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Evaluation of patients' anxiety on colorectal cancer screening in global health burde conditions such as COVID-19

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ABSTRACT

Aims: Colorectal cancer (CRC) remains to be the third most common cancer and could be detected earlier with screening programmes. The coronavirus disease 2019 (COVID-19) pandemic has disrupted routine health care globally including CRC screening. In this study we aimed to assess and compare the Hospital Anxiety and Depression Scale (HADS) scores in patients who were planned to undergo screening before and during COVID-19.

Methods: In this cross sectional study we compared data of patients who were planned to undergo CRC screening during COVID-19 period (February 1 to February 28, 2021) with those of the same period of 2019 (pre-COVID-19). Groups were compared in terms of age, gender, education level, incidence of unwillingness and cancelling the colonoscopy for CRC and HADS scores.

Results: The mean (±SD) age of the whole cohort was 51.1 (±12.45) years. Sixteen (28%) of the patients were unwilling to undergo screening and 3 (5.2%) of them cancelled the colonoscopy in COVID-19 period group, however none of the patients had an anxiety to undergo screening and cancelled colonoscopy in pre-COVID-19 group. The subscales of Hospital Anxiety and Depression Scale; HADS-A and HADS-D scores were significantly higher in COVID-19 period group.

Conclusion: CRC prevention efforts depend largely on screening. Therefore, the effectiveness of the screening method depends both on the test sensitivity, specificity and the patients' compliance. Due to the fear of patients' to be exposed to COVID-19, the rate of CRC screening has been decreased worldwide. Especially in the global health burden circumstances like COVID-19, less invasive, easily applicable and screening tests with high sensitivity and specifity could be the preferred option in order to improve patients' compliance.

Keywords: Colorectal cancer, colonoscopy, screening, COVID-19, oncology, Hospital Anxiety and Depression Scale, HADS, patient compliance

INTRODUCTION

World Health Organization (WHO) announced global pandemic of COVID-19 in March 2020 and in response to the increase in the prevalence of this disease, the Centers for Disease Control and Prevention (CDC) implemented guidelines to diminish exposure and reduce transmission risk especially for people those considered high risk for COVID-19.[1] Because of the fear of developing COVID-19 infection, cancer screening programs, have been disrupted in many countries.[2] It is well known that colorectal cancer (CRC) is the second common leading cause of cancer death in the world.[3] Therefore CRC screening and early detection via invasive or non-invasive methods, have been known to improve the morbidity and mortality of this disease. Since COVID-19 lead dramatic decline in cancer screening, CRC has been showed to be most affected, because diagnosis at advanced stages are associated with lower survival.[4,5] Impact of COVID-19 pandemic on CRC screening has been investigated and restrictions that have been implemented in different countries were shown to reduce screening.[6] Colonoscopy is the most preferred method for CRC screening despite the invasiveness of the procedure, sedation or anesthesia requirement and unpleasent bowel preparation. As well as fear of developing COVID-19 infection additionally to the abovementioned limitations, people have canceled or delayed their colonoscopy appointments.

It is important to understand the impact of the pandemic on the patients' mood that colonoscopy recommended and whether the pandemic altered patient compliance to the screening. In order to recognize emotional disorder, we provided simple questionnaire to the patients prior to procedure. Hospital Anxiety and Depression Scale (HADS) is a psychometric test that was created especially for assessing the possible cases of anxiety and depression in the clinical settings.[7] In our study we performed HADS to the patients who were planned to undergo colonoscopy and compared the scores in two similar time periods in 2019 and 2021 in order to assess the effect of COVID-19 pandemic on the CRC screening.

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METHODS

This study was approved by the the Ankara Bilkent City Hospital Clinical Researches Ethics Committee (Date: 17.02.2021, Decision No: E1-21-1547). Informed consent of the participants were obtained. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

In this cross sectional study data of patients who were planned to undergo CRC screening via screening colonoscopy during COVID-19 period (March 1 to March 28, 2021) were compared to same month in 2019 in General Surgery endoscopy unit of University of Health Sciences Ankara Bilkent City Hospital. Groups were compared in terms of age, gender, education level, incidence of unwillingness and cancelling the colonoscopy for CRC screening and HADS scores.

The screening colonoscopy interval were recommended according to the national guidelines. HADS were performed to the patients who were planned to undergo screening colonoscopy in pre-COVID-19 and COVID-19 period group. HADS is composed of two subscales and each consists 7- item for depression (HADS-D) and anxiety (HADS-A). Each item is scored on a four-point (0-3) format and scores range from 3 most severe to 0 for absence. So, the scores range from 0 to 21 for each anxiety and depression. Score 0 to 7 for either subscale is being in the normal range, 8 to 10 being suggestive of the presence of the respective state, score of 11 or higher reflects caseness of the mood disorder.[8] The scores of HADS-A and HADS-D according to gender and education level of the patients were evaluated.

Statistical Analysis

Data analysis was conducted using the Statistical Package for the Social Sciences (SPSS), version 23.0 for Windows (SPSS Inc., Chicago, IL, USA). Descriptive statistics were given as mean (standart deviation) for normally distributed variables or median (minimum-maximum) for variables that for not normally distributed. Categorical data were expressed as percentages. The normal distribution of the data was assessed by the Kolmogorov-Smirnov test. The Chi-square test or Fisher's exact tests were performed to compare categorical variables as appropriate. The Mann-Whitney U test was conducted for nonnormally distributed continuous variables. A p-value <0.05 was considered statistically significant.

RESULTS

A total of 100 patients were included in this study, 43 of them were in pre-COVID-19 group, 57 were in COVID-19 period group. The mean (±SD) age of the whole cohort was 51.1 (±12.45) years. The characteristics of the two groups are presented in **Table**. No significant difference was found in age, gender and education level of the groups (p=0.314, p=0.686 and p=0.306; respectively). Sixteen (28%) of the patients were unwilling to undergo screening and 3 (5.2%) of them cancelled the colonoscopy in COVID-19 period group, however none of the patients had an anxiety to undergo screening and cancelled colonoscopy in pre-COVID-19 group. The median (minimum-maximum) HADS-A and HADS-D scores were 8 (0-20) and 6 (0-18) in pre-COVID-19 group and 20 (12-25) and 16 (13-24) in COVID-19 group (p<0.001 and p<0.001; respectively). No significant difference was found in HADS-A and HADS-D scores according to gender (p=0.77 and p=0.65; respectively) and no significant difference was found in HADS-A and HADS-D scores according to education level of the patients (p=0.28 and p=0.27; respectively).

Table. Comparison of the characteristics of the pre-COVID-19 group and COVID-19 group

Characteristics	Pre-COVID-19 group (n=43)	COVID-19 group (n=57)	p-value
Age (years)*	56 (21-82)	50 (21-85)	0.314
Gender, n (%)			
Female	20 (46.5)	30 (52.6)	0.68
Male	23 (53.5)	27 (47.4)	
Educational status, n (%)			
Primary school	22 (52.3)	36 (63.1)	0.30
High school and graduate	21 (47.7)	21 (36.9)	

*Median (minimum-maximum)

DISCUSSION

To the best of our knowledge, no previous studies have investigated the impact of the COVID-19 pandemic on the mood of patients who were recommended colonoscopy for CRC screening in Turkish society. We found that the subscales of HADS scores were significantly higher in COVID-19 period group. However no significant difference was found in HADS-A and HADS-D scores according to gender and education level of the patients.

Colorectal cancers are the second and third leading causes of cancer-related death in men and women, respectively, to deal with CRC, colonoscopy is considered as an effective diagnostic method, which gives option to remove adenomatous polyps and can improve CRC outcomes with early detection of presymptomatic malignancies. Also, fecal immunochemical test (FIT) has become popular because it has high sensitivity to identify patients with the highest risk of CRC. However increased time lag between a patient's positive FIT result and colonoscopic examination results in the more advanced lesions. Lee et al.[9] showed that patients who had a positive FIT result but failed to undergo timely colonoscopic examination, had the increased risk of any CRC or advanced-stage CRC with the increased time lag. They compared patients who underwent colonoscopy within 1-3 months and patients who underwent colonoscopy more than 6 months and found that delayed group had a significantly increased risk of any CRC and advanced-stage disease. Meester et al.[10] compared patients who underwent colonoscopy within 2 weeks of positive FIT results and patients who underwent colonoscopy 12 months later and found that any CRC and CRC related death was increased about 4% and 16%, respectively. So it should be kept in mind the importance of timely colonoscopy after a positive FIT result.

