Gynecologic Oncology xxx (xxxx) xxx

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Voiding recovery after radical parametrectomy in cervical cancer patients: An international prospective multicentre trial – SENTIX

Ignacio Zapardiel [a,*], Roman Kocian [b], Cristhardt Köhler [c], Jaroslav Klat [d], Anna Germanova [b], Anna Jacob [c], Sylva Bajsova [d], Gerd Böhmer [c], Laura Lay [e], Blanca Gil-Ibañez [f], Pavel Havelka [g], Barbara Kipp [h], Grzegorz Szewczyk [i], Robert Toth [j], Juan Carlos Staringer [k], Javier De Santiago [l], Pluvio J. Coronado [m], Robert Poka [n], Rene Laky [o], Mathieu Luyckx [p], Maxime Fastrez [q], Ladislav Dusek [r], Alicia Hernandez [a], David Cibula [b]

[a] Gynaecologic Oncology Unit, La Paz University Hospital-IdiPAZ, Madrid, Spain
[b] Gynaecologic Oncology Centre, Department of Obstetrics and Gynaecology, First Faculty of Medicine, Charles University and General University Hospital, CEEGOG, Prague, Czech Republic
[c] Department of Special Operative and Oncologic Gynaecology, Asklepios-Clinic Hamburg, Hamburg, Germany
[d] Department of Obstetrics and Gynaecology, University Hospital Ostrava, Ostrava, Poruba, Czech Republic
[e] Department of Gynaecology, Institute of Oncology Angel H Roffo University of Bueno s Aires, Buenos Aires, Argentina
[f] Unit of Gynaecological Oncology, Institute Clinic of Gynaecology, Obstetrics and Neonatology (ICGON), Hospital Clinic of Barcelona, Barcelona, Spain
[g] Department of Obstetrics and Gynaecology, Bata Hospital Zlin, Czech Republic, CEEGOG, Zlin, Czech Republic
[h] Department of Obstetrics and Gynaecology, Cantonal Hospital of Lucerne, Lucerne, Switzerland
[i] Department of Obstetrics and Gynaecology, Institute of Mother and Child, Warsaw, Poland
[j] Oncology Institute of East Slovakia, Košice, Slovakia
[k] Department of Gynaecology and Obstetrics, Hospital Español de Buenos Aires, Buenos Aires, Argentina
[l] Gynecologic Oncology Unit, MD Anderson Cancer Centre, Madrid, Spain
[m] Departamento de Obstetricia y Ginecología, Hospital Clínico San Carlos, Madrid, Spain
[n] Institute of Obstetrics and Gynaecology, Faculty of Medicine, University of Debrecen, Debrecen, Hungary
[o] Gynaecology, Medical University of Graz, Graz, Austria
[p] Department of Gynaecology, Universite catholique de Louvain, Cliniques Universitaires St Luc, 1200, Brussels, Belgium
[q] Department of Obstetrics and Gynaecology, St Pierre University Hospital, Université Libre de Bruxelles, Brussels, Belgium
[r] Institute of Biostatistics and Analyses, Faculty of Medicine, Masaryk University, Brno, Czech Republic

HIGHLIGHTS

- The extent of parametrectomy is the most significant factor influencing voiding recovery.
- Type-B parametrectomy is associated with a higher risk of delayed voiding recovery than the nerve-sparing C1 technique.
- Previous pregnancy significantly increases the risk of delayed voiding recovery after parametrectomy.
- 98% of patients recover the voiding function within one month post-surgery.
- Minimally invasive surgery is not associated with faster voiding recovery.

ARTICLE INFO

Article history:
Received 24 October 2020
Accepted 15 December 2020
Available online xxxx

Keywords:
Radical hysterectomy
Parametrectomy
Cervical cancer
Voiding recovery
Nerve-sparing techniques

ABSTRACT

OBJECTIVE: Voiding dysfunctions represent a leading morbidity after radical hysterectomy performed in patients with early-stage cervical cancer. The aim of this study was to perform ad hoc analysis of factors influencing voiding recovery in SENTIX (SENTinel lymph node biopsy in cervIX cancer) trial.

METHODS: The SENTIX trial (47 sites, 18 countries) is a prospective study on sentinel lymph node biopsy without pelvic lymphadenectomy in patients with early-stage cervical cancer. Overall, the data of 300 patients were analysed. Voiding recovery was defined as the number of days from surgery to bladder catheter/epicystostomy removal or to post-voiding urine residuum ≤50 mL.

RESULTS: The median voiding recovery time was three days (5th–95th percentile: 0–21): 235 (78.3%) patients recovered in <7 days and 293 (97.7%) in <30 days. Only seven (2.3%) patients recovered after >30 days. In the multivariate analysis, only previous pregnancy ($p = 0.033$) and type of parametrectomy ($p < 0.001$) significantly influenced voiding recovery >7 days post-surgery. Type-B parametrectomy was associated with a higher

* **Corresponding author at:** Ignacio Zapardiel MD, PhD; Gynaecologic Oncology Unit, La Paz University Hospital. Paseo de la Castellana 261, 28046, Madrid, Spain.
E-mail address: ignaciozapardiel@hotmail.com (I. Zapardiel).

https://doi.org/10.1016/j.ygyno.2020.12.018
0090-8258/© 2020 Elsevier Inc. All rights reserved.

