 5 years. Due to the small number of studies giving early survival in the literature and the time period they take as a basis to evaluate survival is at least 2 years, a comparison of the literature with the cohort of our clinic could not be made.

Limitations of our study are the monocentric and retrospective character, the relative short follow-up time and the consideration of various tumor entities including different previous therapies and the number of patients is relatively low. However – as well as the limited number of patients suitable for PE - small retrospective studies like this one remain viable in order to understand pelvic exenteration as a last resort intervention for recurrent or advanced gynecologic malignancies with the goal to improve patient outcomes.

Conclusion

Pelvic exenteration is a radical operation, involving en bloc resection of pelvic organs, including reproductive structures, bladder, and rectosigmoid. PE provides about a 50% chance to save patients with cancer of the lower and middle female genital tract that persists, recurs, or originates de novo after pelvic radiotherapy. It is most commonly indicated for the treatment of advanced primary or locally recurrent cancer. A comprehensive evaluation is required in order to exclude unresectable or metastatic disease. The ultimate goal of curative intent PE is to achieve R0 resection, which is the most important factor affecting prognosis. Patients need to be carefully selected and counseled about risks and long-term issues related to the surgery. Although treatment-related mortality has fallen greatly to less than 5%, severe morbidity is still high (>50%). The prognosis of this group of patients is not perfect, survival and recurrence rates still have not reached the desired rates. Therefore, close and meticulous follow-up of patients should be continued.

References

1. Diver EJ, Rauh-Hain JA, Del Carmen MG. Total Pelvic Exenteration for Gynecologic Malignancies. Int J Surg Oncol. 2012;2012:693535.
2. Höckel M, Dornhöfer N. Pelvic exenteration for gynaecological tumours: achievements and unanswered questions. Lancet Oncol. 2006 Oct;7(10):837-47.
3. Brunschwig A. Complete excision of pelvic viscera for advanced carcinoma; a one-stage abdominoperineal operation with end colostomy and bilateral ureteral implantation into the colon above the colostomy. Cancer 1948; 1: 177–83.
4. Lakhman Y, Nougaret S, Miccò M, Scelzo C, Vargas HA, Sosa RE, et al. Role of MR Imaging and FDG PET/CT in Selection and Follow-up of Patients Treated with Pelvic Exenteration for Gynecologic Malignancies. Radiographics. 2015 Jul-Aug;35(4):1295-313.
5. Lambrou NC, Pearson JM, Averette HE. Pelvic exenteration of gynecologic malignancy: indications, and technical and reconstructive considerations. Surg Oncol Clin N Am 2005; 14: 289–300.
6. Seebacher V, Sturdza A, Bergmeister B, Polterauer

S, Grimm C, Reinthaller A, et al. Factors associated with post-relapse survival in patients with recurrent cervical cancer: the value of the inflammation-based Glasgow prognostic score. Arch Gynecol Obstet 2019; 299: 1055–62.

7. Yoshida K, Kajiyama H, Utsumi F, Niimi K, Sakata J, Suzuki S, et al. A post-recurrence survival-predicting indicator for cervical cancer from the analysis of 165 patients who developed recurrence. Mol Clin Oncol 2018; 8: 281–5.
8. Kolomainen DF, Barton DPJ. Pelvic exenteration for recurrent gynaecological cancer after radiotherapy. Obstet Gynecol 2017; 19: 109–18.
9. Andikyan V, Khoury-Collado F, Sonoda Y, Gerst SR, Alektiar KM, Sandhu JS, et al. Extended pelvic resections for recurrent or persistent uterine and cervical malignancies: an update on out of the box surgery. Gynecol Oncol 2012; 125: 404–8.
10. Sagebiel TL, Viswanathan C, Patnana M, Devine CE, Frumovitz M, Bhosale PR. Overview of the role of imaging in pelvic exenteration. Radiographics 2015; 35: 1286– 94.
11. Maggioni A, Roviglione G, Landoni F, Zanagnolo V, Peiretti M, Colombo N, et al. Pelvic exenteration: Ten-year experience at the European Institute of Oncology in Milan. Gynecol Oncol. 2009 Jul;114(1):64-8.
12. Van Wijk FH, Van den Burg MEL, Burger CW, Vergote I, van Doorn HC. Management of recurrent endometrioid endometrial cancer. An overview. Int J Gynecol Cancer. 2009;19:314Y320.
13. Fleisch MC, Pantke P, Beckmann MW, Schnuerch HG, Ackermann R, Grimm MO, et al. Predictors for long-term survival after interdisciplinary salvage surgery for advanced or recurrent gynecologic cancers. J Surg Oncol 2007;95:476–84.
14. Hatch KD, Berek JS. Pelvic exenteration. In: Berek JS, Hacker NF, editors. Practical Gynecologic Oncology. 4th ed. Philadelphia' Lippincott Williams and Wilkins; 2005. p. 801–16.
15. Berek JS, Howe C, Lagasse LD, Hacker NF. Pelvic exenteration for recurrent gynecologic malignancy: Survival and morbidity analysis of the 45-year experience at UCLA. Gynecol Oncol 2005;99:153–9.
16. Goldberg GL, Sukumvanich P, Einstein MH, Smith HO, Anderson PS, Fields AL. Total pelvic exenteration: The Albert Einstein College of Medicine/ Montefiore Medical Center Experience (1987 to 2003). Gynecol. Oncol 2006. 101, 261–268.
17. Chiantera V, Rossi M, De Iaco P, Koehler C, Marnitz S, Fagotti A, et al. Morbidity after pelvic exenteration for gynecological malignancies : A retrospective multicentric study of 230 patients. Int. J. Gynecol 2014. Cancer 24, 156–164.
18. Urh A, Soliman PT, Schmeler KM, Westin S, Frumovitz M, Nick AM, et al. 2013. Postoperative outcomes after continent versus incontinent urinary diversion at the time of pelvic exenteration for gynecologic malignancies. Gynecol. Oncol. 129, 580–585.
19. Matsuo K, Mandelbaum RS, Adams CL, Roman LD, Wright JD. Performance and outcome of pelvic exenteration for gynecologic malignancies: a population-based study, Gynecol. Oncol. 153 (2) (2019) 368–375.
20. Chiantera V, Rossi M, De Iaco P, Koehler C, Marnitz S, Ferrandina G, et al. Survival after curative pelvic exenteration for primary or recurrent cervical cancer: a retrospective multicentric study of 167 patients, Int. J. Gynecol. Cancer 24 (5) (2014) 916-922.
21. Westin SN, Rallapalli V, Fellman B, Urbauer DL, Pal N, Frumovitz MM, et al. Overall survival after pelvic exenteration for gynecologic malignancy, Gynecol. Oncol. 134 (3) (2014) 546–551.
22. Lee RK, Abol-Enein H, Artibani W, Bochner B, Dalbagni G, Daneshmand S, et al. Urinary diversion after radical cystectomy for bladder cancer: options, patient selection, and outcomes. BJU Int. 2014 Jan;113(1):11-23.
23. ter Glane L, Hegele A, Wagner U, Boekhoff J. Pelvic exenteration for recurrent or advanced gynecologic malignancies - Analysis of outcome and complications. Gynecol Oncol Rep. 2021 Mar 31;36:100757.
24. Moolenaar LR, van Rangelrooij LE, van Poelgeest MIE, van Beurden M, van Driel WJ, van Lonkhuijzen LRCW et al. Clinical outcomes of pelvic exenteration for gynecologic malignancies. Gynecol Oncol. 2023 Apr;171:114-120.
25. Kaur M, Joniau S, D'Hoore A, Van Calster B, Van Limbergen E, Leunen K, et al. Pelvic Exenterations for Gynecological Malignancies A Study of 36 Cases. Int J Gynecol Cancer. 2012 Jun;22(5):889-96.
26. Jäger L, Nilsson PJ, Rådestad AF. Pelvic exenteration for recurrent gynecologic malignancy: a study of 28 consecutive patients at a single institution. Int J Gynecol Cancer. 2013 May;23(4):755-62.
27. Nielsen CKP, Sørensen MM, Christensen HK, Jonas Amstrup Funder. Complications and survival after total pelvic exenteration. Eur J Surg Oncol. 2022 Jun;48(6):1362-1367.