COVID-19 has caused the cancellation of elective surgeries and suspended CRC screenings like the other screening programmes.[11] The effects of the disruption of this primary health care procedures have impaired the timely manner cancer diagnosis and results late diagnosed cancer cases with increased morbidity and mortality.[12] A study from Italy showed that diagnosis of CRC was decreased (62%) after the COVID-19 pandemic has initiated and compared to other cancers CRC had the most third delay in diagnosis following prostate and bladder cancer.[13] Wassie et al.[14] showed that during April-June 2020, the number of performed colonoscopies decreased by 51.1% compared to the same months in 2019. In another study Lantinga et al.[15] observed a significant reduction in endoscopic procedures during March to May 2020, especially gastroscopies (57%) and colonoscopies (45%). They concluded that during that time period infection was more prevalant in Netherlands and resulted in postponed or cancelled elective endoscopic procedures. Previous studies have shown that patients' unwillingness to attend hospitals because of the fear of infection and exposure the virus, has decreased hospital admissions.[16-18] Unfortunately delays in screening and surveillance colonoscopies might facilitate the progression of cancer in people who are prone to CRC. In a study from our country Guven et al.[19] compared the stages of the newly referred patients to medical oncology clinic during the first 10 months with the year before. They showed that the incidence of inoperable or metastatic diseases were significantly increased but percentage of patients diagnosed via the screening methods were significantly decreased during the pandemic. And they observed that the metastatic disease at first visit were more prominent in breast and colorectal cancer.

Korean national data reported a 43.8% reduction in the number of diagnostic colonoscopies and a 37.5% reduction in that of therapeutic colonoscopies. Western countries also showed that a reduction in colonoscopy volume during the COVID-19 pandemic was over 90% in the New York metropolitan area, up to 85.6% using the French national health data, 92% based on 4 population-based datasets of England, and 59% in the population-based study from Hong Kong compared to those prior to COVID-19.[20] A study conducted in Turkiye found that the number of colorectal screenings in 2020 decreased by 46.1%, 81.9%, and 72.2%, respectively, compared to the three previous years (2017, 2018, and 2019).[21]

Similarly we have observed the negative effects of COVID-19 on the compliance of CRC screening in our colonoscopy unit. In order to evaluate the patients' mood who were planned to undergo screening colonoscopy, we performed the subscales of Hospital Anxiety and Depression Scale; HADS-A and HADS-D scores. We found that HADS-A and HADS-D scores were significantly higher in COVID-19 period group than pre COVID-19 group ($p<0.001$ and $p<0.001$; respectively). In the COVID-19 period 16 (28%) of the patients were unwilling to undergo screening and three (5.2%) of them cancelled the colonoscopy. We think that the most important reason for this situation is the COVID-19 infection, because in the pre-COVID-19 group none of the patients had an anxiety to undergo screening and cancelled colonoscopy. As it is well known invasiveness of the colonoscopy, requirment of sedation or anesthesia and dietary preparation for bowel cleansing contribute to low compliance with colonoscopy screening. Also, COVID-19 pandemic have detrimental effects and shown to be an important contributory factor to the distress of undergoing colonoscopy. HADS have been most commonly performed in oncology as well as in other somatic illnesses in many studies.[22] Annunziata et al.[23] conducted a study in order to evaluate HADS accuracy in cancer patients, comparing its two subscales (HADS-A and HADS-D) against tools not in use in psychiatry, which are able to detect prolonged negative emotional states. They concluded that HADS scores could help clinicians in order to recognise anxious and depressive states in cancer patients in clinical settings.

CONCLUSION

As a result, CRC prevention efforts depend largely on screening. Therefore, the effectiveness of the screening method depends both on the test sensitivity, specifity and the patients' compliance. It is very difficult to compare all screening methods against each other but theoretically ideal screening test could detect most incipient CRCs, or CRC at an early stage. Especialy in the global health burden conditions like COVID-19, less invasive, easily applicable even could be performed at home screening tests could be preferred option. Future studies are required in order to identify innovative, non-invasive alternative screening methods like novel biomarkers in CRC.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study was approved by the Ankara Bilkent City Hospital Clinical Researches Ethics Committee (Date: 17.02.2021, Decision No: E1-21-1547).

Informed Consent

Written informed consent was obtained from all individual participants prior to their inclusion in the study. Participants were fully informed about the study's aims, procedures, potential risks and benefits, and their rights-including the right to withdraw at any time without consequence. All participants voluntarily signed a written informed consent form.

Peer Review Process

This manuscript was subject to external peer review.

Conflict of Interest

The authors declare no conflicts of interest related to this study.

Financial Disclosure

The authors received no financial support for the conduct or publication of this research.

Author Contributions

All authors contributed significantly to the study's conception, design, data acquisition, analysis, and interpretation. All authors reviewed and approved the final version of the manuscript.

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Original Article

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Cervical human papillomavirus infection and cytologic abnormalities in patients with vulvar squamous cell carcinoma

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ABSTRACT

Aims: To assess the prevalence of cervical human papillomavirus (HPV) infection and related cytologic or histopathologic abnormalities in patients with vulvar squamous cell carcinoma (VSCC), and to explore their association with HPV-related and HPV-independent tumor subtypes.

Methods: This retrospective study included 41 surgically treated VSCC patients at Ankara Bilkent City Hospital (2019-2024). Clinical, cytologic, and pathologic data, including vulvar and cervical HPV status, were analyzed. Cervical HPV testing was performed by polymerase chain reaction (PCR), and cytology was classified according to the Bethesda system.

Results: HPV-associated VSCC was identified in 17.1% of patients, and cervical HPV positivity in 7.1%. Among 34 cytology results, 32.4% showed abnormalities (ASCUS, ASC-H, or HSIL). Cervical biopsy revealed LSIL or HSIL in 6 patients and invasive carcinoma in 1. Preinvasive or invasive cervical lesions were more frequent in HPV-associated VSCC (57.1%) than in HPV-independent cases (28.6%), though not statistically significant (p=0.204).

Conclusion: Cervical HPV infection and cytologic abnormalities were uncommon, likely reflecting the predominance of HPV-independent tumors in this older cohort. Nevertheless, abnormal cytology in a subset of patients supports comprehensive cervical assessment and risk-adapted surveillance, particularly in HPV-associated VSCC.

Keywords: Vulvar squamous cell carcinoma, human papillomavirus, cervical cytology

INTRODUCTION

Vulvar carcinoma is a relatively rare but **clinically significant** malignancy that predominantly affects postmenopausal women. Human papillomavirus (HPV), especially types 16 and 18, has been significantly associated with the development of precancerous lesions and invasive vulvar carcinomas.[1] This framework, formalized in the 2020 World Health Organization (WHO) Classification of Female Genital Tumours, aligns with molecular surrogates (diffuse p16 expression for HPV-related disease and aberrant p53 patterns for HPV-independent disease), and it increasingly informs diagnostic workup and treatment planning.[2,3] In invasive vulvar cancer, squamous cell carcinoma (SCC) accounts for the vast majority of cases (>90%), whereas the remainder is composed of adenocarcinomas (many arising from the Bartholin gland), melanomas, basal cell carcinomas and other rare histologies.[1]

Clinically, multifocal lower genital tract disease involving the vulva, cervix, vagina and perianal/anal epithelium may occur synchronously or metachronously. In patients with HPV-associated vulvar squamous cell carcinoma (VSCC), synchronous or metachronous high-grade cervical intraepithelial neoplasia or invasive cervical carcinoma has been reported in approximately 19% of cases during long-term follow-up. Following treatment for vulvar carcinoma, subsequent surveillance reveals high-grade cervical or vaginal dysplasia in roughly 8% of patients.[2] Although tumor-based meta-analyses indicate HPV involvement in approximately 34-43% of VSCCs overall, comprehensive and standardized data regarding cervical HPV DNA prevalence within these cohorts remain limited.[3]

The present study examines the accompanied of cervical HPV infection with vulvar SCC and correlates it with cervical cytology and pathology, testing its value as a prognostic indicator with potential therapeutic implications. The aim of this study was to determine the prevalence of cervical human papillomavirus infection and cytologic and histopathologic abnormalities in patients with vulvar squamous cell carcinoma and to explore their relationship with HPV-related and HPV-independent tumor subtypes.

