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ORIGINAL RESEARCH

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Is long-term survival possible when conventional cervical cancer treatment options are exhausted?

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Abstract

When local recurrence happens, treatment options are limited due to the frequent use of pelvic irradiation for primary cervical cancer. Reirradiation is usually contraindicated and chemotherapy is ineffective at controlling tumors located within the previously irradiated tissue, in the case of persistent or recurrent cervical cancer, pelvic exenteration (PE) is on of the few options to offer patients a radical treatment. This is the first analysis from Estonia evaluating prognostic factors associated with locally advanced cervical cancer and the potential for long-term survival with pelvic exenteration. Between 2001 and 2021, PE was performed in 25 patients with recurrent or persistent pelvic cancer after radical radiochemotherapy. Included were 22 cervical cancer and 3 vaginal cancer cases who were followed until 01 June 2022. Clinicopathological characteristics of patients were described in univariate analysis and prognostic factors were estimated with Cox proportional hazard analysis. The median age was 58 years (range 34–80). Median tumor diameter was 6 cm (range 2–14 cm). Total PE, anterior PE and PE with rectal anastomosis consisted of 44%, 36% and 20% of cases respectively. Additional vulvectomy was performed 28% of patients. The median follow-up was 92 months. The overall postoperative complication rate was 32%; the postoperative mortality rate was 0%. Median hospitalization was 16 days (range 9–34). Overall survival was as follows: 1 year 64%, 3 year 40%, 5 year 32% and 15 year 24%. In this case series, we find that even in patients with recurrent or persistent locally advanced cervical cancer, at least a quarter of patients treated with pelvic exenteration can achieve a survival of more than 15 years. PE can be performed with a low postoperative complication rate and zero mortality. PE allows significantly longer survival for patients who have exhausted other treatment modalities.

Keywords

Cervical cancer; Pelvic exenteration; Complications; Long-term survival

1. Background

Complete resection with clear microscopic resection margins is the most important prognostic factor in surgery for pelvic tumors [1]. In locally advanced and recurrent pelvic malignancies, radical margins are sometimes difficult to obtain because of close relation to or growth in adjacent organs/structures. Total pelvic exenteration (TPE) is an exenterative operation for these advanced tumors and involves en bloc resection of the rectum, bladder, internal genital organs and vulva. Thus, the primary indication for pelvic exenteration is recurrent or persistent cervical cancer after full radiation therapy [2].

Total pelvic exenteration has been performed in primary or recurrent and locally advanced pelvic tumors [3, 4] and was first described by Brunswig and colleagues from the Memorial Hospital in New York [5]. Initially, pelvic exenteration was utilized for palliative surgical management of advanced and recurrent gynecologic cancer. Perioperative mortality was over 23% and there were no long-term survivors. Since its first description in 1948 [6] the procedure has undergone modifications and improvements in neoadjuvant treatment, operative techniques and peri- and postoperative anesthetic management [5, 7, 8]. However, morbidity is still high and 15–68% patients have complications after TPE [3, 7]. Furthermore, the postoperative mortality rate can be as high as 14% [8].

Outcomes in surgical oncology depend on the skill of the surgeon as well as the volume of surgery performed [9]. After TPE, the five-year survival rates for patients with primary disease range between 15% and 77.6% and in patients with recurrent disease from 0% to 23% [7, 10, 11]. Careful selection for TPE is of paramount importance [12] yet no previous study has been conducted in Estonia to inform patient selection parameters. Hence, this study was planned to evaluate morbidity and outcomes of patients undergoing TPE in the Department of Surgical Oncology of University of Tartu.

Further, long-term outcomes studies are scarce and sample

sizes are small. The three most recent studies provide 6.7 years of follow-up among 24 patients [13] to 5 years' follow-up among 61 patients [14] and 9 years among 47 patients [15]. Our study extends the literature by providing 20 years of follow-up among 25 patients.

2. Patients and methods

2.1 Study type

This work was planned as observational study on advanced cervical cancer patients treated with pelvic exenteration after cancer recurrence or due to persistent cancer after radical radiochemotherapy.

