Molecular subtype and risk of local recurrence after nipple-sparing mastectomy for breast cancer

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Abstract. The present study aimed to investigate whether local recurrence (LR) after nipple-sparing mastectomy (NSM) and reconstruction was associated with i) Ki67 values and molecular subtypes of the initial lesions, and ii) the size of the initial tumor and the size of the implant. A total of 156 patients with breast cancer with a mean age of 51.58 years (age range, 26-75 years) who underwent NSM with primary implant breast reconstruction were analyzed. After surgery, the mean follow-up time was 59.26 months (range, 17-85 months). Molecular subtypes, Ki67 values, estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) status were recorded for each patient. Additionally, information regarding the size of the implant and the initial tumor size were collected. The information was used to assess LR. For univariate analyses of risk factors, χ^2 test, Fisher's exact test, Mann-Whitney U test and Student's t-test for independent samples were used. For multivariate analyses, a Cox proportional-hazards model was used. NSM was the primary treatment for breast cancer in 34/156 patients (21.8%), while 122/156 (78.2%) of patients received neoadjuvant chemotherapy followed by surgery. Luminal B was the most frequent molecular subtype, detected in 82/156 patients (52.6%), whereas the luminal A subtype was detected in 37 patients (23.7%) and the HER2-enriched subtype was detected in 17/156 patients (10.9%). Ki67 expression was low in 13/156 patients (8.3%), while medium expression was detected in 78/156 patients (50.0%) and high expression was present in 58/156 patients (37.2%). LR was noted in 17/156 patients (10.9%). As determined by univariate analysis, lower ER (P=0.010) and PR (P=0.008) expression were indicated to be significant risk factors for LR. In conclusion, in the present patient cohort, low ER and PR expression were risk factors for LR of breast cancer, whereas Ki67 status and molecular subtype were not statistically significant risk factors for LR. Additionally, the size of the initial tumor and the size of the implant were not risk factors for LR. These findings are consistent with the current literature, and should be utilized when discussing treatment options and potential clinical outcomes with patients prior to surgical management.

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Introduction

Breast cancer is one of the most prevalent types of cancer worldwide, and 7.8 million women were diagnosed with this disease between 2015 and 2020. There prevalence of breast cancer is growing globally, with 2.3 million diagnoses and 685,000 mortalities associated with breast cancer recorded in 2020 (1). Regardless of nationality or ethnicity, any woman can develop breast cancer, with the likelihood progressively increasing with age. Notably, early detection of breast cancer increases the probability of long-term survival.

Due to a high degree of heterogeny, breast cancer cannot be considered one entity, but should instead be subdivided into different groups. In 2000, Perou *et al* (2) suggested molecular-based classification of breast cancer, which included gene expression. Immunohistochemical detection of estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) status can be used to divide breast cancer into luminal A (ER^+ and/or PR^+, and $HER2^-$), luminal B (ER^+ and/or PR^+, and $HER2^+$), triple-negative (ER^-, PR^- and $HER2^-$) and HER2-positive ($HER2^+$, ER^- and PR^-) molecular subtypes. Previous studies have shown that triple-negative and HER2-positive breast cancer types have worse prognoses, and respond differently to chemotherapy compared with luminal A tumors (3,4). In the context of cancer diagnosis and treatment, Ki67, a cellular marker of proliferation, has emerged as a powerful tool for assessing tumor growth and predicting how tumors may respond to therapy (5).

Over the past four decades, important progress has been made in the development of less aggressive surgical techniques for breast cancer treatment, offering better outcomes. These techniques have moved away from radical mastectomies, which were recommended by Halsted, and have resulted in less aggressive options for patients with breast cancer. Subsequently, surgery has become more conservative. The 1980s saw a turning point for patients with breast cancer due to the successful demonstration of breast conservation carried out by Bernie Fisher. This progress continued in the 1990s with the development of more precise techniques, such as sentinel lymph node evaluation and skin-sparing mastectomy (SSM) (6). Regarding surgical techniques, over the last 20 years, nipple-sparing mastectomy (NSM) has become widely accepted compared with the already existing simple mastectomy and SSM techniques. Notably, the first NSM was performed while treating benign diseases in 1951 (7). These procedures (SSP and NSM) refer to the removal of total breast tissue while preserving the skin envelope, and the nipple-areolar complex (NAC) in cases of NSM. Conservative mastectomies have been increasingly used due to the improved cosmetic outcomes and the enablement of primary breast reconstruction. As such, NSM is often the first choice in surgical treatment for patients with breast cancer in the early stages of the disease. Several studies have demonstrated increased patient satisfaction and aesthetic outcome with NSM (8-11).