Please cite this article as: I. Zapardiel, R. Kocian, C. Köhler, et al., Voiding recovery after radical parametrectomy in cervical cancer patients: An international prospect..., Gynecologic Oncology, https://doi.org/10.1016/j.ygyno.2020.12.018

risk of delayed voiding recovery than type-C1 (OR = 4.69; $p = 0.023$ vs. OR = 3.62; $p = 0.052$, respectively), followed by type-C2 (OR = 5.84; $p = 0.011$). Both previous pregnancy and type C2 parametrectomy independently prolonged time to voiding recovery by two days.

CONCLUSIONS: Time to voiding recovery is significantly related to previous pregnancy and type of parametrectomy but it is not influenced by surgical approach (open vs minimally invasive), age, or BMI. Type B parametrectomy, without direct visualisation of nerves, was associated with longer recovery than nerve-sparing type C1.

Importantly, voiding dysfunctions after radical surgery are temporary, and the majority of the patients recover in less than 30 days, including patients after C2 parametrectomy.

© 2020 Elsevier Inc. All rights reserved.

Introduction

Cervical cancer is the most frequent cancer-related cause of death among young women [1]. Approximately 570,000 new cases are diagnosed worldwide every year, which makes the burden of the disease quite considerable [2].

A standard of care procedure in FIGO stage IB cervical cancer is radical hysterectomy followed by pelvic lymph node dissection [3]. As demonstrated by the LACC trial, oncological outcome after primary surgery is excellent in early disease stages; however, radical hysterectomy is associated with a serious postoperative morbidity [4]. Despite the development of nerve-sparing techniques, bladder dysfunctions remain the leading type of morbidity associated with parametrectomy performed as part of radical hysterectomy [4].

The most frequent bladder dysfunctions include urinary retention and urinary incontinence. Delayed spontaneous voiding has been reported in up to 85% of patients after radical hysterectomy (here add reference!) and urinary incontinence in up to 83% of patients at 3 months postoperatively [4,5]. Nevertheless, previous data reported in the literature are inconsistent, and predominantly related to short-term follow-up.

Voiding dysfunctions are caused mostly by damage to the autonomous pelvic nerves, including the sympathetic nervous system coming from T12 to L1 and parasympathetic branches coming from S2 to S4. The common trunks and specific bladder nervous branches control the detrusor muscle and internal sphincter. During a radical hysterectomy, these nerves may sustain damage in all three parts of the parametrium, ventrally in the bladder pillar, in the lateral parametrium, or in the uterosacral ligaments [5].

Data on voiding recovery after radical hysterectomy varies substantially in the literature, including its prevalence and duration after surgery [6–8]. The extent of parametrectomy is considered one of the most important factors influencing the bladder dysfunction, whereas the role of other factors, such as surgical approach, tumour size, patient age, history of vaginal deliveries, or BMI is not clear [9]. These factors, especially type of parametrectomy, can help us to anticipate type and duration of bladder dysfunctions, and as such help us to adjust postoperative management accordingly.

The SENTIX trial is an international multicentric prospective trial that aims to prove the non-inferiority of sentinel lymph node biopsy compared to full pelvic node dissection in early-stage cervical cancer [9]. The trial comprises different types of radical parametrectomy classified using the Querleu-Morrow classification of radical hysterectomy [10] and performed according to the presence of negative prognostic factors. The aim of the present study was to analyse the factors influencing voiding recovery in the SENTIX trial cohort as an ad hoc analysis of data from the first 300 patients treated per protocol with at least six months' of follow-up data available.

Material and methods

Study population.

SENTIX, an international multicentric observational study, was carried out in 47 sites from 18 countries. Presented ad hoc analysis included SENTIX trial patients operated between June 2016 and January 2019 in the approved sites who were treated per protocol and had at least six months' of follow-up data availability. In all, 300 patients were included in this study.

The patients were pre-registered into the trial before surgery if they met the following inclusion criteria: (i) FIGO 2009 stage IA1 + lymphovascular space invasion (LVSI), or IA2, or IB1 [11]; (ii) no evidence of bulky or suspicious pelvic lymph nodes or distant metastases in conventional preoperative imaging studies; (iii) performance status ECOG 0–1; (iv) age ≥ 18 years and ≤ 75 years; (v) squamous cell carcinoma, adenocarcinoma, or adenosquamous carcinoma; (vi) suitable candidate for primary surgical treatment (radical hysterectomy in tumours ≤4 cm in the largest diameter; fertility-sparing treatment in tumours ≤2 cm in the largest diameter); (vii) history of second primary cancer only if >5 years with no evidence of disease. After the surgery, patients were registered into the trial if they complied with the additional intraoperative criteria: (i) bilateral SLN detection; (ii) negative intraoperative pathologic SLN evaluation (frozen section); (iii) no intraoperative evidence of more advanced disease (>IB1). Exclusion criteria comprised: (i) treatment with neoadjuvant chemotherapy; (ii) pregnancy; (iii) history of pelvic or abdominal radiotherapy; (iv) HIV positivity or AIDS, (v) tumour histology not mentioned among the inclusion criteria.