TÜRK JİNEKOLOJİK ONKOLOJİ DERGİSİ
2023-2, Sayfa 33-36
Case Report

Sudden Onset of a Sister Mary Joseph's Nodule: A Case Report

Gamze Sönmez Ünal[1], Neşe Yeldir[2], Cağlar Yildiz[3], İrem Küçükyıldız[3]

ABSTRACT

Sister Mary Joseph's nodule is an umbilical metastasis rarely seen in cancer patients. The primary focus usually is on the abdomen or pelvis. We aimed to present an umbilical metastasis detected in a 34-year-old female patient who was referred to our clinic for an umbilical mass without complaint.

ÖZET

Sister Mary Joseph nodülü kanser hastalarında nadiren görülen bir umbilikalmetastazıdır. Birincil odak genellikle karın veya pelvis üzerindedir. Bu olguda kliniğimize umblikal kitle şikayeti ile başvuran 34 yaşındaki kadın hastada saptanan umblikal metastazı sunmayı amaçladık.

Received Date: 25/10/2023 Accepted Date: 09/05/2023

[1]Department of Obstetrics and Gynecology, Sivas Numune Hospital, Sivas, Turkey
[2]Department of Pathology, Medipol University, Istanbul, Turkey
[3]Department of Obstetrics and Gynecology, Sivas Cumhuriyet University Faculty of Medicine, Sivas, Turkey

Corresponding Author: Dr. Gamze Sonmez Unal
Department of Obstetrics and Gynecology,
Sivas Numune Hospital
Sivas, Turkey

Tel: +90 5300749158
E-mail: gmzsnmz@hotmail.com

Orcid no: 0000-0002-3818-5552

Introduction

Skin metastasis seen on umbilicus is defined as the Sister Mary Joseph's nodule. Sister Mary Joseph's nodule is a poor prognostic indicator in cancer patients and survival is reported to be 2-11 months in the patients who diagnosed of any cancer [2]. Primary cancer is frequently originated from gastric, colon and pancreas. The most commonly seen gynecologic malignancies with umbilical mass are ovarian and uterine cancers [3].

Case Presentation

A 34-year-old female patient admitted to clinic because of an umbilical mass. She had no systemic disease and had cesarean one year ago and there was no pathological finding then. Patient has complaining of umbilical mass that developed within 2 weeks and she has no abdominal distension or unexplained weight loss. Her umbilical nodule was about 2 centimeters diameter an irregular, ulcerated, painless nodule with blood (**Figure 1**). The lower abdomen CT revealed diffuse lesions in the right ovary and periovarian region, implants in the peritoneum and a mass of 8,5x5,5 cm in size, with cystic areas, heterogeneous contrast enhancement, and a clearly indistinguishable between uterine and bowel. Upper and lower gastrointestinal endoscopy was normal. Ca125 level was 691 U/mL. During laparotomy, primary tumour was on the right adnex. There was infiltration on the bladder, Douglas peritoneum and intestinal surfaces. Intraoperative frozen section was resulted as high-grade serous carcinoma. Total abdominal hysterectomy, bilateral salpingooophorectomy, bilateral pelvic and para-aortic lymphadenectomy, infracolic omentectomy, peritonectomy, appendectomy and debulking surgery were performed.

Histopathologic examination revealed bilateral tubo ovarian high grade serous carcinoma with invasion of the uterin serosa, myometrium, omentum, peritoneum (**Figure 2**). The subcutaneous tissue metastasis around umbilicus and one lymph node metastasis in the paraaortic region were found (**Figure 3**). The tumoral areas demonstrated solid, labyrinthine and cribriform architecture containing markedly atypical cells with large nuclei and high mitotic activity (**Figure 4**). Immunohistochemically, p53 diffuse strong nuclear positivity was detected in the tumor cells (**Figure 5**). Estrogen receptor (ER) ve progesteron receptor (PR) were negative.

The patient received adjuvant chemotherapy containing carboplatin paclitaxel after surgery but since the patinent's treatment were performed in other center, other data could not be accessed. There is no recurrence in the patient's last PET-CT. The patient is living good health in the 6th year after the surgery.

Discussion

Sister Mary Joseph (1856-1939) was born in New York in 1856 and was born in St. She started working as a nurse at Mary's Hospital.

She made a connection between intra-abdominal cancers and umbilical nodules. Spread to the umbilicus in intra-abdominal cancers occurs in 4 ways: 1) through the superficial or deep lymphatic system, 2)