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METHODS

This retrospective study was approved by the Ankara Bilkent City Hospital Clinical Researches Ethics Committee (Date: 22.11.2023, Decision No: E2-23-5674) and was conducted in accordance with the principles of the Declaration of Helsinki.

This retrospective, cross-sectional study included patients diagnosed with vulvar cancer at Ankara Bilkent City Hospital from September 2019 to December 2024. A total of 67 patients with VSCC underwent surgical treatment. Inclusion criteria was, patients were eligible if they had a histopathologically confirmed diagnosis of vulvar SCC and available cervical HPV test results or cervical cytology reports. Patients with missing data were not excluded; instead, any unavailable information was documented as "not reported". Ultimately, the study was conducted with 41 patients.

Demographic, clinical, and histopathological data were extracted from the hospital electronic database and medical records. Collected variables included age, tumor size, International Federation of Gynecology and Obstetrics (FIGO) 2021 stage, and vulvar cancer HPV status (positive, negative, or not reported). The results of the cervical HPV test and cytology findings were documented, encompassing normal cytology, atypical squamous cells of undetermined significance (ASCUS), low-grade squamous intraepithelial lesion (LSIL), atypical squamous cells-cannot exclude high-grade squamous intraepithelial lesion (ASC-H), and high-grade squamous intraepithelial lesion (HSIL), with missing values classified as "not reported". Furthermore, colposcopy and cervical biopsy results were obtained from pathology reports.

Etiologic classification of vulvar squamous cell carcinoma as HPV-related or HPV-independent was abstracted from the original pathology reports. During the study period, systematic p16 and p53 immunohistochemistry was not applied to all vulvar tumors; therefore, HPV status largely reflected documented HPV DNA testing and the descriptive histopathologic diagnosis.

HPV testing was conducted by the polymerase chain reaction (PCR) method, and cervical cytological evaluations were classified according to the Bethesda system. According to cytological findings and HPV test results, a cervical biopsy was indicated in 11% of cases.

The colposcopy and biopsy results were evaluated according to the histopathology reports.

Statistical Analysis

All data analyses were performed utilizing IBM SPSS Statistics version 22.0 for Windows (SPSS Inc., Chicago, IL, USA). Continuous variables were represented as mean±standard deviation and median (min-max), while categorical variables were given as frequencies and percentages. The correlation between HPV status of vulvar SCC and cervical smear results was assessed using the chi-square test or Fisher's exact test, while cervical biopsy outcomes were examined by cross-tabulations. Missing data were classified as a separate group and evaluated to evaluate their distribution and possible impact on the findings. A p-value below 0.05 was considered statistically significant.

RESULTS

General characteristics are detailed in **Table**. A total of 41 patients diagnosed with vulvar cancer were included in the study. The mean age at diagnosis was 65.2±10.76 years and the 22 (53.7%) patients were in geriatric age (65 years or older). The mean tumor size was 43.9±29.91 mm. The majority were classified as stage IB (41.5%), followed by stage IIIC (22%).

Table. Patients' characteristics

Features		Mean±SD	Median (min-max)
Age at initial diagnosis		65.2±10.76	66 (40-87)
Tumor size (mm)		43.9±29.91	40 (4-130)
		n	%
Geriatric age	<65 years	19	46.3
	≥65 years	22	53.7
Stage	IA	4	9.8
	IB	17	41.5
	II	4	9.8
	IIIA	4	9.8
	IIIB	3	7.3
	IIIC	9	22
HPV-related vulvar SCC	Negative	18	43.9
	Positive	7	17.1
	Not reported	16	39
Cervical HPV testing	Negative	26	63.4
	Positive	2	4.8
	Not reported	13	31.7
Cervical smear	Normal cytology	23	56.1
	ASCUS	7	17.1
	ASC-H	2	4.9
	HSIL	2	4.9
	Not reported	7	17.1

The "not reported" category represents cases with incomplete clinical records; these patients were retained as a separate analytic group rather than being excluded from the analyses.
SD: Standard deviation, Min: Minimum, Max: Maximum, SCC: Squamous cell carcinoma, HPV: Human papillomavirus, ASCUS: Atypical squamous cells of undetermined significance, ASC-H: Atypical squamous cells-cannot exclude high-grade lesion, HSIL: High-grade squamous intraepithelial lesion

HPV-dependent vulvar cancer was present in 7 patients (17.1%), while 18 (43.9%) patients showed no evidence of HPV involvement. HPV association was not documented in 16 patients. Cervical HPV testing was conducted in 28 patients, of whom 2 were positive and 26 were negative. Among the 34 patients with available cervical cytology, normal findings were reported in 23 cases, ASCUS in 7, ASC-H in 2, and HSIL in 2. Colposcopic cervical biopsy was performed in 11 (26.8%) patients due to the presence of cervical pathology or abnormal cytological findings. LSIL was identified in 3 patients, HSIL in 3 patients, and cervical SCC in 1 patient (**Table**).

Among patients with HPV-dependent vulvar cancer, 42.9% had benign cervical cytology, whereas 57.1% showed preinvasive or invasive abnormalities. In comparison, 71.4% of those with HPV-independent vulvar carcinoma had benign cytology, and 28.6% had preinvasive or invasive findings. However, the association between HPV status and cervical cytology results was not statistically significant (p=0.204). Similarly, no significant association was found between HPV status and age group (p=0.409).

DISCUSSION

The association between cervical HPV infection, cytology, and pathology results and vulvar cancer was examined in the present study. In our cohort, HPV-associated vulvar SCC was identified in 17.1% of patients, and cervical HPV positivity was detected in only 4.8% of patients. Although not statistically significant, cervical smear abnormalities (preinvasive or invasive cytological findings) were more frequently observed in patients with HPV-associated vulvar SCC compared to those with HPV-independent disease.

In our study, cervical preinvasive and invasive lesions were identified in 57.1% of patients with HPV-associated vulvar SCC, whereas this rate was 28.6% in the HPV-independent group. Although the difference was not statistically significant, the higher prevalence in the HPV-dependent group may indicate a tendency towards multicentric HPV-driven carcinogenesis involving the lower genital tract. This observation is consistent with the findings of de Bie et al.,[2] who reported cervical HSIL in 35% of patients with HPV-associated vulvar SCC, compared to only 2% in those with HPV-independent disease. These results underscore the importance of considering synchronous or metachronous HPV-related lesions across the lower anogenital tract in patients with HPV-associated vulvar malignancies.

The etiologic dichotomy formalized in the 2020 WHO classification-HPV-associated tumors (diffuse p16 overexpression) versus HPV-independent tumors (frequently p53-aberrant)-has improved risk stratification beyond anatomic metrics and is increasingly used to anchor treatment algorithms. Population-based studies indicate that overall trends in vulvar cancer reflect both etiologic routes: modest contributions from HPV-associated disease in some settings against a backdrop of aging populations in whom HPV-independent tumors remain prevalent.[4]

Classic and modern series demonstrate that HPV-associated disease across the lower genital tract may occur synchronously or metachronously, sometimes with clonal relationships across vulvar and cervical compartments, consistent with field oncogenesis and/or seeding from a cervical progenitor lesion.[5,6] These data justify comprehensive evaluation of the cervix, vagina and, where appropriate, the perianal/anal epithelium at baseline and during surveillance.