At the Department of Surgical Oncology at the University of Tartu, 25 TPE surgeries were performed from January 2001 to February 2021 for gynecological malignancies. Of the 25 TPEs, 22 patients had cervical cancer, and 3 had vaginal cancer; 8 patients (31%) had previously undergone surgery for cervical or vaginal cancer and received radio-chemotherapy after recurrence and operated for persistent cancer. Four (15%) patients were admitted to surgery without proper neoadjuvant therapy: 2 received 2 palliative chemotherapy courses before surgery and 2 were operated on in an emergent situation due to bleeding from the tumor. Thirteen patients (54%) had a persistent tumor after radical radiotherapy and chemotherapy. Preoperative evaluations were performed with computed tomography or magnetic resonance imaging scanning or both.

All patients received perioperative prophylactic antibiotics and patients with a positive urine sample had antibiotic treatment based on the antibiogram. Since 2012, we have used the ultrasonic instrument Harmonic Focus which has reduced mean operative blood loss from 960 mL to 650 mL while maintaining post-operative survival at 100%.

All operations were performed by the same team of surgical oncologists.

2.2 Pathology

All staging was performed according to the American Joint Committee on Cancer (AJCC) Tumour, Node, Metastasis (TNM) criteria. All resection borders were analyzed to confirm the completeness of resection. Histological tumor type, margin status, lymphatic and/or vessel invasion and nodal status were obtained from pathology reports.

2.3 Evaluation of morbidity and mortality

Case histories and charts were collected and analyzed to obtain patient data, operation techniques and follow-up. The data gathered included the demographics, diagnosis, TNM, earlier treatment, operation time and length, blood loss, postoperative complications and bed rest time, histological parameters, follow up data and overall survival.

Operation types were divided as follows: (A) supralevator exenteration; (B) infralevator exenteration; and (C) infralevator exenteration with vulvectomy; (D) anterior exenteration with vulvectomy.

All complications were studied and categorized as minor and major complications requiring reoperation. Early complications were defined as those occurring within 30 days of surgery.

All follow-up data were gathered until the patient's death or until 01 June 2022.

2.4 Statistical analysis of survival

Categorical variables are described with frequencies and percent's, continuous variables are described with medians and ranges.

Overall survival time was calculated from the date of resection of the tumor until the last follow-up attendance or death. The data lock was 01 June 2022, after which time patients were censored. Survival time by risk factors is presented as 5-year and 10-year survival.

Survival after surgery was calculated using the Kaplan-Meier method [2]. All survival indicators were presented with 95% confidence intervals. Univariate survival comparisons were executed using the log-rank test. Cox proportional hazard analysis was used for multivariate analysis of prognostic factors for overall survival [1]. The level of significance was defined as $p < 0.05$.

3. Results

All 25 patients had similar preoperative preparation, including: anesthesiologist examination and risk evaluation according to the American Society of Anesthesiologists (ASA) scale, a complication risk assessment, confirmation of the ordered blood reserve, bowel preparation if needed, low molecular weight heparin (LMWH) to reduce the risk of thromboembolism, preoperative skin preparation, shaving, informed consent and prophylactic antibiotic 30 minutes before skin incision.

3.1 Surgery

Study characteristics are presented in Table 1. Median patient age was 58 years (range, 34–80). The median operation time was nearly 4 hours (235 minutes, range 121–470 minutes). For 2 patients (8%), operation time was about 3 hours (range 121–180 minutes), for 16 patients (64%), operative time was 3 to 5 hours (range 181–300 minutes), and for 7 patients (28%), operative time was 5 to nearly 8 hours (range 301–470 minutes) (Fig. 1).

The median blood loss was 816 mL (range 100–1640) mL. For 11 patients (44%), blood loss was 100–500 mL, for 7 patients (28%), blood loss was 501–1000 mL, and for 7 (28%) patients' blood loss was 1001–1640 mL. Median blood loss decreased from 960 mL to 650 mL following the introduction of ultrasonic instruments in 2012.