The protocol was approved by the institutional review board at the leading institution (General University Hospital in Prague, Czech Republic) in June 2016, and was subsequently approved by the institutional review boards at all participating institutions. All patients signed a written informed consent according to institutional and federal guidelines before enrolment. All details regarding the full SENTIX trial protocol can be found in the trial-in-progress article by Cibula et al. [12] and under the trial registration number NCT02494063 (www.clinicaltrials.gov). STROBE statement was followed to construct the manuscript.

Surgical management.

Surgery consisted of sentinel lymph node biopsy and different types of hysterectomy or trachelectomy. The type of performed radical hysterectomy (B, C1, C2) [10] was at the discretion of the attending surgeon, based on the prognostic risk factors.

Type B procedure corresponds to nerve-sparing radical hysterectomy. The ureter indicates the major resection margin ventrally and laterally. Identification of the autonomic nerves is not required, and the hypogastric plexus remains hidden in a deeper part of the parametria, thus remaining fully preserved. Type C corresponds to extended radical hysterectomy. The uterine artery origin indicates the resection margin of lateral parametria. There are significant differences, particularly in the vertical (deep parametrial) dimension, between type C1, which corresponds to the nerve-sparing procedure, and type C2, which aims for a complete parametrial resection. Even more important is the vertical resection margin on the ventral parametria, which must be at the level of the ureter to preserve the bladder branches of the hypogastric plexus, localized below the course of the ureter. In type C2, a more complete dissection of the ureter from the ventral parametria is required, which allows for a complete resection of the ventral parametria. Dorsally, type C1 requires the preservation of the main branches of the

hypogastric plexus, while the recto-uterine and recto-vaginal ligaments can be resected at the level of its rectal attachment. C2 aims to a complete resection of the dorsal parametria deeply below the rectal attachment so that the separation of the major branches of the hypogastric plexus is not needed and these nerves are sacrificed [10].

Assessment of postoperative morbidity.

Data on factors influencing voiding recovery included preoperative characteristics, surgical details, and postoperative complications. All intraoperative and early postoperative complications (30 days after surgery) were reported and classified using a Clavien-Dindo grading system [12]. All adverse events manifesting during the follow-up after the 30th postoperative day were classified as late postoperative complications, classified using Common Terminology Criteria for Adverse Events (CTCAE) v5.0. All data were collected via an online encrypted database.

Voiding recovery was defined as the number of days from surgery to bladder catheter or epicystostomy removal with post-voiding urine residuum (PVR) <50 ml. The first attempt of catheter removal was done 48–72 h after radical parametrectomy and 12–24 h after simple hysterectomy. If the post-voiding residuum was 50–150 ml, patient continued voiding spontaneously and the residuum was measured again after 12–24 h. If the residuum exceeded 150 ml, Foley catheter was reinserted for additional 1–2 days, when the post-voiding residuum was repeatedly assessed. Each patient with epicystostomy was educated to close the epicystostomy from the third postoperative day temporarily for 3–4 h intervals, to try to void spontaneously and to measure the volume of residual urine after each interval. If the amount of urine exceeded 150 ml at any interval during the day, patient left epicystostomy open during the night. Epicystostomy was removed if all measured post-voiding residuum volumes during the day remained below 50 ml.

Statistical analyses.

All quantitative variables were presented as median and 5th–95th percentile and qualitative variables as absolute values and percentages. A multivariate analysis by means of a logistic regression was carried out in order to determine the risk factors associated with late voiding recovery. A Kaplan-Meier survival analysis was performed to identify the relation between the type of radical hysterectomy and the time to voiding recovery. The alpha error was set at 5%. The software used for the analysis was SPSS v. 25.0 (IBM Inc. SPSS, Armonk, NY, USA).

Table 1
Main characteristics of patients ($N = 300$).