Historic and contemporary data show enriched rates of cervical abnormalities (HSIL) and/or HPV positivity among women with usual-type Vulvar intraepithelial neoplasia (VIN)-related vulvar SCC, and measurable risks of cervical/vaginal dysplasia after vulvar surgery.[7] Our cohort's low point-prevalence of cervical high-risk HPV likely reflects its older age structure and predominance of HPV-independent disease; nonetheless, the presence of abnormal cytology in a minority of patients underscores the importance of guideline-concordant evaluation and risk-adapted follow-up.

Baseline and longitudinal assessment of the cervix (cytology±HPV testing, colposcopy as indicated) should be integrated into care pathways, with shorter surveillance intervals considered in patients with p16-positive/HPV-positive VSCC or prior cervical disease.[8] Standardized pathology reporting that captures p16/p53 on the index vulvar tumor-and hrHPV status when relevant-enables risk-aligned counseling and adjuvant planning.[9] Evolving guideline recommendations regarding surgical margins, sentinel lymph node (SLN) strategies, and adjuvant therapy in VSCC can be contextualized by etiologic subtype as prospective evidence accrues.

Limitations

Strengths of our study are; a focus on the cervical compartment in a vulvar SCC cohort and alignment with contemporary etiologic taxonomy. Prospective, protocolized testing (p16/p53 for all primaries; extended cervical genotyping) and multi-institutional collaboration are needed to refine estimates and test risk-adapted surveillance. A key limitation of this study is the lack of uniform p16 and p53 immunohistochemical evaluation for all primary vulvar tumors, which restricted strict application of the WHO 2020 etiologic classification and may have led to misclassification of some cases.

CONCLUSION

As a result, our findings reinforce the clinical relevance of integrating cervical assessment into the management of vulvar squamous cell carcinoma, particularly in cases of HPV-associated disease. In this study, we observed low cervical hrHPV positivity and infrequent high-grade cytology yet sufficient abnormalities to support guideline-concordant cervical assessment and risk-adapted surveillance. Consequently, all patients with vulvar squamous cell carcinoma should undergo baseline cervical cytology and, when indicated, colposcopic assessment, and shorter surveillance intervals may be considered in HPV-associated VSCC in line with contemporary guideline-based, risk-adapted follow-up strategies.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study was approved by the Ankara Bilkent City Hospital Clinical Researches Ethics Committee (Date: 22.11.2023, Decision No: E2-23-5674).

Informed Consent

As this was a retrospective study, formal written informed consent was not required and was therefore not obtained.

Peer Review Process

This manuscript was subject to external peer review.

Conflict of Interest

The authors declare no conflicts of interest related to this study.

Financial Disclosure

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Author Contributions

All authors contributed significantly to the study's conception, design, data acquisition, analysis, and interpretation. All authors reviewed and approved the final version of the manuscript.

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Cytoreductive surgery and HIPEC in peritoneal metastases: from Sugarbaker's concept to modern evidence*

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ABSTRACT

Peritoneal metastases (PM) are a common manifestation of advanced gastrointestinal and gynecological cancers and are traditionally associated with poor prognosis. Historically, the peritoneal–plasma barrier and limited drug diffusion have restricted the efficacy of systemic chemotherapy, resulting in short survival times. Since the 1980s, the treatment landscape has been transformed by the locoregional approach introduced by Paul H. Sugarbaker. The combination of cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) has redefined peritoneal surface malignancies as a potentially local-regional disease entity. Recent phase III trials [PRODIGE-7 (colorectal), OVHIPEC-1 (ovarian), and GASTRIPEC-I (gastric)] have refined the evidence base, showing that CRS remains the strongest prognostic factor, while HIPEC may provide survival benefits in carefully selected cases, depending on primary tumor type and protocol parameters. Despite persistent heterogeneity in HIPEC regimens, growing efforts in biomarker-guided patient selection, AI-assisted imaging, and international data-sharing networks (e.g., PSOGI, RENAPE) are expected to improve standardization and predictability. These developments may optimize both safety and long-term outcomes in the management of peritoneal metastases.

Keywords: Cytoreductive surgery, HIPEC, peritoneal carcinomatosis

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INTRODUCTION

Peritoneal metastases (PM) are a common clinical presentation in advanced stages of gastrointestinal and gynecological malignancies, often associated with poor prognosis. The presence of PM, particularly in colorectal and gastric cancers, has historically been associated with short survival and limited treatment options.[1,2] Population-based studies in this patient group have reported median survival remaining at the level of months, even during the era of widespread palliative chemotherapy.[3] The peritoneal-plasma barrier inherent in PM and limited drug diffusion to tumor nodules have historically limited the effectiveness of systemic chemotherapy on peritoneal surfaces.[4,5]

This bleak picture has changed fundamentally since the 1980s with the locoregional treatment approach pioneered by Paul H. Sugarbaker. Sugarbaker conceptualized peritoneal surface malignancies as a potentially "local-regional" disease area with distinct biology from systemic metastasis; he defined a treatment paradigm involving the removal of macroscopic tumor burden through CRS and the targeting of residual microscopic disease with hyperthermic intraperitoneal chemotherapy (HIPEC).[6] The pharmacological rationale for this approach is based on the high peritoneal/blood exposure ratio of intraperitoneal administration and the cytotoxic enhancing effect of hyperthermia.[4,7]

Disease burden is scored by the Peritoneal Cancer Index (PCI) (0-39 across 13 regions), and surgical efficacy by the completeness of cytoreduction (CC) score; detailed definitions are provided in Section 2.1.[8,9]

In current practice, CRS±HIPEC is applied in carefully selected cases-particularly in PM associated with colorectal, ovarian, and gastric cancer-based on the decision of multidisciplinary tumor boards. However, global standardization has not been achieved in areas such as agent selection, temperature-time parameters, and perfusion technique.

The 2022 PSOGI (Peritoneal Surface Oncology Group International) consensus gave a weak-positive vote for MMC-based HIPEC regimens (particularly the "Dutch protocol") in PM-CRC, while expressing a strong-negative opinion on the short-course high-dose oxaliplatin protocol; it emphasized that advanced studies clarifying the role of HIPEC should be a primary research priority[10]. Similarly, in other primaries, patient selection, tumor biology, and protocol-specific variables emerge as the main factors determining survival contribution.[1]

Most reviews in the current literature address CRS+HIPEC therapy solely from a surgical and chemotherapeutic perspective. This study, however, offers a multidisciplinary

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perspective by examining the historical framework from Sugarbaker to the present day, biomarker-based selection, artificial intelligence-supported patient assessment models, and data standardization initiatives together. The aim of this review is to evaluate the historical development of CRS and HIPEC, starting from the conceptual foundation laid by Sugarbaker, their biological and technical principles, current clinical evidence, and future research agenda through an interdisciplinary and critical lens. Within this framework, the following sections will detail primary-specific evidence (colorectal, ovarian, and gastric), randomized trials and meta-analyses, protocol parameters, and nuances related to patient selection.

THE HISTORICAL DEVELOPMENT AND FUNDAMENTAL PRINCIPLES OF CYTOREDUCTIVE SURGERY AND HIPEC

The concept that peritoneal surface malignancies have a distinct disease biology from systemic metastasis emerged in the 1980s as a conceptual revolution pioneered by Paul H. Sugarbaker. Sugarbaker redefined the peritoneal cavity as a "treatable anatomical compartment," thereby developing a locoregional approach aimed at overcoming the limitations of systemic treatment.[6]

Historical Development

Sugarbaker's first applications were extensive surgical procedures involving peritoneal stripping and organ resection performed at the Washington Cancer Institute in the late 1980s. During this period, the concept of the "peritoneal-plasma barrier" defined the limited passage of systemic agents into the peritoneal cavity and formed the pharmacological rationale for the idea of intraperitoneal (IP) chemotherapy[7].