For 4 patients, the operation type was total exenteration with vulvectomy; additionally, there were 5 total infralevator exenterations, 2 total infralevator exenterations with omentoplasty, 5 total supralevator exenterations with rectal anastomosis 6 anterior exenterations, and 3 anterior exenterations with vulvectomy.

For urinary derivation, in most patients a Bricker conduit was formed and for uretroenteric anastomosis the Wallace techniques was used. While for two patients the Lundiana

TABLE 1. Characteristics of the study population.

Patient characteristics	Estimate, range	Percent, %
Age (yr)		
Median	58	
Range	34–80	
Tumor type		
Cervical	22	88
Vaginal	3	12
Operation time (min)		
Median	269	
Range	121–470	
Blood loss (mL)		
Median	816	
Range	100–1995	
Operation type		
Total + vulvectomy	4	16
Total infralevator	5	20
Total supralevator + rectal anastomosis	5	20
Anterior	6	24
Anterior + vulvectomy	3	12
Total + omentoplasty	2	8
Urinary derivation		
Bricker conduit	23	92
Lund pouch	2	8
Tumor diameter (cm)		
Median	6.5	
Range	2–14	
Histological subtype		
Squamous cell carcinoma	23	92
Adenosquamous carcinoma	1	4
Adenocarcinoma	1	4
Tumor stage		
pT1	2	8
pT2/2b	4	16
pT3/3b	7	28
pT4	12	48
Lymph node metastases N1/2	10	40
R1	4	16
Distant metastases M1	2	8
Hospitalization (d)		
Median	16	
Range	9–34	
Postoperative complications	8	32
Operated due to complication	2	8
Postoperative mortality	0	0
Follow up (mon)		
Median	92	
Range	70–245	

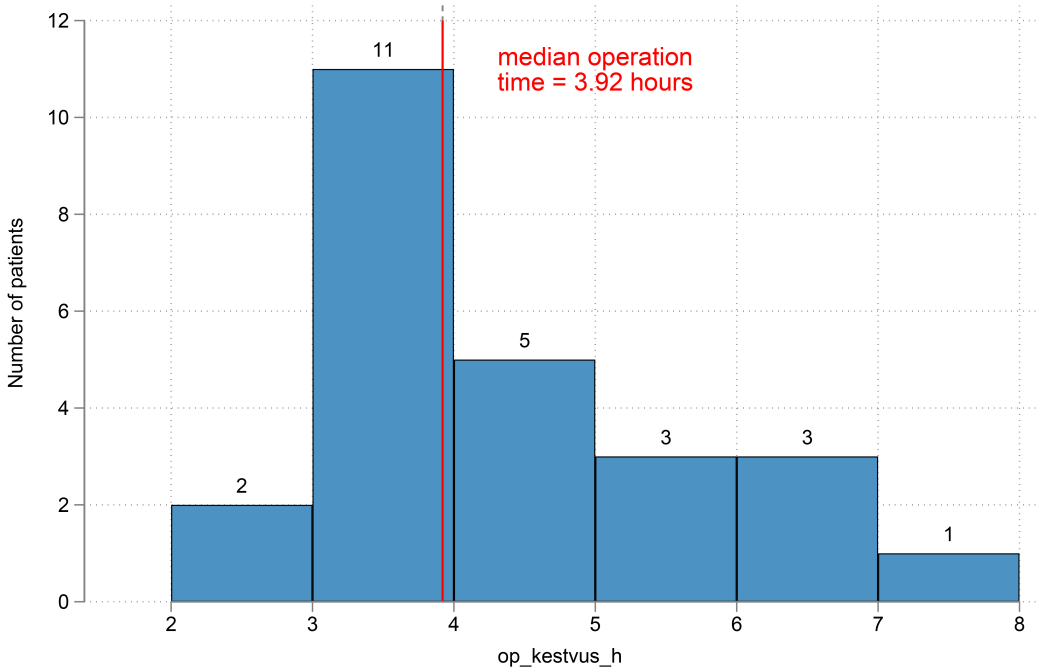

FIGURE 1. Operating time.

pouch for continent cutaneous diversion was constructed from detubularized right colonic segment.