PREOPERATIVE Characteristics		N (%) / median (5th–95th percentile)
Age (continuous)		41 (28.1; 65)
Age category [years]	≤40	129 (43.0%)
	41–60	139 (46.3%)
	>60	32 (10.7%)
BMI (continuous)		24.4 (18.7; 36.5)
BMI category [kg/m^2]	≤25	172 (57.3%)
	26–30	68 (22.7%)
	>30	59 (19.7%)
	unknown	1 (0.3%)
Number of pregnancies		2 (0; 6)
Number of deliveries		1 (0; 4)
Diagnostic procedure	Biopsy	118 (39.3%)
	Conization	185 (61.7%)
Stage (preoperative)	T1a1 + LVSI	16 (5.3%)
	T1a2	24 (8.0%)
	T1b1	259 (86.3%)
	≤2 cm	172 (66.4%)
	>2 cm	87 (33.6%)
	unknown	1 (0.3%)
Grade	G1	72 (24.0%)
	G2	160 (53.3%)
	G3	64 (21.3%)
	unknown	4 (1.3%)
Tumour type	Squamous cell carcinoma	211 (70.3%)
	Adenocarcinoma usual type (HPV related)	84 (28.0%)
	Adenosquamous carcinoma	4 (1.3%)
	unknown	1 (0.3%)
SURGICAL Characteristics		**N (%) / median (5th–95th percentile)**
Surgical approach	Laparotomy	92 (30.7%)
	Laparoscopy / Robotic / Vaginal	208 (69.3%)
Radical hysterectomy type	B	68 (22.7%)
	C1	117 (39%)
	C2	54 (18%)
	C1 + C2	2 (0.7%)
	SH or ST	59 (19.7%)
Fertility-sparing surgery	No	256 (85.3%)
	Yes	44 (14.7%)
Duration of surgery [min]		182.5 (90; 320)
Blood loss [ml]		150 (10; 647.5)

BMI: body mass index; SH: simple hysterectomy; ST: simple trachelectomy.

Results

Three hundred patients were recruited and included in this study. The main baseline characteristics of the patients that concern their preoperative status and surgical data are shown in Table 1. The median age of the patients was 41 years (5th–95th percentile 28.1–65). Previous urologic surgery was not reported in any patient. The majority of patients, 259 (86.3%), had a FIGO stage IB1; from these, 72 (66.4%) had a tumour sized under 2 cm. Regarding the surgical data, 208 (69.3%) cases were managed by a minimally invasive approach (laparoscopy, robotic, or vaginal) and a nerve sparing C1 radical parametrectomy was the most frequent technique, carried out in 117 (39.0%) patients. The median operating time was 182.5 min (5th–95th percentile 90–320).

Median voiding recovery was three days (5th–95th percentile: 0–21). Bladder function was recovered by 235 patients (78.3%) within less than seven days, while the vast majority of the patients, 293 (97.7%), recovered in less than 30 days. Among the seven (2.3%) remaining patients with recovery that surpassed one month, only two cases, which recovered the voiding function after 39 and 300 days, were not associated with severe urological perioperative complications. In the rest of the cases, we observed three cases with ureterovaginal fistulisation, one case with severe uretero-hydronephrosis due to ureteral obstruction, and one case with intraoperative ureteral transection (Table 2). Among 56 (18.7%) patients who underwent non-nerve sparing C2 radical surgery, only four presented a delayed voiding recovery, all of whom had serious complications associated with the performed surgery (Table 2).

A univariate analysis of the whole cohort revealed that neither age, BMI, nor grade is associated with the delayed (>7 days) voiding recovery (Table 3). On the other hand, a whole cohort analysis revealed a significantly longer voiding recovery time ($p = 0.001$) in the laparotomy group when compared to the rest (Fig. 1a). This difference, however, did not remain significant in the subgroup analysis of patients who underwent the same C1 type of (nerve-sparing) radical hysterectomy ($p = 0.382$) (Fig. 1b).

The results of the multivariate analysis of the independent factors predicting voiding recovery longer than seven days postoperatively are shown in Table 4. The absence of previous pregnancy was proven to be a protective factor with an odds ratio (OR) of 0.298 ($p = 0.033$).

Type B parametrectomy was associated with a higher risk of delayed voiding recovery (>7 days) than type C1 (OR = 4.698; $p = 0.023$ vs. OR = 3.623; $p = 0.052$, respectively). Type C2 radical surgery was associated with the longest interval to voiding recovery ($p < 0.001$) (Fig. 2) and with the highest risk of voiding recovery delay over one week OR = 5.843 ($p = 0.011$) (Table 4).

Table 2
Main characteristics of patients who recovered voiding function after ≥30 days ($N = 7$).

Patient number	Voiding recovery (days)	Age (years)	FIGO stage	Tumour size (mm)	Surgical time (min)	Surgical approach	Extent of radicality	Intraoperative complications	Hospital stay (days)	Adjuvant treatment	Postoperative complications
1	**47**	44	IB1	38	410	LSC	C2	None	30	None	UV fistula
2	**45**	31	IB1	28	320	LSC	C2	None	13	None	UV fistula
3	**37**	38	IB1	10	330	Open	C2	Ureteral transection	9	None	None
4	**54**	49	IB1	10	180	Open	C1	None	5	None	Hydronephrosis and hydroureter due to ureteral obstruction
5	**31**	46	IB1	25	173	Open	C2	None	6	None	UV fistula and urinoma
6	**39**	40	IB1	11	145	Open	C1	None	11	None	None
7	**300**	47	IB1	40	212	RBT	C1	None	8	None	None

UV: uretero-vaginal; LSC: laparoscopy; RBT: robotic.