By the 1990s, Sugarbaker[11] had systematized the strategy of surgically removing the macroscopic tumor burden (CRS) in combination with hyperthermic intraperitoneal chemotherapy (HIPEC), bringing the concept of combined therapy into clinical practice. The pharmacokinetic rationale for HIPEC is based on the advantages of intraperitoneal administration, such as creating a high local drug concentration compared to systemic circulation, increasing tissue penetration with heat, and keeping systemic toxicity relatively limited.[5,12]

Since the mid-1990s, the CRS+HIPEC concept has begun to be applied clinically, and during this period, the concepts of PCI and CC have gained widespread acceptance. The PCI, developed by Jacquet and Sugarbaker,[13] quantifies tumor burden by scoring lesion size across 13 abdominal regions, with a total range of 0-39 points. The CC score, on the other hand, grades the amount of residual disease after surgery (CC-0: no macroscopic disease, CC-1: residual nodules ≤2.5 mm, CC-2/3: >2.5 mm). Both indices are key prognostic determinants and guide treatment planning in CRS + HIPEC. Jacquet and Sugarbaker presented the methodology in this field in detail in their study "Clinical research methodologies in diagnosis and staging of patients with peritoneal carcinomatosis". Multicenter data from Glehen[14] and Gilly[15] showed that better survival was achieved in cases where cytoreduction was performed at the CC-0/1 level.

Since the mid-2000s, CRS+HIPEC has begun to show curative potential in selected patient groups. Particularly in colorectal and appendix-derived peritoneal metastases, median survival has reached 30-40 months, with 5-year survival rates of 30-40% in some series.[16]

These successes have led to the international acceptance of the concept and the establishment of peritoneal surface oncology centers (such as the PSOGI, BIG RENAPE, and PERISCOPE II networks).[10]

Basic Biological and Pharmacological Principles

The therapeutic success of HIPEC is based on the pharmacokinetic profile that limits systemic toxicity through the biochemical and immunological effects of hyperthermia.

The increase in temperature accelerates cell death through DNA damage, increases the permeability of the tumor cell membrane, and facilitates the diffusion of agents such as cisplatin and mitomycin-C into the cel.[14]

Hyperthermia also enhances antitumor activity in the peritoneal microenvironment by activating the local immune response.[17]

Pharmacokinetically, intraperitoneal administration provides 20-100 times higher local drug concentrations compared to systemic circulation, creating cytotoxic concentrations in residual tumor clusters.[5]

Surgical Principles and Technical Approach

Cytoreductive surgery aims to systematically remove peritoneal surfaces (peritonectomy procedures) and achieve macroscopic clearance of the tumor. The six basic peritonectomy areas defined by Sugarbaker-anterior parietal, diaphragmatic, pelvic, omentectomy, spleen resection, and segmental colon resection-form the basis of CRS today.[6]

The degree of surgical completion (CC score) is one of the factors that directly determines the effectiveness of HIPEC; even in the presence of microscopic residue, the penetration depth of HIPEC is limited to 1-3 mm.[4]

In current approaches, CRS+HIPEC is no longer a single procedure but a multidisciplinary treatment algorithm. It requires integration between surgical oncologists, medical oncologists, anesthesiologists, and intensive care teams; in this respect, it is the central practice of modern peritoneal oncology.[1]

CURRENT EVIDENCE-BASED CLINICAL RESULTS

The combination of CRS (cytoreductive surgery) and HIPEC is an approach aimed at achieving local-regional control in peritoneal metastases, but its efficacy is sensitive to the primary tumor type, tumor burden (PCI), degree of surgical completeness (CC score), the HIPEC protocol used, and center experience. This section summarizes current evidence in peritoneal metastases associated with colorectal, ovarian, and gastric cancers (CRC-PM, EOC-PM, GC-PM).

Peritoneal Metastases Caused by Colorectal Cancer (CRC-PM)

PM can be observed at a significant rate in the diagnosis or follow-up of colorectal cancer; a population-based study based on Swedish national registries has detailed the incidence and risk factors of peritoneal carcinomatosis in CRC.[18]

In the PRODIGE-7 study (265 cases), one of the strongest randomized trials evaluating the added benefit of CRS+HIPEC in CRC-PM, the addition of short-course oxaliplatin-based HIPEC (460 mg/m², 30 min, ~43 °C) did not show superiority in overall survival compared to CRS alone, with a median OS of approximately 41 months in both arms. Late (post-60 days) complications were reported more frequently in the HIPEC arm. Although the study has been debated methodologically (agent/duration selection, etc.), it is a turning point that questions the "HIPEC for everyone" approach.[19]

The reflection of these results in clinical practice has also been incorporated into international consensus documents. The 2022 PSOGI consensus (HIPEC regimens for CRC-PM) takes a "conditionally positive" approach to mitomycin-C-based, longer-duration protocols under conditions of low PCI and complete cytoreduction (CC-0/1), while expressing clear reservations about the short-duration oxaliplatin protocol.[10]

On the other hand, large multicenter cohort and systematic reviews reiterate that survival can be significantly improved with CRS±HIPEC in the presence of successful adjuvant surgery (CC-0/1) and low tumor burden (low PCI); however, due to heterogeneity in the agent (mitomycin-C/oxaliplatin), temperature, and duration, it is emphasized that the benefit is strictly dependent on patient- and protocol-selection.[10]

Beyond efficacy, evidence comparing long-term morbidity and health-economic outcomes between CRS alone and CRS±HIPEC remains limited and heterogeneous. Preliminary analyses suggest increased procedural costs and late complications in the HIPEC arm, yet prospective cost-effectiveness evaluations are warranted to contextualize these findings.

Clinical implication: CRS retains its position as the primary treatment in CRC-PM; the role of HIPEC should be individualized, particularly in cases with low PCI and CC-0/1, favoring mitomycin-C-based protocols, taking into account center experience and morbidity management.[10,19]

Peritoneal Metastases Caused by Ovarian Cancer (EOC-PM)

Peritoneal spread is part of the natural course of advanced epithelial ovarian cancer. In the OVHIPEC-1 phase III randomized trial, the addition of intraoperative HIPEC (cisplatin 100 mg/m², 90 min, 40°C) significantly improved progression-free and overall survival compared to surgery alone (initial report in NEJM 2018). A final survival analysis was published in 2023, reporting an increase in median OS from 33.3 months to 44.9 months and a hazard ratio (HR) of 0.70 (p=0.011) for the risk of death. This high-level evidence strongly supports the addition of HIPEC to interval surgery in appropriately selected stage III patients.[20,21]

These findings suggest that HIPEC may add value to the standard of care in platinum-sensitive, well-selected EOC-PM cases; however, careful standardization of hydration and heat-duration parameters is required to mitigate renal toxicity and perioperative morbidity.[20,21]

Peritoneal Metastases Caused by Stomach Cancer (GC-PM)

The prognosis for peritoneal metastasis associated with gastric cancer is generally poor, and survival with systemic treatments is limited. In the GASTRIPEC-I phase III trial, the effect of adding HIPEC after CRS in synchronous GC-PM cases was evaluated; the published results of the study did not show a significant superiority in OS, but details on endpoints and safety profile were provided. This randomized data indicates that additional evidence is needed to support the routine use of HIPEC in GC-PM.[22]

The European multicenter PERISCOPE II (phase III) study was designed to compare gastrectomy + CRS + HIPEC after neoadjuvant systemic therapy with systemic chemotherapy alone in cases of GC with limited peritoneal spread and/or cytology-positive GC. As the final results are awaited, patient selection and center experience remain decisive factors in clinical practice.[23,24]

Clinical implication: CRS+HIPEC should still be considered an investigational option in GC-PM; cases with low PCI, high likelihood of R0/R1 resection, and appropriate performance status should be evaluated in prospective protocols at experienced centers.[22,24]

General Evaluation

The total body of evidence indicates that CRS is the primary curative component; HIPEC, however, can provide additional benefit in primary-specific, PCI-dependent, and CC-0/1 cases when the agent/duration/temperature parameters are appropriately selected. Oxaliplatin-short-course protocols have not shown an OS benefit in colorectal cancer; in ovarian cancer, an OS gain with cisplatin-HIPEC in interval surgery has been confirmed; in gastric cancer, results are heterogeneous, and the approach will become clearer as phase III data mature.[19-22]

Key phase III randomized trials across different primary tumors are summarized in Table, highlighting study designs, HIPEC regimens, and main survival outcomes to facilitate direct comparison of evidence.