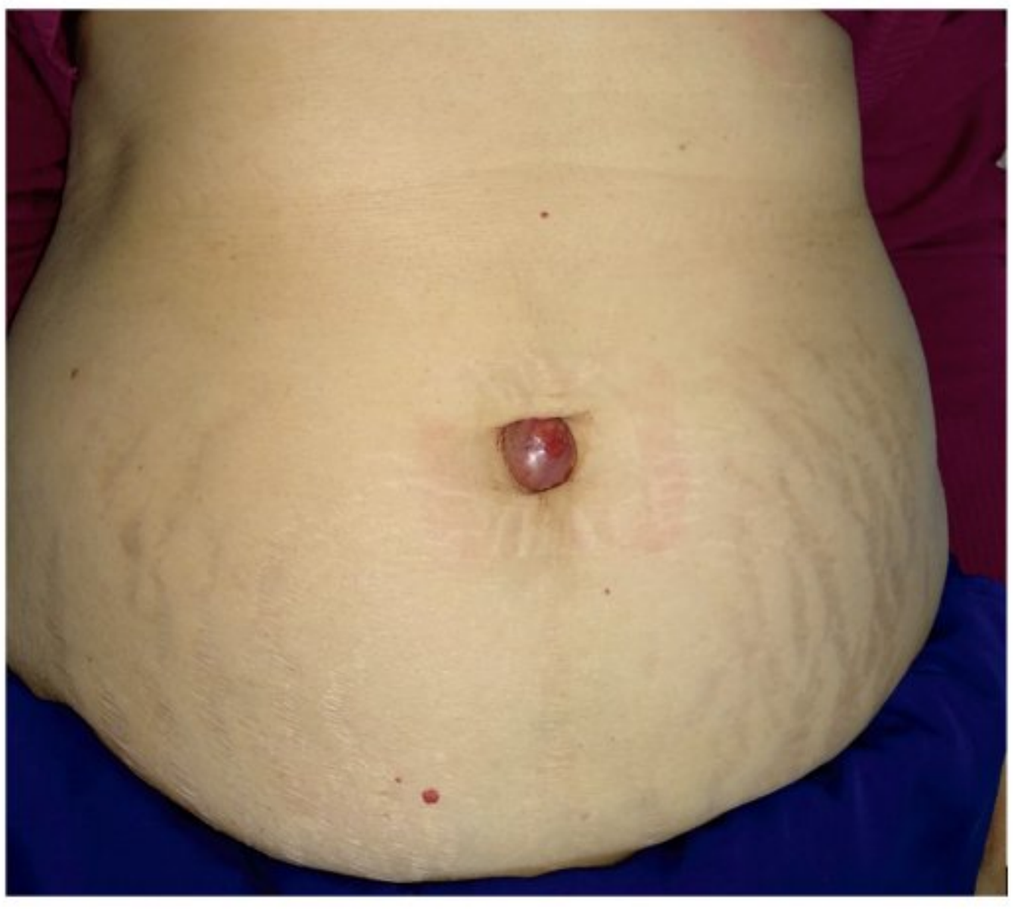

Figure 1: Sister's Mary Joseph Nodule

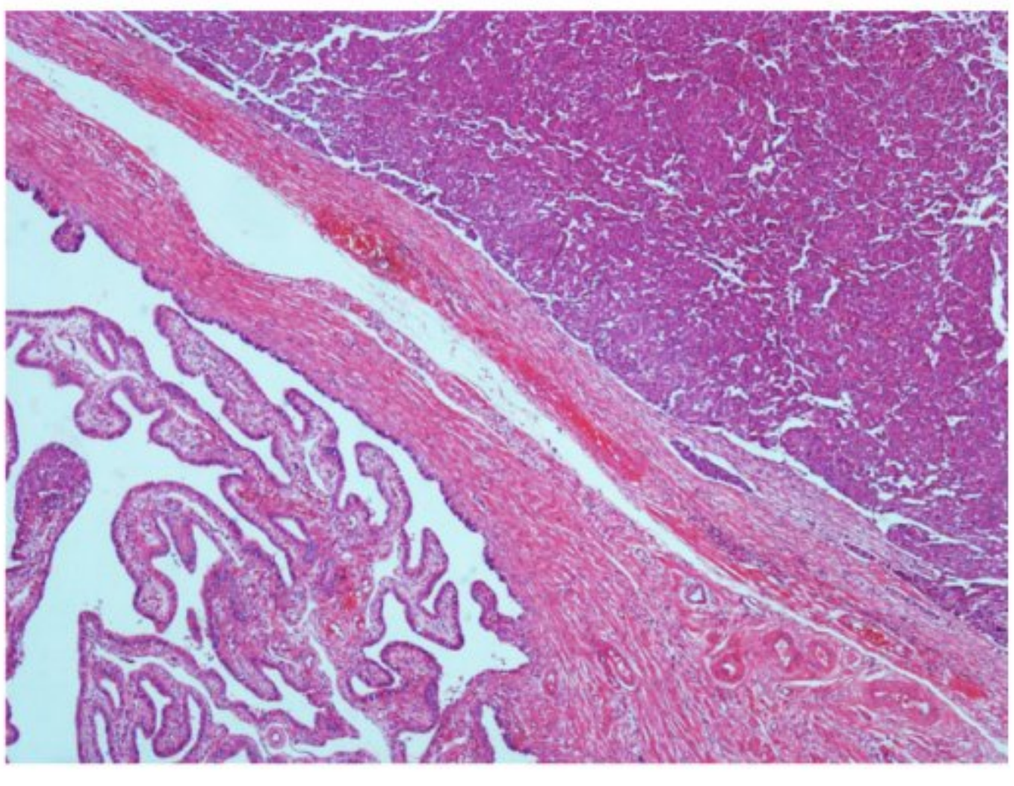

Figure 2: High grade serous carcinoma on the right and tubal epithelium on the left (H&E).

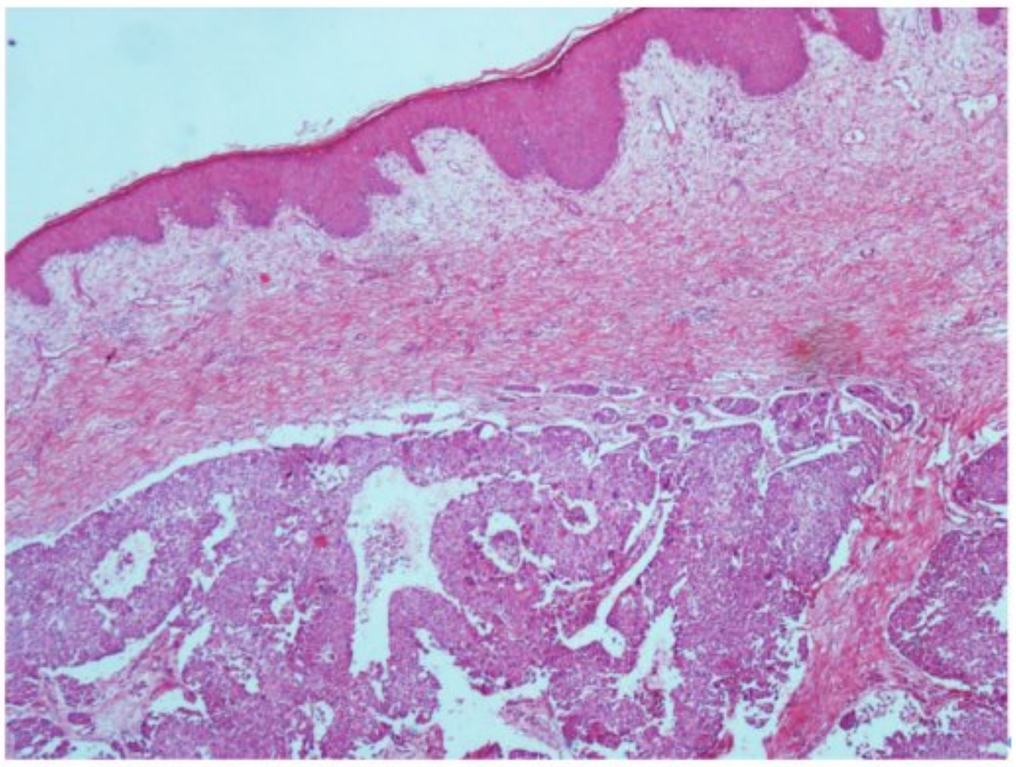

Figure 3: High grade serous carcinoma metastasis in the subcutaneous tissue around umbilicus (H&E).