The present study reports on a single-institution experience with the aim to analyze local recurrence (LR) of breast cancer after NSM with primary implant reconstruction, and to assess the potential association with Ki67 values and the molecular subtype of the tumor.

Materials and methods

Patients. The present retrospective study was approved by the Board of Ethics of the Oncology Institute of Vojvodina (Sremska Kamenica, Republic of Serbia; approval no. 4/21/1-1797/2-8). Patient data were collected between January 2013 and December 2016 at the Department of Surgical Oncology, Oncology Institute of Vojvodina, and all of the medical records were from the same institution. A total of 156 patients who were diagnosed with breast cancer and underwent NSM with primary implant reconstruction were analyzed (the senior surgeon for all cases was ZR). During this period, a total of 156 NSM procedures were performed with fixed volume silicone prosthesis (MENTOR® CPGTM gel breast implants). The study included patients who had initial NSM with primary breast reconstruction, as well as those who underwent neoadjuvant therapy or previously had breast-conserving surgery (BCS). The group of patients who had BCS included patients who were ≥5 years disease-free since the primary tumor and, in those cases, if the tumor recurred, it was considered a second primary breast cancer. The exclusion criteria for NSM included inflammatory breast cancer, extensive skin involvement and Paget's disease. Rapid changes in the skin overlying the affected breast (erythema, edema and peau d'orange affecting a large area of the breast) and pathological evidence of invasive carcinoma were used as basic elements for the diagnosis of inflammatory breast cancer. Additionally, all breast cancer lesions with direct extension to the skin beyond the dermis were considered as tumors that were locally advanced.

Prior to surgery, all patients had a preoperative diagnostic assessment that included clinical examination, ultrasound, mammography [or magnetic resonance imaging (MRI) in cases of difficult visualization with mammography] and core biopsy. A total of 122 patients received neoadjuvant therapy and had evidence of locally advanced disease. All patients were informed about the treatment plan, with the risks and benefits thoroughly discussed. A shared decision-making process was implemented in all cases.

Surgery. During the subcutaneous mastectomy, a lateral incision was used, which allowed for excision towards the upper outer quadrant to have better access for sentinel node biopsy and/or axillary dissection. In cases where prior excisional biopsy was performed, or a patient had undergone BCS, the incision was adjusted to achieve appropriate aesthetics of the future scar. The breast and fat tissue were completely removed, and the NAC was spared. Subareolar tissue was sampled and a frozen section was generated intraoperatively to assess the potential presence of malignant cells, and it was removed appropriately in cases of positive findings. The priority during every surgery was respect for oncological principles. In cases where the surgeon had any doubt that the tumor had invaded subcutaneous tissue and sent a sample of tissue for ex tempore detection, the final decision depended on the response of the pathologist. NSM could only be continued in cases where there were no tumor cells at the margins of the removed subcutaneous tissue. Two of the patients with T4 tumors had infiltration of pectoralis muscle, but not the skin since skin infiltration is a contraindication for NSM. In patients with T3 tumor close to the subcutaneous tissue, a clinical decision was made about the safety of the margin (tumor cells must not be present on the margins of removed tissue).

Pre-operatively, the implants were determined based on the dimensions of the breast. Finally, the removed tissue was measured, and volume calculation was used to determine the appropriate size of the implant. During breast reconstruction, a gel-filled silicone implant (MENTOR Contour Profile®, fixed-volume implant) was used and placed in the previously created space between the pectoralis major and serratus anterior muscle. The present study employed a technique that has been used previously, as described by Radovanovic *et al* (12). In 144 cases, sentinel node biopsy and/or axillary dissection was performed. In the remaining 12 patients, this step was conducted during prior BCS.

Immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH). Evaluation of ER and PR by immunohistochemistry (IHC) was routinely performed (data not shown). Allred score 2 was used for ER and PR nuclear positivity, and the proportion score (PS) (0-5) and the percentage of positive tumor cells [0 (0%), 1 (<1%), 2 (1-10%), 3 (11-33%), 4 (34-66%) and 5 (67-100%)] were determined. The intensity of staining (IS) for the nuclear positivity of the cells was graded as 0, 1, 2 and 3, which corresponded to none, mild, moderate and strong, respectively. The total scores for ER and PR were calculated as TS=PS + IS. TS 0-2 were considered negative scores, whereas 3-8 were considered positive scores (13).

IHC staining with a monoclonal antibody against Ki67 (MIB-1) was used to assess the proliferative level of a population of neoplastic cells. Notably, the Ki67 cut-off values used in different studies vary, and the International Ki67 Working Group (IKWG) has had difficulties in reaching a consensus on the ideal cut-off value that could be used in clinical practice (14-16). The IKWG consensus is that ≤5% or ≥30% Ki67 may be used to estimate prognosis (17). According to this consensus, the present study split patients into three groups: Low (≤5%), medium (6-29%) and high (≥30%) Ki67 values.

Common methods such as IHC and FISH (data not shown) were used for HER2 analysis. HER2 scores 0 and 1+ were considered HER2-negative, whereas score 2+ was considered borderline and score 3+ was considered HER2-positive (18). If the IHC test results were borderline, the cancer tissue sample underwent an additional FISH test to determine if the tumor was HER2-positive (≥2 in FISH analysis).

Follow-up. Each patient in the current study underwent an oncology council where a decision on further therapy was made as a team. This decision depended on molecular subtype, definitive histopathological findings and axillary node evaluation. Postoperative treatment included systemic (chemotherapy, hormonal therapy for ER/PR-positive breast tumors and target therapy for HER2-positive breast tumors) and local therapy (radiation). Per National Comprehensive Cancer Network guidelines, radiation boost therapy was not recommended. The recommended chest wall radiation dose was 45-50.4 Gy at 1.8-2 Gy/fx in 25-28 fractions. Additionally, when the patient was not amenable to BCS, as was the case in our study, tumor bed marking and boost radiotherapy were not performed since all the tissue was removed. The current study followed The National Comprehensive Cancer Network guidelines (19).

After surgery, patients were followed up by a medical oncologist and a surgeon. During the 1st year, follow-ups included a control examination every 3 months. For the following 2 years, patients were monitored every 6 months. Subsequently, examinations were scheduled every year. In addition to the results of ultrasound or mammography, patient follow-up included skeletal X-rays, and ultrasound or computed tomography of the abdomen. In certain cases, such as an unclear mammography and ultrasound findings, MRI was performed. LR was considered any occurrence of cancer in the same breast or armpit area, chest wall or in the skin near the original site or scar within 5 years. Any suspicion of LR was verified by histopathological evaluation.

The mean follow-up period was 59.26 months (range, 17-85 months; standard deviation, 14.06), while the median was 56 months. All early and late postoperative complications were recorded, alongside the effect of Ki67 value and molecular subtype on LR.

Statistical analysis. To assess which individual factors were associated with LR, univariate analyses using χ^2 test, Fisher's exact test, Mann-Whitney U test and Student's t-test for independent samples were conducted. Subsequently, a Cox proportional hazards model was applied in multivariate analysis to examine how multiple factors influenced the risk of LR. Data analysis was performed using SPSS version 24.0 software (IBM Corporation). P<0.05 was considered to indicate a statistically significant difference.

Table I. Indication for mastectomy.

Indication	n (%)
Size of invasive cancer (large breast tumor/ breast size)	53 (34.0)
Multicentric cancer	56 (35.9)
Extensive DCIS	17 (10.9)
Second primary tumor after BCS	15 (9.6)
Invasive cancer + DCIS	15 (9.6)
Total	156 (100)

BCS, breast-conserving surgery; DCIS, ductal carcinoma *in situ*.