Table 3
Predictors of voiding recovery >7 days: univariate analysis.

Predictors		OR (95% CI)	*p*
Age category [years]	≤40	reference	
	41–60	1.733 (0.979; 3.07)	0.059
	>60	0.770 (0.270; 2.200)	0.626
BMI category [kg/m^2]	≤25	reference	
	26–30	0.964 (0.498; 1.866)	0.912
	>30	0.784 (0.380; 1.616)	0.510
Radical hysterectomy type	B	7.943 (2.222; 28.396)	**0.001**
	C1	6.008 (1.744; 20.700)	**0.005**
	C2	10.133 (2.793; 36.768)	**<0.001**
	C1 + C2	–	
	SH or ST	reference	
Pregnancy	no	0.169 (0.059; 0.483)	**0.001**
	yes	reference	
Delivery	no	0.206 (0.085; 0.498)	**<0.001**
	yes	reference	
Grade	G1	0.634 (0.290; 1.387)	0.254
	G2	0.620 (0.321; 1.199)	0.156
	G3	reference	
Duration of surgery [min]		1.004 (1.000; 1.008)	0.079
Blood loss [mL]		1.002 (1.001; 1.003)	**0.002**

BMI: body mass index; SH: simple hysterectomy; ST: simple trachelectomy.

Median time to catheter/ epicystostomy removal was delayed 1–2 days in patients after radical parametrectomy by previous pregnancy (Day 2–3 versus Day 4) and by 2 days by more radical type of parametrectomy (Day 4 after type B or C1 versus Day 6 after type C2) (Table 5).

Discussion

In this prospective study, the data shows that the extent of parametrectomy and previous pregnancy are the most important factors that influence voiding recovery following the radical surgery of cervical cancer patients. Interestingly, type B parametrectomy, characterised by parametria resection without hypogastric nerve visualisation, was observed to have a more unfavourable impact on voiding than nerve-sparing C1 technique.

Overall, urinary morbidity seems to be an unavoidable consequence of radical hysterectomy; however, voiding dysfunctions were shown to be only temporary, and the vast majority of patients recovered within one month after surgery, including those patients with more extended radicality if no other complications occurred (19% underwent type C2 parametrectomy).

Previously reported data regarding urinary dysfunctions after radical hysterectomy are not uniform, neither in terms of methodology for the assessment nor in the threshold for post-voiding recovery considered as a dysfunction [8,13]. The PVR volume considered a threshold of voiding dysfunction differs between 50 and 150 ml [8,13,14]. In our study, a threshold of PVR of more than 50 ml was introduced, since it seems to be an objective predictor of bladder function after surgery, with a good correlation with urodynamic evaluation that does not need a specific instrumentation to measure it [14–16].

In spite of the data heterogeneity, the extent of the parametrectomy was uniformly shown to have a key role in the postoperative bladder dysfunctions [6]. Duration of voiding function recovery in patients who underwent nerve-sparing radical hysterectomy (type C1) ranges from seven to 13 days, in contrast to the voiding recovery in patients after a non-nerve-sparing surgery (type C2), which is significantly longer in most of the studies, ranging from 15 to 26 days [4,5,17].

In our cohort, the median time to voiding recovery was quite short (3 days post-surgery) and only 65 (21.7%) patients recovered after one week or later. Moreover, in only seven (2.3%) patients was a recovery reported after more than 30 days. However, in five of them, a need for longer urinary bladder catheterization was due to either intraoperative ureteral injury (1 case) or early postoperative ureteral obstruction (1 case) or a uretero-vaginal fistula (3 cases) (Table 2). Therefore, a recovery delayed by more than 30 days occurred in only two cases, both after type C1 radical hysterectomy. In one patient with an extremely long 300 days interval to spontaneous voiding after robotic radical hysterectomy, we did not find any additional underlying cause. The outcome in our cohort is in agreement with the available literature, in which only around 1% of patients were described as still experiencing voiding dysfunctions at 3–4 months post-surgery [7].

The interesting observation in our study is the increased risk of delayed voiding recovery in the type B radical hysterectomy group when compared with the type C1 patients. Even if C1 is described as a nerve-sparing technique, it is still a more radical surgery [10]; therefore, type B should, in theory, offer better voiding recovery results due to a lower probability of damage to the pelvic autonomous nerves. We can only hypothesise that without visualisation, pelvic nerves are more likely to be damaged while performing type B radical hysterectomy.

Univariate analysis showed that neither patient age nor BMI was associated with prolonged voiding recovery (more than 7 days). This result opposes our previous single institutional retrospective study, in which we observed delayed voiding recovery in patients with lower body mass index [10]. In this study, however, type C2 and even type D parametrectomy were performed more likely (29.2% and 26.4% of all cases, respectively) with a trend toward higher radicality in slimmer women [10].