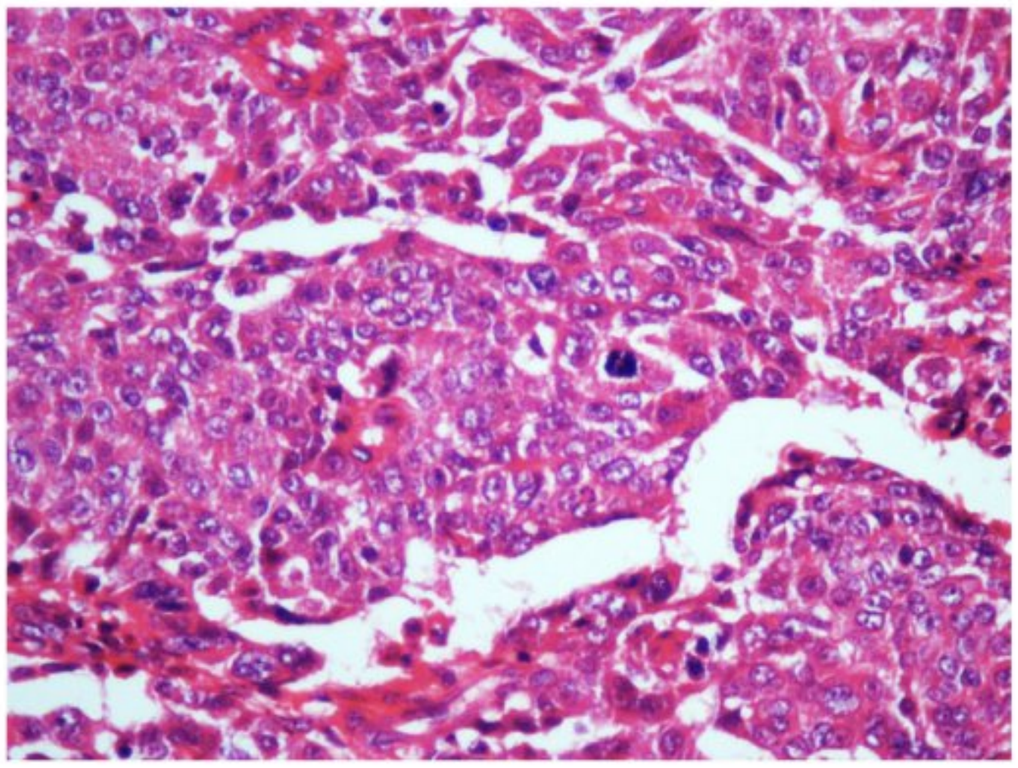

Figure 4: High grade serous carcinoma. Pleomorphic cells with large atypical nuclei and high mitotic activity (H&E).

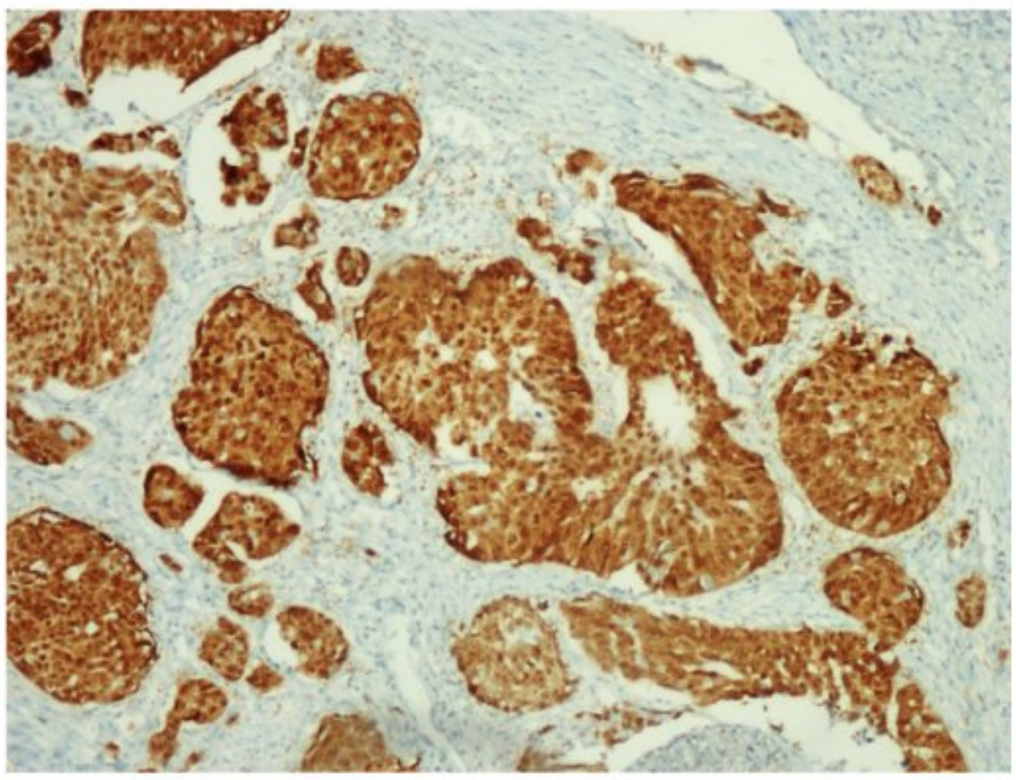

Figure 5: Mutant-pattern p53 immunostaining with diffuse strong nuclear expression.

by direct intraperitoneal spread, 3) by hematogenous spread, and 4) through the embryonic ligaments (4).

Galvan detected 24 uterine cancers in 407 umbilical tumor cases and reported that these were recurrent cases(5).

Primary tumors of the umbilicus are rare. It mostly occurs with metastasis of gastrointestinal system tumors. Distant metastases are thought to be caused by the hematogenous pathway. Umbilical hernia, endometriosis, granuloma and pilonidal sinus should be considered in the differential diagnosis. The tumoral mass may also be seen after the diagnosis of the primary tumor. The most common histological type is adenocarcinoma. The prognosis is bad. The average survival time has been reported to be 11 months (6). There is no consensus on treatment.

Malignancies originating from the pelvic organs should be kept in mind in people presenting with an umbilical nodule in the reproductive age. Differential diagnoses should be considered. Tissue sampling and imaging methods should be used for diagnosis. Systemic pelvic and paraaortic lymphadenectomy has been widely used in the surgical treatment of patients with advanced ovarian cancer, although supporting evidence from randomized clinical trials has been limited(7). During surgery was not associated with longer overall or progression -free survival than no lymphadenectomy and was associated with a higher incidence of postoperative complications(7).

Conclusion

Umbilical masses may occur with different clinical presentations like pyogenic abscess, epidermal cyst, hemangioma, abscess, umbilical hernia, endometriosis and primitive umbilical carcinoma. The physician should be careful about the umbilical mass that may be misdiagnosed as an umbilical hernia. Umbilical metastasis of primary malignancies is called as Sister Mary Joseph's nodule and it is rarely seen. The underlying causes of umbilical nodules should be well researched. As a result, although there are no specific clinical features of underlying condition, every umbilical mass should be examined carefully due to primary malignancies.