Results

The mean patient age was 51.58 years (range, 26-75 years, with a standard deviation of 10.01). Indications for mastectomy are presented in Table I. In 53 patients, the indication for NSM was size of invasive cancer (large tumor/breast size ratio). For patients who had large tumors and a smaller breast size, a BCS would result in poor aesthetics, explaining why such patients received NSM. NSM was the primary treatment for breast cancer in 34 patients (21.8%), while 122 patients (78.2%) were operated on after neoadjuvant chemotherapy (four cycles of doxorubicin and cyclophosphamide followed by four cycles of docetaxel). A sentinel lymph node biopsy was carried out in 48 patients (30.8%). Luminal B was the most frequent molecular subtype, and was detected in 82 patients (52.6%). Luminal A was detected in 37 patients (23.7%), while the HER2-enriched subtype was detected in 17 patients (10.9%). Ki67 expression was low in 13 patients (8.3%), while medium expression of Ki67 was detected in 78 patients (50.0%) and high Ki67 expression was present in 58 patients (37.2%). Among the 156 women, 123 (78.8%) received radiotherapy; the treatment regimen consisted of 50 Gy delivered in 25 fractions. LR was noted in 17 patients (10.9%) (Table II).

As determined by univariate analysis, lower expression of ER and PR were identified as independent risk factors for LR [ER: odds ratio (OR)=1.238, confidence interval (95% CI)=1.09-2.387, P=0.010; PR: OR=1.211, 95% CI=1.158-2.471, P=0.008), which indicated that patients with lower ER or PR status had a ~1.2 times higher risk of developing LR. As determined by multivariate analysis, lower expression of PR was identified as the only independent risk factor for LR (OR=1.423, 95% CI=1.108-6.892, P=0.021), which indicated that patients with lower PR status had a ~1.4 times higher risk of developing LR. By contrast, molecular subtype, stage of breast cancer, expression of Ki67 and HER2, size of implant or size of tumor were not risk factors for LR of disease (Table III).

Discussion

Implant-based breast reconstruction is gaining increasing popularity, with a steady upward trend observed in recent

Table II. Tumor characteristics and treatment.

Variable	n (%)
Stage	
0	4 (2.6)
I	33 (21.2)
IIA	29 (18.6)
IIB	30 (19.2)
IIIA	31 (19.9)
IIIC	13 (8.3)
IV	3 (1.9)
DCIS	13 (8.3)
Tumor classification	
Ductal	138 (88.5)
Lobular	18 (11.5)
T stage	
DCIS	16 (10.3)
T1	57 (36.5)
T2	67 (42.9)
T3	11 (7.1)
T4	2 (1.3)
Not assessed	3 (1.9)
Nodal status	
N0	64 (41.0)
N1	48 (30.8)
N2	30 (19.2)
N3	14 (9.0)
Molecular subtype	
Luminal A	37 (23.7)
Luminal B	82 (52.6)
Triple-negative/basal like	4 (2.6)
HER2-enriched	17 (10.9)
Not assessed	16 (10.3)
Ki67 expression[a]	
Low (0-5%)	13 (8.3)
Medium (6-29%)	78 (50.0)
High (≥30%)	58 (37.2)
Axillary evaluation	
Sentinel lymph node biopsy	48 (30.8)
Axillary dissection	80 (51.3)
Axillary dissection after SNB	16 (10.3)
Not performed	12 (7.7)
Local recurrence	
Yes	17 (10.9)
No	139 (89.1)
Neoadjuvant chemotherapy	
Yes	122 (78.2)
No	34 (21.8)
Radiotherapy	
Yes	123 (78.8)
No	33 (21.2)

[a]Data are not available for seven patients. DCIS, ductal carcinoma *in situ*; SNB, sentinel node biopsy.

years (20,21). The decision to offer NSM to patients with breast cancer has recently become more nuanced, with concerns raised about potentially higher LR rates and the possibility of future cancer development in residual breast tissue after NSM. This is the main reason why NSM in breast cancer is continuously investigated and its efficacy demonstrated. Standard SSM removes the mammary gland and the NAC, but keeps the skin and fold (22). This approach is safe and aesthetically pleasing, and exhibits high tumor control rates (22-24). By contrast, while similar, NSM also retains the NAC, but concerns have been raised about the potentially increased LR risk. Despite such concerns, NSM has shown success in treating peripheral and even advanced breast tumors, achieving outcomes similar to those of SSM (25). Accurately predicting LR after NSM with immediate reconstruction is crucial for managing patients with breast cancer. As NSM becomes more popular (26), improved methods for estimating LR risk are needed to guide patient care and prognosis.