The median length of stay following surgery was 16 days (range, 9–34).

3.2 Pathology

The median tumor diameter was 6 cm (ranges, 2–14 cm). In 23 (92%) patients, the finding was squamous cell carcinoma, 1 adenocarcinoma, and 1 adenosquamous carcinoma. In four cases (16%), the tumor reached the resection line (16%). Ten patients (40%) had metastatic regional lymph nodes in the specimen, and two patients (8%) had distant lymph node metastases.

A description of postoperative complications is provided in Table 2. Overall, the postoperative complication rate was 32% (n = 8); 8% (n = 2) were operated upon due to a complication.

3.3 Survival

The overall survival rate was 64% for 1 year, 44% for 2 years, 40% for three years, 32% for 5 years, 24% for 10 and 15 years, and 12% for up to 20 years (Fig. 2).

The median survival time was estimated to be 32 months (95% CI 10–120 months).

The reverse Kaplan-Meier estimate of the median follow-up was 92 months, ranging from 70 months for the lower quartile to 245 months for the upper quartile. Overall survival by patient characteristics is presented in Fig. 3.

3.4 Prognostic factors

Blood loss (hazard ratio (HR) = 1.00, 95% CI: 0.99–1.00, p = 0.841), lymph node metastasis (HR = 1.15, 95% CI: 0.41–3.19, p = 0.0789), and distant metastasis (HR = 1.85, 95% CI: 0.41–8.28, p = 0.423) were prognostic of 5-year survival.

Operation time (p = 0.33, hazard ratio, HR = 0.997, 95% CI: 0.992–1.002) was not related to survival. After categorizing the operation time into 3 different groups (2–3 hours, 3–5 hours and >5 hours), we compared survival between the groups yet no statistically significant differences were detected (p = 0.798) (Fig. 1).

Age was similarly unrelated to overall survival (p = 0.21). The 5-year overall survival was 50% for patients younger than 50 years, 16.7% for patients 51 to 70 years, and 50% for patients 70 to 80 years. We suspect that variation in survival by age is associated with small subgroups rather than a true difference in survival for those 51 to 70 years of age.

Finally, neither complications nor tumor diameter were found to be associated with survival (p = 0.73 and p = 0.37, respectively) in our Cox proportional hazards model.

4. Discussion

Total pelvic exenteration as a technique was introduced mainly for palliation of advanced pelvic malignancy [5, 8, 16–18]. However, in recent years it has been performed with curative intent in the treatment of locally advanced and recurrent pelvic malignancies [11]. In locally advanced pelvic tumors, TPE which achieves complete resection is the only chance for cure. High 5-year survival rates (41–48%) with excellent local control after TPE have been reported [15, 16, 19, 20]. Historically, this procedure was associated with high mortality and morbidity [21] with mortality rates as high as 23% described in the mid twentieth century [5]. Over the last 60 years, important health care advances have made TPE much safer and efficacious [18, 22].

The main aim of this study was to evaluate the results of this

TABLE 2. Description of postoperative complications.

Complication	Count	Percentage, %	Operation due to complication
Urinary tract infection	2	8	
Laparotomy wound infection	2	8	
Perineal wound infection	1	4	
Partial femoral nerve paresis	1	4	
Bowel obstruction, adhesions	1	4	Ileotransverse Stoma
Rectal anastomosis dehiscence	1	4	Colostoma
Total	8	32	

The postoperative mortality rate was 0%.