Table. Key phase III trials and outcomes of CRS±HIPEC in peritoneal metastases

Trial	Primary Cancer	Design/N	HIPEC Regimen	Primary Endpoint	Main Results (OS/PFS)	Notes
PRODIGE-7	Colorectal (CRC-PM)	RCT/265	Oxaliplatin 460 mg/m², 30 min at ~43°C	OS	No OS benefit vs CRS alone (median OS ~41 months both arms; HR≈1.00; p=0.99)	Late (≥60 d) complications higher in HIPEC arm
OVHIPEC-1	Ovarian (EOC, stage III, interval)	RCT/245	Cisplatin 100 mg/m², 90 min at 40°C	PFS	Improved PFS & OS (median OS 44.9 vs 33.3 m; HR 0.70; p=0.011)	Final survival analysis (2023) confirms long-term OS benefit
GASTRIPEC-I	Gastric (GC-PM)	RCT	MMC/Cisplatin-based HIPEC after CRS	OS	No OS advantage; **PFS and MFS improved** in CRS+HIPEC	Safety acceptable; further exploration warranted
PERISCOPE II	Gastric (limited PM/positive cytology)	RCT	Gastrectomy + CRS + HIPEC vs systemic chemotherapy	OS	ESMO 2025 presentation: **no OS advantage** for CRS+HIPEC vs chemotherapy	Awaiting peer-reviewed full publication

CRS: Cytoreductive surgery, HIPEC: Hyperthermic intraperitoneal chemotherapy, PFS: Progression-free survival, RCT: randomized controlled trial, OS: Overall survival, CRC-PM: Peritoneal metastases caused by colorectal cancer

DISCUSSION AND FUTURE PERSPECTIVES

Clinical Significance and Current Interpretation

CRS and hyperthermic intraperitoneal chemotherapy (HIPEC) have created a paradigm shift in the treatment of peritoneal metastases over the past thirty years. The concept of “locoregional disease,” defined by Paul H. Sugarbaker[25] in the 1980s, challenged the understanding of systemic metastasis and demonstrated the need to consider peritoneal surfaces as a separate biological environment.

Today, CRS is accepted as a fundamental treatment component with curative potential in selected cases. However, the contribution of HIPEC to survival is tightly linked to the primary tumor type, tumor burden (PCI), degree of surgical completeness (CC), and the protocol used. The results of randomized controlled trials clearly demonstrate this variability.

In colorectal cancers, the PRODIGE-7 study showed that adding short-term (30 min) oxaliplatin-based HIPEC after CRS did not improve overall survival (median OS was 41 months in both groups, HR: 1.00; p=0.99).[19] However, it has been suggested that the study did not fully reflect the pharmacokinetic advantage of HIPEC due to agent selection and duration limitations.

The OVHIPEC-1 study in ovarian cancer and the long-term follow-up analysis published in 2023 demonstrated that HIPEC significantly prolonged progression-free and overall survival in platinum-sensitive stage III patients.[20,21] These results suggest that CRS+HIPEC in ovarian cancer may provide added value to the standard of care in appropriately selected cases.

In the phase III GASTRIPEC-I trial conducted in gastric cancer with peritoneal metastasis, the addition of HIPEC did not have a significant effect on overall survival; however, the safety profile and subgroup analyses revealed that HIPEC remains an area for further investigation.[22]

These three high-level studies show that the curative potential of CRS is more decisive than that of HIPEC; HIPEC, however, may improve local control and disease-free survival in selected cases with low PCI and complete cytoreduction (CC-0/1).

Limitations in the Literature

The current literature presents difficulties in comparison due to the heterogeneity in HIPEC applications. Agent selection (mitomycin-C, oxaliplatin, cisplatin), temperature range (41-43°C), application duration (30-120 min), and perfusion technique (open or closed system) vary between centers. This complicates standardization in survival analyses.[10] This multidimensional variability is summarized schematically in **Figure**, which illustrates the key domains of protocol heterogeneity and the steps toward standardized, comparable HIPEC datasets.

Furthermore, many studies are single-center or retrospective in design, carrying a risk of bias in patient selection. The heterogeneity in HIPEC protocols, with different combinations of agent-duration-temperature used in studies, limits the comparability of results.26 Reviews on ovarian cancer also frequently highlight platinum-sensitive patient selection, HIPEC regimen variations, and study design heterogeneity as methodological limitations.[27]

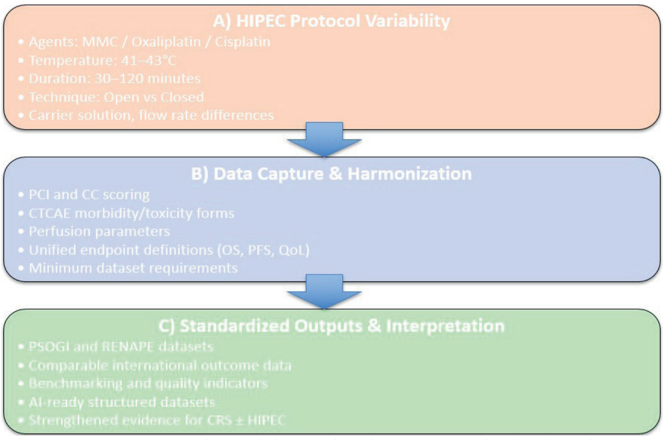

Figure. HIPEC protocol variability and pathway to standardized evidence

(A) HIPEC protocol variability (“chaos”): Across centers, agents (e.g. mitomycin-C, oxaliplatin, cisplatin), temperature (41-43 °C), perfusion duration (30-120 minutes), technique (open vs closed), and additional parameters (carrier solution, flow rate, dosing) differ substantially.

(B) Data capture and harmonization (“process”): Systematic documentation of PCI and CC scores, standardized morbidity/toxicity reporting, and recording of perfusion and protocol parameters within a minimum dataset and unified endpoint framework (OS, PFS, QoL) allows cross-study comparability.

(C) Standardized outputs and clinical interpretation (“solution”): Multicenter registries (PSOGI, RENAPE and others) integrate these harmonized data into comparable international datasets, enabling benchmarking, quality indicators, and AI-ready structured data that strengthen evidence generation for CRS±HIPEC.

Finally, the PSOGI 2024 consensus report states that international standardization of HIPEC agent, duration, and temperature parameters has not yet been achieved, and therefore protocols must be adapted on a center-by-center basis.[10]

From a meta-analytic standpoint, substantial between-study heterogeneity (high I^2) and non-uniform endpoint definitions (OS, PFS, morbidity) reduce the certainty of pooled estimates and limit the strength of recommendations.

Research Areas for the Future

The future direction in the treatment of peritoneal metastases is focused on developing more biologically based and individualized approaches.

PIPAC (pressurized intraperitoneal aerosol chemotherapy): This is a repeatable, minimally invasive method that aims to achieve more homogeneous distribution and tissue penetration by delivering normothermic, pressurized aerosolized chemotherapy into the peritoneal cavity. Clinical use today is mostly for symptom/ascites control in cases refractory to systemic therapy and for “bridge-to-CRS” purposes in selected patients. Multicenter experience and phase II data show that PIPAC is feasible and safe; it can provide measurable disease control and quality of life gains in groups such as CRC-PM. Current consensus provides practical recommendations regarding agent/protocol standardization (oxaliplatin or cisplatin+doxorubicin), pressure, and cycle planning; however, randomized comparative data are still needed.[28-30]

At present, PIPAC should be regarded as an adjunct or bridge strategy, primarily in refractory disease or for downstaging before CRS, rather than a standard-of-care alternative to CRS±HIPEC.