LR rates after NSM have been extensively analyzed and published. The recurrence rates have been reported to range from 0 to 24% following NSM (27-33). The highest reported LR rate was 24%, as reported by Benediktsson and Perbeck (32), whereas other studies have found LR rates to be ~4% (27-29,31-33). Analyzing data from >12,000 patients across 73 studies, Headon *et al* (34) detected an unexpectedly low average LR rate of 2.38% for patients subjected to NSM, even with follow-up periods ranging from 7.4 to 156 months. Garcia-Etienne *et al* (35) published a review on 1,826 NSM cases with low LR within the NAC (0.16%), and revealed that local failure was related more to tumor biology than to preservation of the NAC. A retrospective analysis by Joo *et al* (36) examined 5,764 mastectomy sites and identified a 4.7% overall LR rate. The most common recurrence location was skin and/or subcutaneous tissue (75.8%), followed by the chest wall (14.2%) and the NAC itself (10%). Notably, the LR rate was slightly higher for NSM (5.2%) compared with SSM (3.5%). Additionally, autologous tissue reconstruction had a lower LR rate (2.9%) compared with implant reconstruction (5.6%). Across all mastectomies and reconstructions, skin and subcutaneous tissue exhibited the highest LR rates (62.5-85%). Notably, 81.4% of LR lesions reappeared in the same quadrant as the original tumor. It should be noted that certain studies analyzed the frequency of LR after simple mastectomy. Siponen *et al* (37) reported a 7-year LR rate of 6.5% in the first group of patients <40 years of age at the time of breast cancer diagnosis. In the second group of patients aged ≥40 years at the time of cancer detection, LR was 2.5-3.3%. Beadle *et al* (38) reported a higher 10-year LR rate (12.5%) in patients <35 years of age who underwent SM without radiotherapy compared to 7% with radiotherapy. In the current study, LR was recorded in 17 patients (10.9%) at a mean follow-up of 59.3 months. Additionally, it was revealed that larger size of implant and size of tumor were not risk factors for LR of the disease.

The impact of the molecular subtype of breast cancer on LR after NSM has previously been investigated. Mallon *et al* (39) observed a significantly higher LR rate (19.7%) in HER2-positive breast cancer compared with in HER2-negative breast cancer (10.1%). ER positivity was associated with a lower risk of LR (10.8 vs. 14% in patients with ER-negative tumors), with a similar trend observed for

Table III. Univariate and multivariate analyses of risk factors for LR.

			Univariate analysis			Multivariate analysis		
Variables	LR n (%)	No LR n (%)	OR	95% CI	P-value	OR	95% CI	P-value
Molecular subtype								
Luminal A	6 (40.0)	31 (24.8)						
Luminal B	7 (46.7)	75 (60.0)	0.476	0.191-0.732	0.416[a,b]	0.284	0.096-2.391	0.534[b]
Triple-negative	1 (6.7)	3 (2.4)						
HER2-enriched	1 (6.7)	16 (12.8)						
Stage								
0	0 (0.0)	4 (3.1)						
I	3 (20.0)	30 (23.4)						
IIA	2 (13.3)	27 (21.1)						
IIB	3 (20.0)	27 (21.1)	0.289	0.087-0.561	0.893[c,d]	0.721	0.263-1.396	0.686[d]
IIIA	4 (26.7)	27 (21.1)						
IIIC	2 (13.3)	11 (8.6)						
IV	1 (6.7)	2 (1.6)						
Ki67								
Low	1 (6.2)	12 (9.0)						
Medium	11 (68.8)	67 (50.4)						
High	4 (25.0)	54 (40.6)	0.473	0.298-0.891	0.379[a,e]	0.443	0.298-4.752	0.407[e]
Median ER expression (IQR)	5.00 (5.00)	7.50 (2.00)	1.238	1.09-2.387	0.010[f,g]	1.191	0.522-1.596	0.377[g]
Median PR expression (IQR)	5.00 (5.00)	6.00 (4.00)	1.211	1.158-2.471	0.008[f,g]	1.423	1.108-6.892	0.021[g]
Median HER2 expression (IQR)	0.00 (3.00)	0.00 (2.00)	0.347	0.157-0.463	0885[f,g]	0.899	0.641-1.109	0.892[g]
Mean ± SD size of implant, ml	386.76±145.63	346.58±147.99	0.217	0.089-0.681	0.292[g,h]	0.284	0.086-1.671	0.731[i]
Mean ± SD size of tumor, mm	24.53±21.80	25.57±18.03	0.653	0.422-1.219	0.827[g,h]	0.244	0.118-2.816	0.899[i]
Chemotherapy								
No	3 (17.6)	31 (22.3)						
Yes	14 (82.4)	108 (77.7)	0.268	0.153-0.481	0.661[a,i]	0.308	0.105-1.273	0.873[i]
Radiotherapy								
No	3 (17.6)	30 (21.6)						
Yes	14 (82.4)	109 (78.4)	0.296	0.117-0.732	0.141[a,j]	0.311	0.103-1.288	0.890[j]