References

[1] Menzies S, Chotirmall SH, Wilson G, O'Riordan D. Sister Mary Joseph nodule. BMJ Case Reports. 2015.

[2] Gabriele R, Conte M, Egidi F, Borghese M. Umbilical metastases: current viewpoint. World J Surg Oncol. 2005; 3:13.

[3] Fratellone PM, Holowecki MA. Forgotten node: a case report. World J Gastroenterol. 2009; 15:4974–5.

[4] Barrow M. Metastatic tumors of the umbilicus. J Chronic Dis 1966;19:1113-1117

[5] Galvan V. Sister Mary Joseph's nodule: its clinical significance and management. An Med Interna 1999;16:1949–1950.

[6] Piura B. Umblilical metastasis: Sister Mary Joseph's nodule. Harefuah. 2006;145: 505-550

[7] Harter P, Sehouli J, Lorusso D, Reuss A, et al. a randomized trial of Lymphadenectomy in Patients with Advanced Ovarian Neoplasms. N Engl J Med. 2019; 380: 822-832.

TÜRK JİNEKOLOJİK ONKOLOJİ DERGİSİ
2023-2, Sayfa 37-42
Araştırma

Yüksek Dereceli Skuamoz İntraepitelyal Lezyonu Olan Hastalarda Punch ve Loop Biyopsinin Karşılaştırılması

Varol Gülseren[1], Kemal Güngördük[2]

ÖZET

Objective: Servikal punch ve loop biyopsinin performansını karşılaştırmak ve değerlendirmek amaçlanmıştır.

Yöntem: 2019-2020 yılları arasında Pap smear sonucunda yüksek dereceli skuamoz intraepitelyal lezyon (YDSİL) saptanan ve kolposkopi yapılan ve biyopsi alınan hastalar çalışmaya alınmıştır. Hastaların klinik verileri ve demografik özellikleri retrospektif dosya taraması ile değerlendirilmiştir. Çalışmaya 56 tane punch biyopsi (PB) ile 51 tane Loop ile servikal biyopsi alınan hasta dahil edilmiştir.

Bulgular: Hastaların yaş ortalama değerleri PB ve Loop gruplarında sırası ile 35.3 ± 8.2 ve 37.6 ± 10.5 olarak saptandı ve sonuçlarda anlamlı farklılık saptanmadı (P= 0.208). PB grubundaki hastaların %21.4'ü nullipar iken Loop grubunda %21.6 hastanın nullipar olduğu görüldü (P= 0.571). Spesmen genişliği PB ve Loop grubunda ortalama sırası ile 4.9 ± 1.2 mm ve 11.0 ± 1.7 mm olarak saptanmıştır (P< 0.001). Spesmen derinliğinin punch biyopsi alınan grupta daha kısa olduğu gösterildi (PB için 3.9 ± 0.7, Loop için 6.6 ± 1.0; P< 0.001). Minimal kanamalar iki gruptada benzer oranlarda (PB için %8.9, Loop için %9.8) saptandı. Hastalara işlem esnasında ağrı sorgulandığında gruplar arasında farklılık olmadığı tespit edildi (PB için 5.8 ± 1.3, Loop için 6.2 ± 1.8; P= 0.206). Toplam doku puanı 3 parametre kullanılarak hesaplandı. Doku yeterliliği (epitel + stroma içermesi) konusunda gruplar arasında farklılık olmadığı analiz edildi.

Sonuç: Loop grubunda spesmen derinliği ve genişliği daha uzun bulunmasına ve koter artefaktının olmasına rağmen PB ve Loop grupları arasında doku yeterliliği, kanama ve ağrı skorları gruplar arasında benzer bulundu. İki biyopsi şeklinin birbirine üstünlüğü kanıtlanamamıştır.

Anahtar Kelimeler: Yüksek Dereceli Skuamoz İntraepitelyal Lezyon, Serviks Kanseri, HPV

ABSTRACT

Objective: It was aimed to compare and evaluate the performance of cervical punch and loop biopsy.

Methods: Patients who were found to have high-grade squamous intraepithelial lesion (YDSIL) as a result of Pap smear between 2019-2020, and who underwent colposcopy and biopsy were included in the study. The clinical data and demographic characteristics of the patients were evaluated by retrospective file scanning. Patients who had 56 punch biopsy (PB) and 51 Loop cervical biopsies were included in the study.

Results: The mean age of the patients was 35.3 ± 8.2 and 37.6 ± 10.5 in the PB and Loop groups, respectively, and no significant difference was found in the results (P= 0.208). While 21.4% of the patients in the PD group were nulliparous, 21.6% of the patients in the Loop group were nulliparous (P= 0.571). The mean specimen width was 4.9 ± 1.2 mm and 11.0 ± 1.7 mm in the PB and Loop groups, respectively (P< 0.001). It was shown that the specimen depth was shorter in the punch biopsy group (3.9 ± 0.7 for PB, 6.6 ± 1.0 for Loop; P< 0.001). Minimal hemorrhages were found at similar rates in both groups (8.9% for PB, 9.8% for Loop). When patients were questioned about pain during the procedure, no difference was found between the groups (5.8 ± 1.3 for PB, 6.2 ± 1.8 for Loop; P= 0.206). Total tissue score was calculated using 3 parameters. It was analyzed that there was no difference between the groups in terms of tissue adequacy (including epithelium + stroma).

Keywords: High-Grade Squamous Intraepithelial Lesion, Cervical Cancer, HPV

Geliş Tarihi: 26/02/2023 Kabul Tarihi: 30/06/2023

[1]Erciyes Üniversitesi, Tıp Fakültesi, Kadın Hastalıkları ve Doğum Anabilim Dalı, Kayseri
[2]Muğla Sıtkı Koçman Üniversitesi, Tıp Fakültesi, Kadın Hastalıkları ve Doğum Anabilim Dalı, Muğla

İletişim Adresi: Varol GÜLSEREN
Erciyes Üniversitesi, Tıp Fakültesi

Tel: 0544 505 07 41

E-posta: drvarolgulseren@gmail.com

Orcid no: 0000-0002-3818-5552

Giriş

Dünyada en sık görülen 4. kanser tipi serviks kanseridir ve gelişmemiş ülkelerde en sık görülen jinekolojik malignitedir [1]. Gelişmiş ülkelerde serviks kanseri tarama programı sayesinde servikal kanser insidansı son yıllarda giderek azalmaktadır. Tarama programlarında Papanikolau testi veya Human Papilloma Virüs (HPV) testi kullanılmaktadır [2]. En sık cinsel yolla bulaşan enfeksiyon olan HPV'nin bulaşma riski %80'lere kadar ulaşmıştır ve gelişmiş ülkelerde azalan serviks kanseri insidansına rağmen premalign lezyonların insidansı giderek artmaktadır [3]. Türkiye'de uygulanan servikal kanser tarama programında %3,5 oranında HPV pozitifliği görüldü. En sık görülen HPV genotipleri 16, ardından 51, 31, 52 ve 18 oldu. HPV pozitif vakalarda sitolojik anormallik %19,1 oranında saptandı [4].