Normothermic intraperitoneal infusion and immunotherapy combinations: Normothermic intraperitoneal chemotherapy (NIPEC) is being investigated as a sequential regional approach to systemic therapy, particularly in gastric-derived peritoneal metastases; ongoing phase II protocols in Western cohorts (e.g., STOPGAP) are evaluating the feasibility and potential bridging effect of this strategy.[31] Early-phase evidence is also emerging for locoregional combinations with immunotherapies: a phase 1b study of intraperitoneal nivolumab+ipilimumab in gynecologic malignancies reported safety/lesion response signals; and in a phase I expansion cohort receiving intraperitoneal nivolumab after CRS+HIPEC, the approach was found to be feasible, suggesting that antigen release induced by CRS/HIPEC may enhance the immune response.[32,33] These early results support the investigation of normothermic IP infusion strategies in combination with checkpoint inhibitors, particularly in selected cases with reduced tumor burden; however, randomized comparative studies are still needed.

NIPEC and locoregional immunotherapy combinations remain investigational, and their transition into routine clinical practice will depend on forthcoming randomized data and long-term safety confirmation.

Molecular biomarker-based patient selection: Survival in CRS+HIPEC treatment depends not only on surgical completeness and tumor burden, but also on the molecular biology of the tumor. In colorectal peritoneal metastases, the BRAF mutation in particular has been identified as one of the strongest biomarkers associated with poor prognosis.[34,35]

In these studies, survival in BRAF-mutant cases was found to be significantly shorter. In contrast, results for KRAS mutations are more heterogeneous; no significant prognostic effect has been demonstrated in most series. However, it has been suggested that some subtypes (e.g., KRAS G12V and G12D) may exhibit more aggressive biological behavior.[36]

A study by Larsen et al.[37] reported that the adverse effect of BRAF mutation may be partially offset in the presence of the MSI-H phenotype.

These data suggest that molecular profiling may play an important role in personalizing patient selection for CRS+HIPEC strategies in the future.

Artificial Intelligence and machine learning-based prediction models: In recent years, radiomics analyses based on quantitative data extraction from medical images and deep learning-based models have reported promising results for predicting the risk of PM and the PCI from pre-treatment images.

For example, a radiomics-boosted deep learning model derived from PET/CT data has accurately predicted synchronous colorectal PM risk.[38]

Similarly, CT-based radiomic PCI models have shown significant agreement with surgical PCI scores and have surpassed conventional imaging assessments in distinguishing between low and high tumor burden.[39]

Furthermore, machine learning-based radiomics nomograms developed to predict occult PM in gastric and ovarian cancers also show high accuracy signals.[40,41]

Despite encouraging accuracy metrics, radiomics- and AI-based models are not ready for clinical translation; deployment should await multicenter external validation with prespecified endpoints, robust calibration and decision-curve analyses, and prospective demonstrations of clinical impact.

Standardization and international databases: One of the most significant limitations in CRS+HIPEC applications is protocol differences and data heterogeneity. Variability in the agent used, temperature, perfusion time, and evaluation criteria makes it difficult to compare results in the literature.

Therefore, in recent years, organizations such as the Peritoneal Surface Oncology Group International (PSOGI) and the French RENAPE network have established multicenter databases aimed at strengthening data standardization and quality control processes. Through these platforms, clinical and surgical data obtained from different centers are collected in a common format; thus, treatment efficacy, toxicity profile, and survival analyses can be evaluated more reliably with real-world data.[10]

In the future, the integration of these international data infrastructures with phase III clinical trials and the execution of agent-duration comparisons under standardized designs will further strengthen the evidence-based foundations of CRS+HIPEC applications.

CONCLUSION

Current evidence indicates that CRS is the strongest prognostic factor in the management of peritoneal metastases, while HIPEC may provide additional survival benefit in carefully selected cases with appropriate agent, temperature, and duration parameters. However, current data remain limited due to protocol heterogeneity, agent differences, and variability in patient selection criteria. In the future, the CRS+HIPEC approach will become much more individualized, predictable, and standardized thanks to molecular biomarker-based selection strategies, artificial intelligence-assisted imaging analyses, and the integration of international data sharing networks (e.g., PSOGI, RENAPE). Ultimately, the integration of molecular biomarkers, AI-assisted imaging analytics, and real-world multicenter data will redefine patient selection, procedural precision, and long-term outcomes in CRS±HIPEC, steering peritoneal metastasis management toward a more personalized and evidence-based era.

ETHICAL DECLARATIONS

Peer Review Process

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Conflict of Interest

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Author Contributions

All authors contributed equally to the planning, writing, and critical revision of the manuscript. All authors approved the final version for submission.

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Case Report

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Phyllodes tumor of the breast: a case report

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ABSTRACT

Phyllodes tumor is a rare and locally aggressive fibroepithelial tumor of the breast. Patients generally present with a firm, unilateral, rapidly growing and painless breast mass. Phyllodes tumors are often misdiagnosed as radiological and histopathological examinations have an inadequate diagnostic accuracy. In this article, we present the findings of a patient presenting to our clinic with palpable masses in both breasts revealed to be phyllodes tumor.

Keywords: Phyllodes tumor, breast, neoplasm, fibroepithelial

INTRODUCTION

Phyllodes tumor (PT) is a rare and locally aggressive fibroepithelial tumor of the breast that constitutes less than 1% of all breast neoplasms. They typically occur in females between the ages of 35-55 and show a peak incidence at age 45, which is 15-20 years more than the usual age for fibroadenoma.[1] Patients generally present with a firm, rapidly growing and painless breast mass varying between 3-5 cm.[2] Most PTs are unilateral solitary lesions; however, bilateral cases may rarely occur.[3] PTs exhibit a wide range of biological behaviors and are histopathologically classified as benign, borderline and malignant according to WHO criteria.[4] Radiological signs of PTs are similar to fibroadenomas, frequently leading to the misdiagnosis of these lesions. Although "triple assessment", which is comprised of physical, radiological and histopathological examination, is the standard approach to palpable breast lesions, its diagnostic accuracy is inadequate for PTs.[5] Therefore, wide surgical excision is the preferred method of approach for both diagnosis and treatment. However, as pre-operative diagnosis is difficult, initial surgery frequently lacks the adequate margins for complete excision, requiring a secondary operation.[6] This diagnostic challenge may especially be true for bilateral PTs due to their low rate of incidence. For this reason, PTs should consistently be considered in the differential diagnosis of bilateral palpable breast masses, especially in the appropriate clinical setting. In this article, we present a patient presenting to our clinic with palpable masses in both breasts revealed to be phyllodes tumor.

CASE

A 36-year-old female patient presents complaining of breast masses that had previously been present, but recently exhibited rapid growth. Physical examination showed a firm palpable mass in the upper-middle region of the left breast and upper-inner quadrant of the right breast. Other signs such as discoloration, ulceration, nipple retraction and palpable lymph nodes were not present. Ultrasound imaging of both breasts revealed solid appearing lobulated masses containing multiple cystic spaces and slight posterior acoustic enhancement, as shown in Figure 1 and 2. The masses in the left and right breasts measured 2.8x1.35 cm and 2.1x1 cm, respectively. Doppler ultrasound examination demonstrated visible internal vascularity, as demonstrated in Figure 3. Both lesions were classified as BI-RADS 4A and core biopsy was performed. Histopathological evaluation of the specimen revealed a diagnosis of phyllodes tumor. A wide surgical excision was subsequently performed and the diagnosis was confirmed.