Regarding surgical approach, an univariate analysis of the whole cohort showed that the better results in voiding recovery ($p = 0.001$) were obtained if minimally invasive techniques were used. However, when analysing only comparable cohorts after C1 parametrectomy, the surgical approach ceased to be significant ($p = 0.382$), thus disapproving the causality. The explanation of the better results in univariate analysis is explained by the preference toward a minimally invasive approach in smaller tumours and in less radical procedures. Our results are counter to the previously published data of Bogani et al.

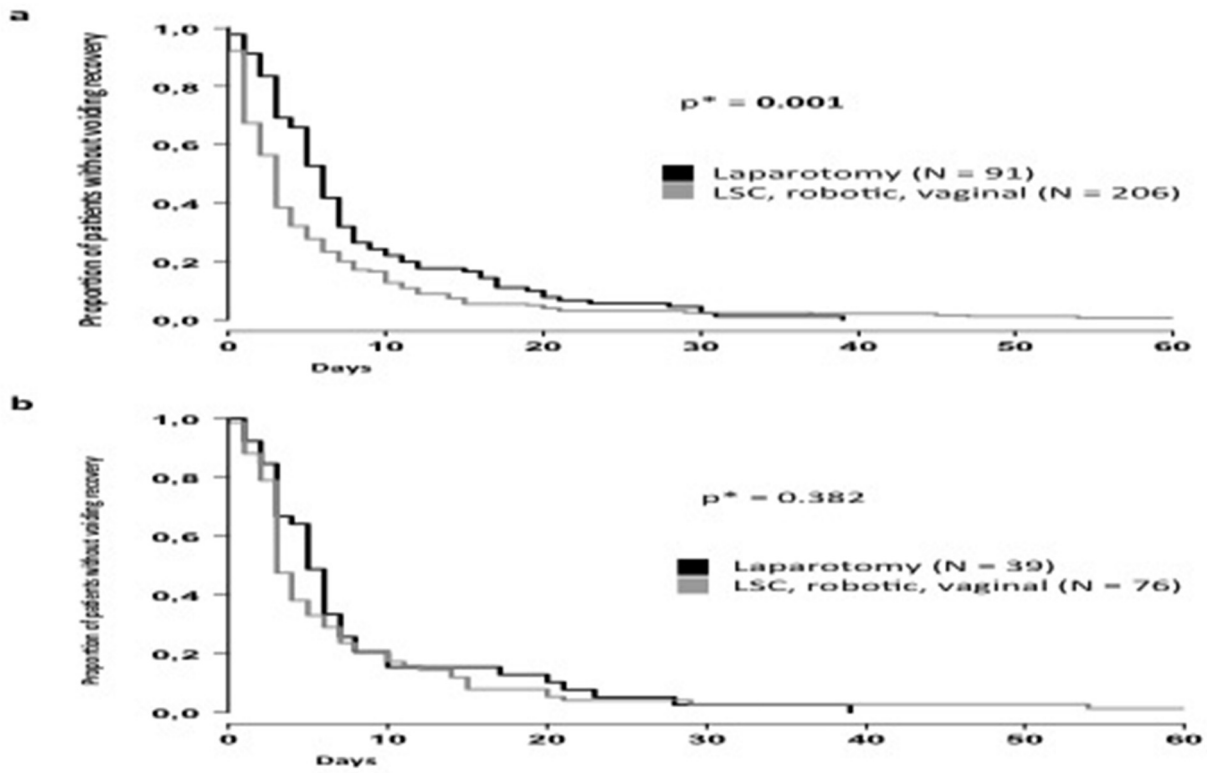


Fig. 1. Kaplan-Meier survival curve for time to voiding recovery: surgery type. **a**: Whole cohort analysis; **b**: subgroup analysis of patients with performed C1 parametrectomy. * Log-rank test.

Table 4
Predictors of voiding recovery >7 days: multivariate analysis.

Predictors		OR (95% CI)	*p*
Radical hysterectomy type	B	4.698 (1.235; 17.871)	**0.023**
	C1	3.623 (0.990; 13.264)	0.052
	C2	5.843 (1.508; 22.632)	**0.011**
	SH or ST	reference	
Pregnancy	no	0.298 (0.098; 0.908)	**0.033**
	yes	reference	

OR: odds ratio; CI: confidence interval; SH: simple hysterectomy; ST: simple trachelectomy.

[14], who reported bladder dysfunctions after 30 days post-surgery in 14% of the laparotomy group patients, compared to 0% in the laparoscopy group, all of whom underwent C1 nerve-sparing technique. However, their laparotomy group was a retrospective cohort, and both groups were relatively small (35 and 35 cases). We should also consider the possibility that, even within the same type of parametrectomy, surgeons may tend to be more radical in open surgery.