Pap testinin sitolojik incelemesi sonucunda prekanseröz lezyon olan yüksek dereceli skuamoz intraepitelyal lezyon (YDSİL) saptanan hastalara kolposkopi altında biyopsi alınması işlemi uygulanmaktadır [5]. Biyopsi genellikle punch biyopsi aleti ile alınmaktadır. Alınan biyopsi materyalleri genellikle 5 mm'den küçüktür. En yüksek dereceli lezyonu bulunan bölge biyopsi ile gözden kaçabilir. Loop Elektrocerrahi Eksizyon Prosedürü (LEEP) tedavide kullanıldığı gibi geniş biyopsi alınması işleminde de kullanılabilmektedir. Loop ile daha derin ve istenilen genişlikte spesmen çıkarılabilmektedir.

Punch biyopsi numuneleri söz konusu olduğunda, mukozanın soyulması, ezilme artefaktları ve gerekli miktar ve derinlikte anormal doku sağlamakta yetersizlik gibi çeşitli faktörler yetersiz numune alınmasına neden olabilir. Bununla birlikte, Loop ile alınan spesmenlerde çoğunlukla termal hasara bağlı tanı problemleri meydana gelebilmektedir. Pıhtılaşma nekrozu, geniş termal hasar bölgeleri ve dokuda uzun süreli temastan kaynaklanan doku distorsiyonu, lezyonun ve eksizyon sınırlarının durumunun doğru teşhisini engeller. Bu çalışma, punch ve loop biyopsinin performansını karşılaştırmak ve değerlendirmek için yapılmıştır.

Gereç ve Yöntem

2019-2020 yılları arasında Pap smear sonucunda YDSİL saptanan ve Muğla Sıtkı Koçman Üniversitesi Tıp Fakültesi Jinekolojik Onkoloji Cerrahisi Kliniğin'de kolposkopi yapılan ve biyopsi alınan hastalar çalışmaya alınmıştır. Hastaların klinik verileri ve demografik özellikleri retrospektif dosya taraması ile değerlendirilmiştir. Çalışmaya 56 tane punch ile servikal biyopsi alınan kadın ile 51 tane Loop ile servikal biyopsi alınan hasta dahil edilmiştir. Lokal etik kurul izni ve bilgilendirilmiş onam formu alınmıştır. Muayene sırasında kanaması olan, belirgin lezyonları olan, klinik akut pelvik enfeksiyon kanıtı olan, daha önce serviks karsinomu tedavisi görmüş hastalar ve hamile kadınlar çalışma dışı bırakıldı.

Kolposkopi mens dışı herhangi bir zamanda yapıldı. Hastalara testin prosedürü açıklandı. Hasta dorsal pozisyonda sistematik olarak muayene edildi. Vulva ve vajina girişine yapılan gözlem ve palpasyon ile muayeneden sonra spekulum takıldı. Eksternal os'u nemlendirmek, vasküler yapıların net görülmesi ve serviksin şeffaflığını arttırması için normal salin kullanıldı. Servikse %3 asetik asit 1-2 dakika süreyle uygulandı. Biyopsiler kolposkopi muayenesi sonrası elde edilen patolojik bulgu olan asetobeyaz alan, lökoplaki alanı, mozaik görünüm, punktuasyon ve atipik damarlanma görünümü sağlayan alanlardan yapıldı. Punch biyopsi grubu (PB grubu) veya Loop grubu olarak ayrıldılar.

Loop grubunda 10 mm'lik halkaya monopolar koter cihazı ile 25-30 W arasında bir akım ile blend modunda işlem yapıldı. Güç ayarları elektrotun uç boyutuna, önceki işlemlerden varsa fibröz skar varlığına ve servikal dokunun kıvamına göre seçildi. Biyopsi dokusunu elde etmek için tel halka, biyopsi bölgesinin hemen yan tarafından servikse dik olarak 5-8 mm derinlikte itildi, içinden çekildi ve ardından diğer taraftan dik olarak dışarı çekildi. Biyopsi örneği alındıktan sonra, bölge aşırı kanama açısından kontrol edildi. Belirgin kanama varsa, bölge 30–50 W'da 5 mm'lik bir top elektrot ile koterize edildi. Her iki gruptada biyopsi ile elde edilen spesmenler %10 formalin içeren kontainer ile Patoloji bölümüne gönderildi.

Hastalar işlem sonrası ağrı ve kanama açısından değerlendirildi. Hastalara biyopsi alma prosedürü sırasında ağrılarını 0'dan 10'a kadar derecelendirdiler. Sıfır en düşük ağrı, 10 en yüksek ağrı olacak şekilde puanlama yapıldı. Biyopsi yerinde kanama görülmesi durumunda homeostaz için ek bir yönteme ihtiyaç duyulup duyulmadığı kaydedildi. Hafif kanamalar tampon yapılarak duran kanamalar, orta-şiddetli kanamalar koterize edilerek duran kanamalar şeklinde not edildi. Patoloji bölümünde incelenen spesmenlerin doku boyutu ve doku hasarı değerlendirildi. Çıkan final histopatolojik tanı kaydedildi.

Tanımlayıcı istatistikler ortalama, medyan ve yüzde ölçümleri, standart sapma, minimum ve maksimum değerler ile değerlendirildi. Parametrik olmayan gruplar karşılaştırılırken ki-kare testi kullanıldı. Parametrik grupların karşılaştırılmasında student-t testi kullanıldı. Tüm istatistiksel analizler Statistical Package fort he Social Sciences (SPSS) programı ile yapıldı. $P<0.05$ değeri istatistiksel anlamlı kabul edildi.

Bulgular

Çalışma için PB grubuna 56 hasta loop grubuna 51 hasta alındı. Hastaların yaş ortalama değerleri PB ve Loop gruplarında sırası ile 35.3 ± 8.2 ve 37.6 ± 10.5 olarak saptandı ve sonuçlarda anlamlı farklılık saptanmadı (P= 0.208). PB grubundaki hastaların %21.4'ü nullipar iken Loop grubunda %21.6 hastanın nullipar olduğu görüldü (P= 0.571). Hastaların sigara kullanımı ve alkol kullanımı gruplar arasında benzer oranlarda saptandı. Hastaların klinik özellikleri ve demografik verileri tablo 1'de verildi.