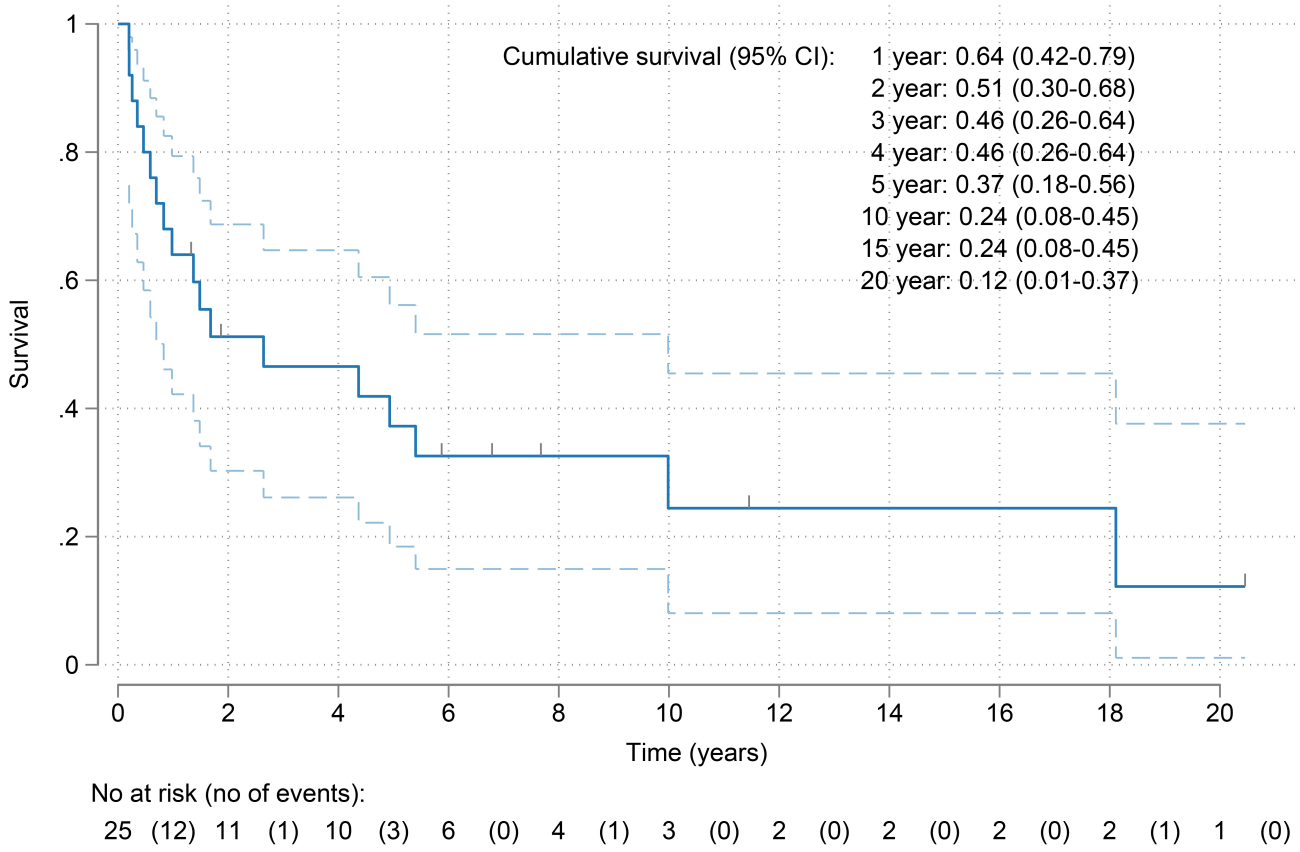

FIGURE 2. Overall survival. CI: Confidence interval.

last-resort surgical cancer treatment method in the only cancer treatment center in Estonia. We were interested in describing prognostic factors for long-term survival given the cohesion of our operating team throughout the duration of the study period. In other words, given that our center is the only one in Estonia, our team has built longstanding relationships among the operating theater clinicians and a honed our techniques over time.

The main finding is the evidence of pelvic exenteration operative success with low morbidity and zero mortality in patients whose cervical cancer treatment options are depleted and cancer is persistent or recurrent after radical chemoradiation.