We, for the first time, also found that previous pregnancy is associated with a significant delay in post-surgery voiding recovery time. Both delivery types, vaginal and caesarean section, were previously described as a risk factor for developing voiding dysfunctions after the

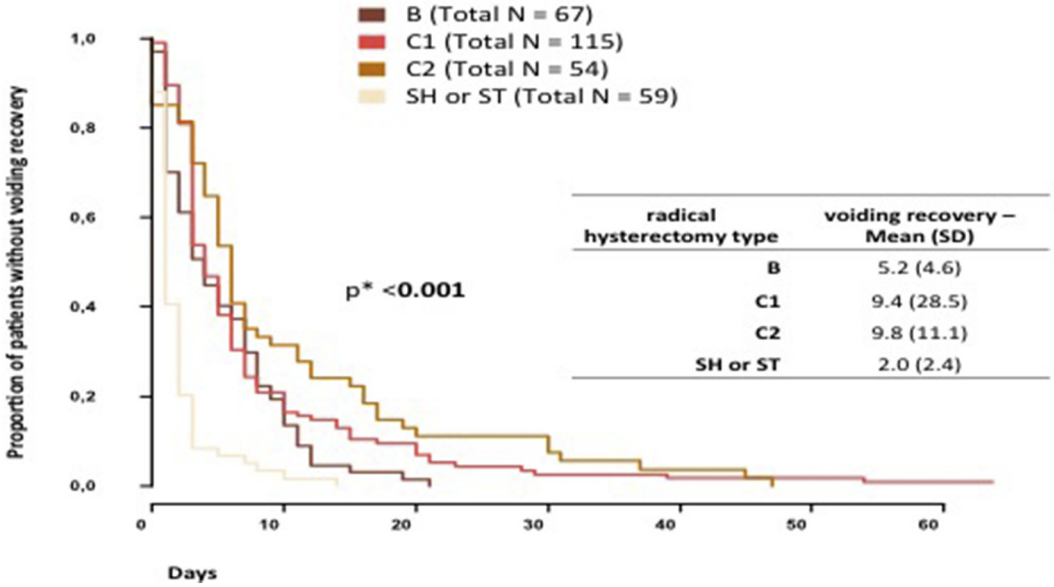


Fig. 2. Kaplan-Meier survival curve for time to voiding recovery: radical hysterectomy type. * Log-rank test; SD: standard deviation; SH: simple hysterectomy; ST: simple trachelectomy.

Table 5
Median time to catheter/ epicystostomy removal according the type of hysterectomy and previous pregnancy status.

		Pregnancy	
		No	**Yes**
Radical hysterectomy type	**B**	$N = 7$; 2 (1–8)	$N = 60$; 4 (1–14)
	C1	$N = 15$; 3 (1–7)	$N = 100$; 4 (1–26)
	C2	$N = 4$; *NA*	$N = 50$; 6 (0−31)
	Simple hysterectomy	$N = 38$; 1 (0–7)	$N = 21$; 1 (1−10)

(N = number of cases; Median time in days (5-95th percentile))
NA: not analysed based on insufficient number of cases.

next childbirth [18]. Vaginal delivery may be connected to the pelvic floor mechanical damage influencing muscles, soft tissues, as well as nerves; caesarean section was described as a risk factor for voiding dysfunction with retraction and fibrosis generated near the urinary bladder as a possible explanation [18].

In conclusion, our data shows that voiding recovery after radical cervical cancer surgery was most significantly affected by the type of parametrectomy, with a surprisingly not better outcome of type B procedure when compared to nerve-sparing C1 technique. Out of many assessed parameters, only previous pregnancy proved its significance as a confounding risk factor for delayed voiding recovery. On the contrary, our data have disapproved the significance of the surgical approach (open vs minimally invasive), as well as of age, or BMI. Based on our findings the first attempt to remove bladder catheter after type B and C1 radical hysterectomy should be at postoperative day 2 in nulliparous women and day 4 in women after previous pregnancy, while it should be postponed until day 6 after type C2 procedure.

Overall, we have shown that voiding dysfunctions after cervical cancer surgery are only temporary and the vast majority of patients recover within one month after the surgery.

CRediT AUTHOR STATEMENT.

Cibula D, Zapardiel I and Kocian R: conceptualization, methodology, validation, formal analysis, investigation, resources, writing – original draft, visualisation, and final approval of the manuscript; additionally, ***Cibula D:*** supervision, project administration, funding acquisition. ***The rest of authors:*** investigation, resources, writing – review and editing, and final approval. ***All authors*** approved the submission of the study to Gynecologic Oncology.

Acknowledgements

The study was supported by a grant from the Czech Health Research Council, Czech Republic (NV19-03-00023).

Conflict of interest statement

Authors do not have any conflicts of interest.