LR, local recurrence; OR, odds ratio; CI, confidence interval. [a]χ^2 test; [b]luminal A vs. luminal B; [c]Fisher's exact test; [d]IIA vs. IIB; [e]low + medium vs. high; [f]Mann-Whitney U test; [g]LR vs. no LR; [h]t-test for independent samples; [i]chemotherapy vs. no chemotherapy; [j]radiotherapy vs. no radiotherapy.

PR positivity. Petit *et al* (40) reported a strong association between HER2 upregulation and LR in NSM, with 9 out of 11 patients experiencing LR exhibiting HER2 upregulation. Lari and Kuerer (41) performed a systematic review, which revealed that it was not simple to understand the prognostic importance of biomarkers in the LR rate of ductal carcinoma *in situ* (DCIS). The reasons were heterogenous treatments and conflicting results from different studies. In addition, an aggravating circumstance was the small number of patients. However, the authors reported an association between low ER expression in the DCIS group and increased risk of LR. The present study found that lower ER and PR expression were significant risk factors for LR of breast cancer, whereas Ki67 status and HER2 expression were not risk factors for LR of the disease after NSM. To the best of our knowledge, there is a scarcity of studies discussing whether the molecular subtype of the tumor has an effect on LR rates, and, therefore, there is a need for further studies to investigate this topic.

Notably, the current study presented potential limitations. Specifically, there was an insufficient number of patients to perform certain types of analyses, such as dividing patients into groups according to tumor type; a power analysis was

performed, which revealed that a significantly higher patient sample was needed to conduct such tests. An additional limitation of the present study was that it did not separate patients with DCIS from other type of patients. Since previous studies included patients with DCIS in similar analyses, the present study followed comparable protocols, since the current cohort did not contain a sufficient number of patients to create two separate groups (7,42-44). Even though the current study analyzed 156 cases of NSM, these results were not compared with classic mastectomies, which represents another limitation of the present study; this may be analyzed further in future studies.

In conclusion, in the current patient cohort, low ER and PR expression were risk factors for LR of breast cancer after NSM, whereas Ki67 status and molecular subtype were not statistically significant risk factors for LR. Additionally, the size of the initial tumor and the size of the implant were not risk factors for LR. The majority of the findings from the present study were consistent with the current literature, and should be utilized when discussing treatment options and potential clinical outcomes with patients prior to surgical management. However, one of the findings (HER2 positivity) was not consistent with the current literature, which demonstrates the need for further research on this topic, since the current literature lacks large high-powered studies.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

DG and ZR conceived the research question and designed the methodology, including the research plan and data collection methods. DR and MĐ were responsible for data acquisition, while AĐ and MĐ ensured the data's accuracy, completeness and organization for analysis (data curation). DR and AĐ confirm the authenticity of all the raw data. SS and DR played a crucial role in ensuring the research methods and findings were valid. This included tasks like checking data collection procedures and analyzing data for consistency. AĐ's contribution was essential in defining the types of statistical analysis applied to the data with a focus on the result interpretation, which was an essential element for forming a key conclusion made in this manuscript. SS and MĐ then performed the formal data analysis using these methods. DG drafted the initial manuscript, while SS reviewed and edited it for clarity, grammar and overall quality. DR created the tables to present the research findings. AĐ secured the resources required for the study. ZR provided overall project supervision, ensuring its progress and quality. DG managed the project, including tasks like overseeing the research timeline and budget. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

The retrospective research has been approved by the Board of Ethics of the Oncology Institute of Vojvodina (4/21/1-1797/2-8). Informed written consent was obtained from all subjects for participation in the present study.

Patient consent for publication

Informed written consent was obtained from all subjects involved in this study for publication purposes.

Competing interests

The authors declare that they have no competing interests.

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