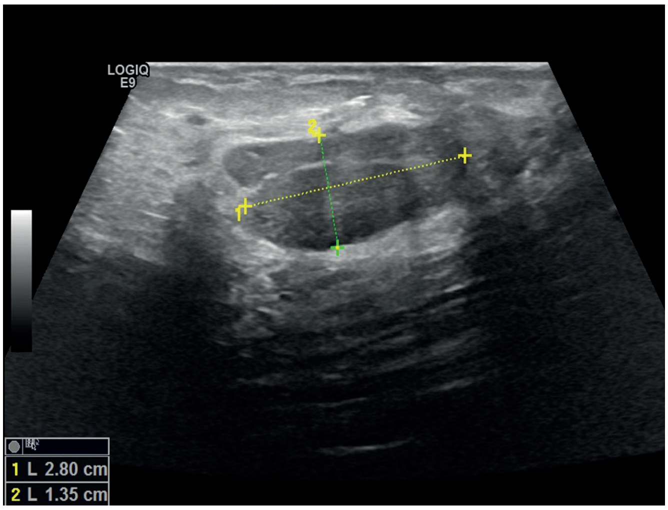

Figure 1. Gray-scale ultrasound of the left breast reveals a solid appearing lobulated mass measuring 2.8x1.35 cm with round cystic spaces and slight posterior acoustic enhancement, suggestive of a fibroepithelial lesion

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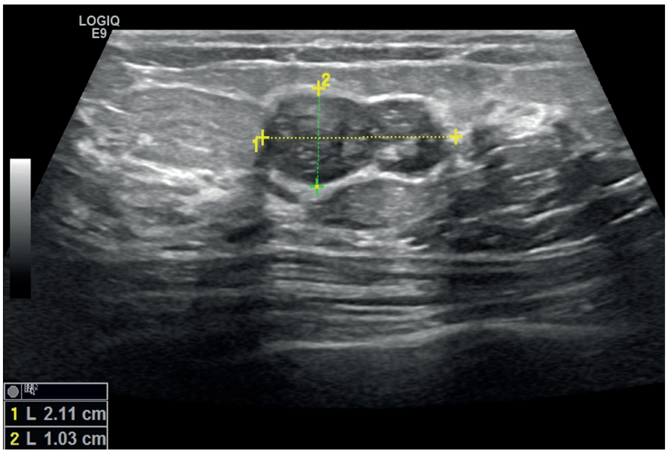

Figure 2. Gray-scale ultrasound of the right breast reveals a solid appearing lobulated mass measuring 2.1x1 cm with round cystic spaces and slight posterior acoustic enhancement, suggestive of a fibroepithelial lesion

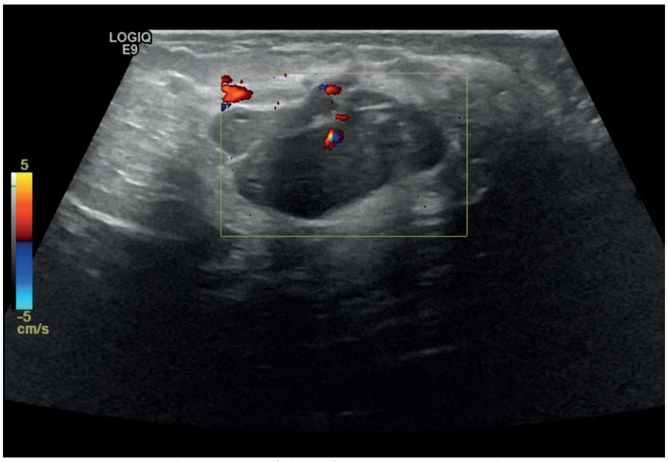

Figure 3. Doppler ultrasound of the left breast mass reveals moderate internal vascularity, increasing suspicion for phyllodes tumor

DISCUSSION

Phyllodes tumors are rare fibroepithelial tumors that generally occur in females between ages 35-55. They frequently present as rapidly growing palpable masses in the upper outer quadrant of the breast. Although the size of PTs may vary, the typical size at presentation is 3-5 cm. Additional findings such as retraction of the skin or nipple and bloody discharge may occur as the tumor expands into the areolar regions. PTs are mostly unilateral, and may rarely present in both breasts. In a study consisting of 293 cases, Barrio and colleagues reported that 3.4% of patients had bilateral PTs.[3] The cohort study of Lin and colleagues reviewed 611 patients in their institution with histopathologically proven PT and reported synchronous bilateral lesions in only 1 patient.[7] In the present case, the patient's age was 36. The patient presented with rapidly growing palpable masses in the upper-middle region of the left breast and upper-inner quadrant of the right breast measuring 2.8x1.35 cm and 2.1x1 cm on ultrasound, respectively. Our case displayed PTs in both breasts. No additional findings were present.

Ultrasound and mammography findings are usually non-specific, and resemble those of fibroadenomas. On mammography, PTs are seen as round or oval lesions with smooth, well-circumscribed margins. A radiolucent halo or calcification(s) may sometimes be present. On ultrasound, PTs typically appear as large, well-defined, solid heterogeneous masses. Round or patchy fluid filled cystic spaces within the lesion with posterior acoustic enhancement is suggestive of PT. Doppler ultrasound frequently shows visible internal vascularity. In the present case, ultrasound of the left and right breasts revealed a solid lobulated oval mass measuring 2.8x1.35 cm and 2.1x1 cm, respectively. Both masses contained round cystic spaces and demonstrated slight posterior acoustic enhancement. Internal vascularity was present on doppler ultrasound examination. These findings were consistent with phyllodes tumor.

CONCLUSION

Phyllodes tumors are rare, typically unilateral neoplasms of the breast that pose a significant diagnostic challenge due to their overlapping histological and radiological findings. Accurate diagnosis is essential, as the recommended treatment is surgical excision with wide margins to reduce the rate of occurrence. Although PTs are typically unilateral solitary lesions, clinicians should be mindful that bilateral lesions may occur. For this reason, in the presence of the relevant clinical and radiological signs, they should consistently be considered in the differential diagnosis of bilateral palpable breast masses, particularly those resembling fibroadenomas.

ETHICAL DECLARATIONS

Informed Consent

Written informed consent was obtained from the patient included in this report. Signed consent forms are retained by the authors and are available upon request.

Peer Review Process

This report underwent external peer review.

Conflict of Interest

The authors declare no conflicts of interest.

Financial Disclosure

This case report did not receive any financial support.

Author Contributions

All authors made substantial contributions to the clinical documentation, interpretation, and manuscript preparation. All authors approved the final version of the manuscript.

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Journal of Comprehensive Surgery

Letter to the Editor

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Letter to the Editor: comment on "Preoperative readiness: the patient is ready-but is the anesthesiologist?"

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Keywords: Clinician well-being, patient safety, preoperative evaluation, fatigue, ergonomics

Dear Editor,

Preoperative preparation primarily focuses on patient optimization, comorbidity management, and informed consent.[1] Professional societies such as the European Society of Anaesthesiology and Intensive Care (ESAIC) and the American Society of Anesthesiologists (ASA) have also highlighted the importance of clinician fatigue and well-being.[2,3] Despite these developments, readiness is still defined almost entirely from the patient's perspective. While the patient's physiological status is routinely assessed, the anesthesiologist's own physical and mental condition is rarely taken into account. However, perioperative safety relies on the preparedness of both the patient and the anesthesiologist.

Anesthesia requires constant attention and quick decision-making under pressure. Fatigue, sleep loss, and circadian disruption reduce psychomotor performance and slow reaction time.[4] Analyses of electronic health records show that documentation workload often exceeds billed activity, creating an additional cognitive load that can reduce situational awareness.[5] Mental and emotional factors also affect clinical performance. Furthermore, burnout among anesthesiologists has been linked to reduced attention and impaired decision-making.[6] Working in unfamiliar settings increases stress and cognitive load.[7] Early identification of these factors, followed by appropriate management, is necessary to maintain readiness.

Ergonomics is another important factor. The design of monitors, alarms, and information displays influences attention. User-centered interface design can reduce workload and improve task performance, thereby making ergonomic adjustments a practical component of maintaining readiness.[8]

In conclusion, although ASA and ESAIC provide recommendations on fatigue management, practice does not always follow these guidelines. Reducing this gap requires measures such as protected rest periods and structured fatigue monitoring. In Türkiye, there is no national policy on the physical and mental readiness of anesthesiologists, which leads to differences in workload, rest policies, and ergonomic conditions across institutions. Developing national guidance based on international standards could improve consistency, support clinicians, and increase patient safety.

ETHICAL DECLARATIONS

Informed Consent

Written informed consent was obtained from the patient for the publication of this correspondence and any related clinical details.

Peer Review Process

This letter was externally peer-reviewed.

Conflict of Interest

The authors declare no conflicts of interest.

Financial Disclosure

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Author Contributions

All authors contributed to the conceptualization and drafting of this correspondence and approved the final version for publication.

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