PB grubunda alınan biyopsilerde en sık rastlanılan sonucun YDSİL olduğu ve %83.9 oranında saptandığı anlaşıldı. Loop grubunda ise %74.5 oranında YDSİL saptandığı sonucuna varıldı. Gruplar arasında anlamlı farklılık olmadığı gösterildi. Spesmen genişliği PB ve Loop grubunda ortalama sırası ile 4.9 ± 1.2 mm ve 11.0 ± 1.7 mm olarak saptanmıştır ve punch biyopsi şeklinde spesmen çıkarılan grupta anlamlı daha kısa olduğu tespit edildi (P< 0.001). Spesmen derinliğinin punch biyopsi alınan grupta daha kısa olduğu saptandı (PB için 3.9 ± 0.7, Loop için 6.6 ± 1.0; P< 0.001). Çalışmada hiçbir hastada sütür işlemi gerektirecek yada koterleme işlemi gerektirecek kadar kanama olmadı. Üç dakikalık bası ile duracak minimal kanamalar iki gruptada benzer oranlarda (PB için %8.9, Loop için %9.8) saptandı. Hastalara işlem esnasında ağrı sorgulandığında gruplar arasında farklılık olmadığı tespit edildi (PB için 5.8 ± 1.3, Loop için 6.2 ± 1.8; P= 0.206). Çalışmanın klinik ve patolojik sonuçları tablo 2'de verildi. Toplam doku puanı 3 parametre kullanılarak hesaplandı. Spesmende artefakt olmaması, genişlik 7 mm veya daha büyük olması, epitel + stroma doku yeterliliği parametreleri değerlendirildi. Loop biyopsi grubunda toplam doku puanının anlamlı daha iyi olduğu saptandı (P< 0.001).

Tartışma

Bu çalışmada, YDSİL nedeniyle kolposkopi yapılan ve sonunda servikal biyopsi yapılan hastalar değerlendirilerek, Loop ve punch biyopsi alınma yöntemleri patoloji sonuçları ve hasta memnuniyeti açısından karşılaştırıldı. Spesmenlerin derinlik ve uzunluk ölçülerinin Loop grubunda daha fazla olmasına rağmen patoloji sonuçları açısından gruplar arasında farklılık olmadığı gözlendi. Ayrıca spesmende koter artefaktı Loop grubunda %15.7 oranında görüldü.

Servikal biyopsi işleminde en sık görülen komplikasyon olan kanama genellikle hafif derecede meydana gelmekte ve kısa süreli kompresyonlar ile düzelebilmektedir [6]. Belirgin kanama nadiren saptanmaktadır ve sıklığı binde 2 olarak tespit edilmiştir [7,8]. Koter gereksinimi olabilecek kadar kanama meydana gelme sıklığı yaklaşık olarak %5'den az olarak bildirilmiştir [7]. Çalışmamızda PB grubunda %8.9 ve Loop grubunda %9.8 oranında kanama meydana geldiği bildirildi. Gruplar arasında kanama sıklığı açısından farklılık olmadığı gösterildi.

Tablo 1 • Hastaların klinik özellikleri ve demografik verileri

	PB (n:56)	Loop (n:51)	P
Yaş (Yıl), Ort ± SS	35.3 ± 8.2	37.6 ± 10.5	0.208
Parite, n (%)			
Nullipar	12 (21.4)	11 (21.6)	0.571
Unipar	6 (10.7)	9 (17.6)	
Multipar	38 (67.9)	31 (60.8)	
Doğum şekli, n (%)			
Vajinal doğum	27 (61.4)	24 (60.0)	0.898
Sezaryen	17 (38.6)	16 (40.0)	
Vajinal doğum, n (%)			
1	8 (29.6)	9 (37.5)	0.552
≥1	19 (70.4)	15 (62.5)	
Alkol kullanımı, n (%)	15 (26.8)	16 (31.4)	0.601
Sigara kullanımı, n (%)	23 (41.1)	21 (41.2)	0.991
Transformasyon zon tipi, n (%)	26 (46.4)	30 (58.8)	0.348
Tip 1	20 (35.7)	12 (23.5)	
Tip 2	10 (17.9)	9 (17.6)	
Tip 3			

Ort ± SS: Ortalama ± Standart sapma, PB: Punch biyopsi

Tablo 2 • Çalışmanın patolojik sonuçları

	PB (n:56)	Loop (n:51)	P
Patoloji sonucu, n (%) DDSİL YDSİL Mikroinvaziv kanser İnvaziv kanser	 7 (12.5) 47 (83.9) 1 (1.8) 1 (1.8)	 10 (19.6) 38 (74.5) 1 (2.0) 2 (3.9)	0.663
Spesmen genişliği (mm), Ort ± SS	4.9 ± 1.2	11.0 ± 1.7	<0.001
Spesmen derinliği (mm), Ort ± SS	3.9 ± 0.7	6.6 ± 1.0	<0.001
Doku yeterliliği (epitel + stroma), n (%)	53 (94.6)	50 (98.0)	0.345
Kanama, n (%)	5 (8.9)	5 (9.8)	0.568
Biyopsi işlemi esnasında ağrı skoru, Ort ± SS	5.8 ± 1.3	6.2 ± 1.8	0.206
Termal artefakt, n (%)	-	8 (15.7)	0.002
Enfeksiyon, n (%)	-	-	-
Toplam doku puanı, n (%) -1 -2 -3	 2 (3.6) 45 (80.4) 9 (16.1)	 - 9 (17.6) 42 (82.4)	<0.001

Ort ± SS: Ortalama ± Standart sapma, DDSİL: Düşük dereceli skuamoz intraepitelyal lezyon, YDSİL: Yüksek dereceli skuamoz intraepitelyal lezyon, PB: Punch biyopsi

Wetcho ve ark. tarafından yapılan randomize kontrollü çalışmada serviksten PB ve Loop ile biyopsi alınan iki grup karşılaştırıldı [9]. Çalışmadaki hastaların neredeyse tamamını reprodüktif dönemde bulunan kadınlar oluşturuyordu. Yeterli bir kolposkopik değerlendirme PB grubunda %81.2 ve Loop grubunda %68.8 oranında bulundu (P= 0.240). Toplam doku puanı, her bir kalite puanının (doku boyutu, doku bölgesi ve doku hasarı) toplamı olarak değerlendirildiğinde, Loop grubunda medyan doku skoru, PB grubundan anlamlı olarak yüksekti (8'e karşı 7) (P= 0.014). Loop grubunda doku boyutu PB grubuna göre daha uzun saptanmıştır (P< 0.001). Loop grubundaki tüm spesmenlerde hem epitelyal hem de stromal dokular vardı ve PB grubunda %93 hastada epitelyal ve stromal doku içeriyordu ve gruplar arasında istatistiksel anlamlı farklılık yoktu. İşleme bağlı ağrı değerlendirildiğinde her iki grupta da medyan VAS ağrı skoru 3 olarak saptanmıştır (P= 0.820) [9]. Bizim çalışmamızda spesmen genişliği ve derinliği Loop yapılan grupta daha fazla saptandı ve sonuçlar anlamlı bulundu. Bunun sebebi, Loop elektrot, özellikle sert kıvamlı dokuda veya stenotik servikal os'ta her şüpheli bölgeye nüfuz edecek şekilde hassas bir şekilde kontrol edilebilen bir elektrik kesiği sağlamasıdır. Forseps ile zımba biyopsisinin aksine, Loop kullanımı kayma olmadan yeterli biyopsiler elde edebilir. Doku yeterliliği, işlem sonrası meydana gelen minimal kanama ve işlem esnasında ağrı skorları iki grupta farklılık olmadığı gösterildi. Dokuda koter artefaktı doğal olarak sadece Loop grubunda %15.7 oranında görüldü. Toplam doku puanı (spesmende artefakt olmaması, genişlik 7 mm veya daha büyük olması, epitel + stroma doku yeterliliği) Loop biyopsi grubunda anlamlı daha iyi olduğu saptandı (P< 0.001).