References

[1] R.L. Siegel, K.D. Miller, A. Jemal, Cancer statistics, 2020, CA Cancer J. Clin. 70 (2020) 7–30, https://doi.org/10.3322/caac.21590.
[2] M. Arbyn, E. Weiderpass, L. Bruni, S. de Sanjose, M. Saraiya, J. Ferlay, et al., Estimates of incidence and mortality of cervical cancer in 2018: a worldwide analysis, Lancet Glob. Health 8 (2020) e191–e203, https://doi.org/10.1016/S2214-109X(19)30482-6.
[3] D. Cibula, R. Potter, F. Planchamp, E. Avall-Lundqvist, D. Fischerova, C. Haie Meder, et al., The European Society of Gynaecological Oncology/European Society for Radiotherapy and Oncology/European Society of Pathology guidelines for the management of patients with cervical cancer, Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology. 127 (2018) 404–416, https://doi.org/10.1016/j.radonc.2018.03.003.
[4] D. Cibula, P. Velechovska, J. Slama, D. Fischerova, I. Pinkavova, D. Pavlista, et al., Late morbidity following nerve-sparing radical hysterectomy, Gynecol. Oncol. 116 (2010) 506–511, https://doi.org/10.1016/j.ygyno.2009.10.061.
[5] Q. Liu, P. Li, Y. Sun, S. Zhang, K. Liu, Effect of laparoscopic nerve-sparing radical hysterectomy on bladder function recovery, Journal of investigative surgery: the official journal of the Academy of Surgical Research. 33 (2020) 381–386, https://doi.org/10.1080/08941939.2018.1502377.
[6] M. Novackova, Z. Pastor, R. Chmel Jr., T. Brtnicky, R. Chmel, Urinary tract morbidity after nerve-sparing radical hysterectomy in women with cervical cancer, Int. Urogynecol. J. 31 (2020) 981–987, https://doi.org/10.1007/s00192-019-04083-9.
[7] D. Zhao, B. Li, Y. Wang, S. Liu, Y. Zhang, G. Yuan, Clinical outcomes in early cervical Cancer patients treated with nerve plane-sparing laparoscopic radical hysterectomy, J. Minim. Invasive Gynecol. 27 (2020) 687–696, https://doi.org/10.1016/j.jmig.2019.04.025.
[8] L. Li, S. Ma, X. Tan, S. Zhong, M. Wu, Surgical, urinary, and survival outcomes of nerve-sparing versus traditional radical hysterectomy: a retrospective cohort study in China, Am. J. Clin. Oncol. 42 (2019) 783–788, https://doi.org/10.1097/coc.0000000000000593.
[9] D. Cibula, J. Dusek, J. Jarkovsky, P. Dundr, D. Querleu, A. van der Zee, et al., A prospective multicenter trial on sentinel lymph node biopsy in patients with early-stage cervical cancer (SENTIX), International journal of gynecological cancer: official journal of the International Gynecological Cancer Society. 29 (2019) 212–215, https://doi.org/10.1136/ijgc-2018-000010.
[10] D. Querleu, D. Cibula, N.R. Abu-Rustum, 2017 update on the Querleu-morrow classification of radical hysterectomy, Ann. Surg. Oncol. 24 (2017) 3406–3412, https://doi.org/10.1245/s10434-017-6031-z.
[11] S. Pecorelli, Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium, International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics. 105 (2009) 103–104, https://doi.org/10.1016/j.ijgo.2009.02.012.
[12] D. Dindo, N. Demartines, P.A. Clavien, Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey, Ann. Surg. 240 (2004) 205–213, https://doi.org/10.1097/01.sla.0000133083.54934.ae.
[13] J. Paek, E. Kang, P.C. Lim, Comparative analysis of genitourinary function after type C1 robotic nerve-sparing radical hysterectomy versus type C2 robotic radical hysterectomy, Surg. Oncol. 30 (2019) 58–62, https://doi.org/10.1016/j.suronc.2019.05.003.
[14] G. Bogani, D. Rossetti, A. Ditto, F. Martinelli, V. Chiappa, C. Leone, et al., Minimally invasive surgery improves short-term outcomes of nerve-sparing radical hysterectomy in patients with cervical cancer: a propensity-matched analysis with open abdominal surgery, J. Gynecol. Oncol. 30 (2019), e27, https://doi.org/10.3802/jgo.2019.30.e27.
[15] W. Yi, A. Pan, J. Li, D. Luo, Q. Huang, Clinical observation on the acupuncture treatment in patients with urinary retention after radical hysterectomy, Chinese Journal of Integrative Medicine. 17 (2011) 860–863, https://doi.org/10.1007/s11655-011-0800-5.
[16] M.A. Zullo, N. Manci, R. Angioli, L. Muzii, P.B. Panici, Vesical dysfunctions after radical hysterectomy for cervical cancer: a critical review, Crit. Rev. Oncol. Hematol. 48 (2003) 287–293, https://doi.org/10.1016/s1040-8428(03)00125-2.
[17] X.Z. Ju, Z.T. Li, H.J. Yang, X.H. Wu, Nerve-sparing radical hysterectomy and radical hysterectomy: a retrospective study, Zhonghua fu chan ke za zhi. 44 (2009) 605–609.
[18] G. Peru Biurrun, E. Gonzalez-Diaz, C. Fernandez Fernandez, Corona A. Fernandez, Prevalence of postpartum voiding dysfunction and related risk factors, Urology. (2020)https://doi.org/10.1016/j.urology.2020.03.061.