This inquiry is relevant to Estonian women because the cervical cancer incidence in Estonia is high. In 2018, cervical cancer was the second most frequent female genital cancer after uterine cancer [23], and in 2019, 161 cervical cancers were diagnosed. Cervical cancer accounts for 4% of all cancers diagnosed in Estonian women, with 32% of the cases diagnosed in the first stage, 16% in the second stage 30% in the third stage, and 15% in the fourth stage. The 5-year relative survival with cervical cancer in Estonia is 68% [23].

The PE complication rate described in the literature varies greatly. Some authors report complication rates of 78–81% [13, 24, 25] whereas others report that up to 62% of the cohort were free of complications [26]. Most authors agree that the more common postoperative complications are urinary tract and wound infections [14, 26]. In this series, 32% of patients had a complication. Of these, 8% of patients

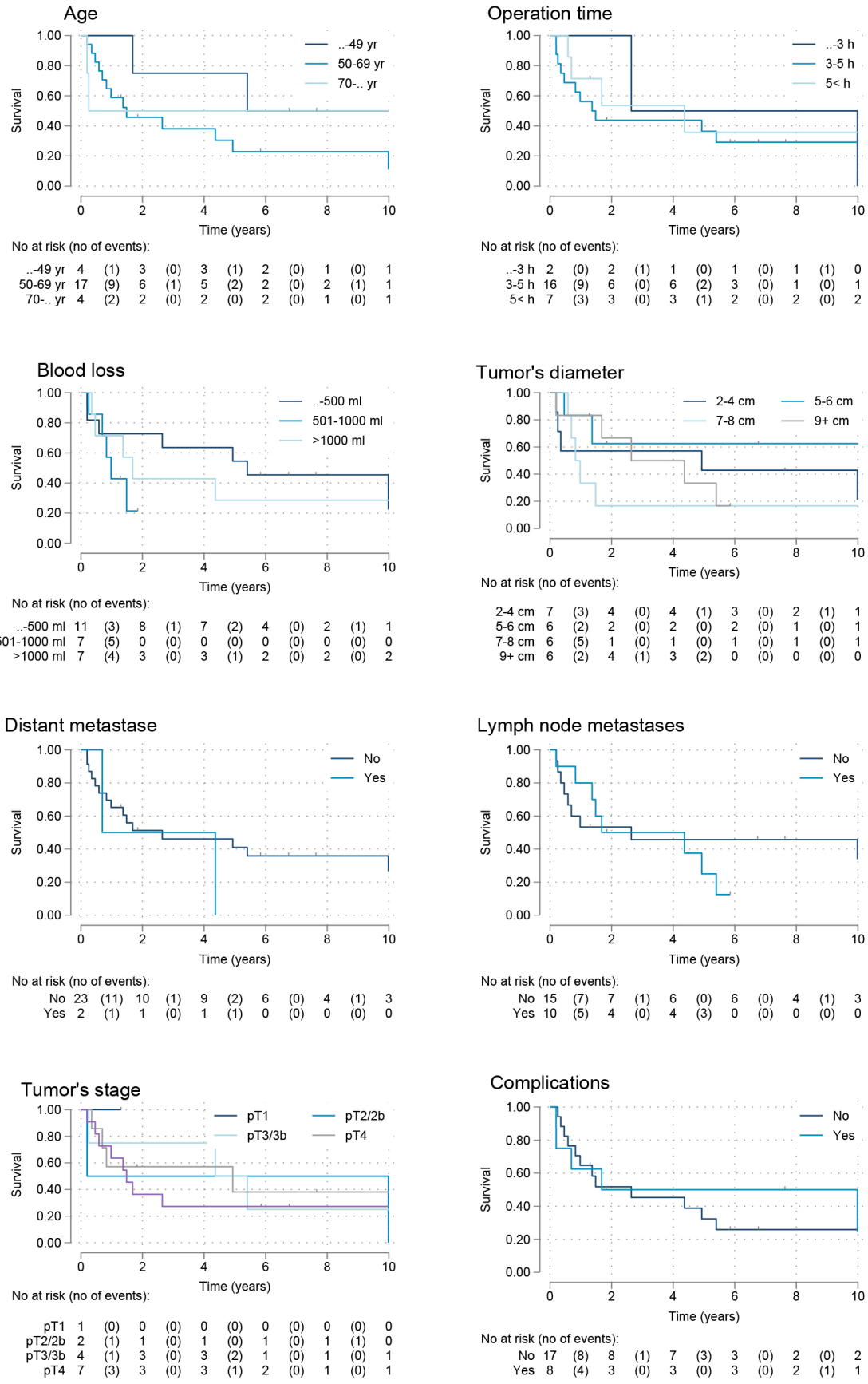

FIGURE 3. Survival prognosis by patient characteristics.

experienced a urinary tract infection and 12% had a wound infection, rates which are comparable to the literature [13, 24, 26]. Follow-up studies found that mild renal failure was present in most patients in the incontinent urinary diversion group and infection was predominant in the continent diversion group. However, complications were not associated with survival in our Cox proportional hazards analysis.

The reoperation rate in our series was 8%, also in line with recent studies [27–29].

Our findings suggest that smaller volume hospitals can perform PE procedures with a low complication and reoperation rate. In our cohort, the postoperative mortality rate was 0%, which is consistent with data reported by other groups (0–5%) [24, 26]. The 5-year survival analysis showed much better outcomes for patients younger than 50 years and older than 70 years; those aged 50–70 years experienced worse outcomes but this disparity may be due to small cell frequency.

In our study, most patients had recurrent or persistent cervical cancers. Due to the heterogeneity of patients, we cannot speculate regarding the reason for their cancer recurrence.

Blood loss was factor that influenced 5-year survival in our study (Fig. 3). Operation time greater than 6 hours was found to be a prognostic factor in another recent study, but our findings suggest that blood loss may be the most important factor.