Literatürde yapılan bir çalışmada sitoloji sonucu HGSIL olan vakalarda kolposkopik biopsi ile eksizyonel işlemler arasında yaklaşık %73.7 oranında uyum bulunduğu tespit edilmiştir [10]. Hastaların %63,5'i CIN2+, %13,8'i ise invaziv kanser saptanmıştır. Punch biyopsi invaziv kanserli hastaların %41'inde eksik patolojik tanı vermiştir [10]. Punch biyopsi sonucu ≤CIN1 gelse bile eksizyonel işlem seçeneği sunulması önerilmektedir. Bu yüzden bizim çalışmamızda değerlendirildiğinde, loop biyopsi daha geniş doku örneği ile daha doğru sonuçlara neden olabilir.

Serviksten gelen ağrı hissi pudendal sinir ve sinirlerin hipogastrik pleksusu tarafından taşınır. Ağrı algısı oldukça sübjektiftir ve bir dereceye kadar hastanın kaygısı ve kaygısına göre değişir. Yalnızca biyopsi alma işleminde lokal anestezi önerilmemektedir [11]. Hastaların işlem esnasında ağrı düzeyleri gruplar arasında farklılık göstermediği tespit edildi (PB için 5.8 ± 1.3, Loop için 6.2 ± 1.8; P= 0.206). Literatürde de çalışmamızla uyumlu olarak ağrı skoru gruplar arasında benzer oranlarda saptandı [9,12,13].

Loop örnekleriyle ilgili temel endişe olan termal artefakt Nagar ve arkadaşları tarafından değerlendirildiğinde, örnek kenarlarında displazi varlığında anlamlı bir fark saptanmadı [14]. Yapılan çalışmalarda hem epitel hem de stromal doku içeriği Loop grubunda tüm hastalarda vardı [12]. PB grubunda çok fazla distorsiyon görülmedi ve patolojik sonuçlarla tüm dokular değerlendirilebildi [12]. 2006 yılında Byrom ve ark. eşleştirilmiş punch biyopsi ve Loop grubunda servikal biyopsi örneklerinde yetersizlik oranını %5.3 olarak bulmuşlardır [15].

Çalışmanın bazı eksik yönleri mevcuttur. İlk olarak retrospektif natürde olması söylenebilir. Bu yüzden dokuların değerlendirilmesine patolojik sınıflama yapılarak doku yeterliliği konusunda puanlama verilebilirdi. İkinci eksik yön spesmenlerin birden fazla sayıda patolog tarafından değerlendirilmesidir. Bu nedenle gözlemciler arasında değerlendirme ve ölçüm farklılıkları meydana gelmesi olasıdır.

Sonuç olarak, Loop grubunda spesmen derinliği ve genişliği daha uzun bulunmasına ve koter artefaktının olmasına rağmen PB ve Loop grupları arasında doku yeterliliği (epitel + stroma içermesi), kanama ve ağrı skorları gruplar arasında benzer bulundu. İki biyopsi şeklinin birbirine üstünlüğü kanıtlanamamıştır. Biyopsi alma şeklinin hastanın durumuna göre seçilmesi önerilmektedir.

Kaynakça

1. Ferlay J, Soerjomataram I, Ervik M, et al. GLOBOCAN 2012 V1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11. (http://globocan.iarc.fr). Accessed 16 July 2014.
2. Labani S, Asthana S. Age-specific performance of careHPV versus Papanicolaou and visual inspection of cervix with acetic acid testing in a primary cervical cancer screening. J Epidemiol Community Health 2015; 2015:205851.
3. Stanley M. Pathology and epidemiology of HPV infection in females. Gynecologic oncology. 2010;117(2 Suppl):S5-10.
4. Gultekin M, Zayifoglu Karaca M, Kucukyildiz I, Dundar S, Boztas G, Semra Turan H, Hacikamiloglu E, Murtuza K, Keskinkilic B, Sencan I. Initial results of population based cervical cancer screening program using HPV testing in one million Turkish women. Int J Cancer. 2018 May 1;142(9):1952-1958.
5. L. S. Massad, Y. C. Collins, and P. M. Meyer, "Biopsy correlates of abnormal cervical cytology classified using the bethesda system," Gynecologic Oncology, vol. 82, no. 3, pp. 516–522, 2001.
6. Arora R, Malik A, Zutshi V, Bachani S. Comparıson Of Cervıcal Bıopsy Usıng Punch Bıopsy Forceps Versus Loop Electrode. Int. j. clin. biomed. res. 2018;4(4):6-12.
7. Wright TC Jr, Richart RM. Loop excision of the uterine cervix. Curr Opin Obstet Gynecol. 1995;7:30-34.
8. Petry KU, Glaubitz M, Maschek H, et al. Electrosurgical loop excision of the transformation zone in treatment of cervix neoplasia. Geburtshilfe Frauenheild. 1996;56:513 516
9. Wetcho T, Rattanaburi A, Kanjanapradit K. Quality of tissue from punch biopsy forceps vs. round loop electrode in colposcopically directed biopsy: a randomized controlled trial. J Gynecol Oncol. 2018 Jul;29(4):e52.
10. Erdem B, Aşıcıoğlu O, Turan G, et al. Sitolojisi HGSIL Gelen Olgularda Kolposkopik Biopsi ile Eksizyonel İşlem Sonuçlarının Korelasyonu: 10 Yıllık Tersiyer Merkez Deneyimi. Zeynep Kamil Tıp Bülteni;2019;50(2):15-18
11. Srisomboon J, Kietpeerakool C, Suprasert P, Sirisunkgul S, Khunamornpong S, Prompittayarat W. Factors affecting residual lesion in women with cervical adenocarcinoma in situ after cone excisional biopsy. Asian Pac J Cancer Prev 2007;8:225-8.
12. Sahai A, Bansal V, Singh P. Comparison of Punch Biopsy and Loop Biopsy for the Management of Severe Cervical Intraepithelial Neoplasia (CIN). J Obstet Gynaecol India. 2022 Aug;72(Suppl 1):248-254.
13. Öz M, Korkmaz E, Cetinkaya N, Baş S, Özdal B, Meydanl MM, et al. Comparison of topical lidocaine spray with placebo for pain relief in colposcopic procedures: a randomized, placebo-controlled, double-blind study. J Low Genit Tract Dis 2015;19:212-4.
14. Nagar HA, Dobbs SP, McClelland HR, Price JH, McClean G, McCluggage WG. The large loop exci-sion of the transformation zone cut or blend ther-mal artefact study: a randomized controlled trial. International Journal of Gynecological Cancer. 2004;14(6):1108-11.
15. Byrom J, Douce G, Jones PW, Tucker H, Millinship J, Dhar K, Redman CW. Should punch biopsies be used when high-grade disease is suspected at initial colposcopic assessment? A prospective study. Int J Gynecol Cancer 2006;16(1):253-6.