For recurrent cervical cancer, the most favorable treatment regimen is radiotherapy which can offer as high as 45% overall survival rates, but not in patients with a history of radiotherapy [28]. When local recurrence happens, treatment options are limited due to the frequent use of pelvic irradiation for primary cervical cancer. Reirradiation is usually contraindicated and chemotherapy is ineffective at controlling tumors located within the previously irradiated tissue, which tends to be less vascularized [19, 29].

In our series, nearly all patients had received previous radical radiotherapy and chemotherapy. Thus, these patients with recurrent or persistent cervical malignancies must rely on surgical intervention as a last resort [30] even in a previously irradiated field. While palliative chemotherapy can provide a median overall survival (OS) of up to 10 months on average [31], PE can provide three times longer median OS for selected patients. Surgery is the only method of treatment that achieves as high as a 40% 5-year survival for these patients [24, 28, 32] whose treatment options have been exhausted.

5. Conclusions

In conclusion, our case series demonstrates a low complication rate and a high post-operative survival rate following pelvic exenteration. At least a quarter of patients in this series survived 15 or more years, extending the information available in the literature substantially. The optimistic long-term survival rate in this case series may be enhanced by the fact that these surgeries were performed by a single operative team in a national tertiary referral center. As such, it is possible that the specific techniques employed here as well as the long-term coordination of the surgical team have optimized outcomes. Larger studies should identify prognostic factors which could suggest patients most appropriate for this intervention.

AVAILABILITY OF DATA AND MATERIALS

The data presented in this study are available on reasonable request from the corresponding author.

AUTHOR CONTRIBUTIONS

OT and AL—designed the research study. OT—performed the research. HP, KT and OT—analyzed the data. OT and KL—wrote the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The Research Ethics Committee of the University of Tartu approved the study on 18 May 2020, identified as: Surgical treatment results for pelvic organs malignancies, protocol nr: 315/T–1. In addition, informed consent has been obtained from the participants involved.

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CONFLICT OF INTEREST

The authors declare no conflict of interest. The authors alone are responsible for the content and writing of the paper.

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