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LETTER TO THE EDITOR

Long-term oncologic outcomes of robot-assisted radical cystectomy: update series from a high-volume robotic center beyond 10 years of follow-up

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Abstract

Long-term oncologic data on patients undergoing robot-assisted radical cystectomy (RARC) for non-metastatic bladder cancer (BCa) are limited. The purpose of this study is to describe long-term oncologic outcomes of patients receiving robotic radical cystectomy at a high-volume European Institution. We analyzed data of 107 patients treated with RARC between 2003 and 2012 at a high-volume robotic center. Clinical, pathologic, and survival data at the latest follow-up were collected. Clinical recurrence (CR)-free survival, cancer-specific mortality (CSM)-free survival, and overall survival (OS) were plotted using Kaplan–Meier survival curves. Cox proportional hazard models investigated predictors of CR and CSM. Competing-risk regressions were utilized to depict cumulative incidences of death from BCa and death from other causes after RARC at long term. Pathologic nonorgan-confined BCa was found in 40% of patients, and 7 (7%) patients had positive soft tissue surgical margins. Median (interquartile range [IQR]) number of nodes removed was 11 (6, 14), and 26% of patients had pN + disease. Median (IQR) follow-up for survivors was 123 (117, 149) months. The 12-year CR-free, CSM-free and overall survival were 55% (95% confidence interval [CI] 44%, 65%), 62% (95% CI 50%, 72%), and 34% (95% CI 24%, 44%), respectively. Nodal involvement on final pathology was associated with poor prognosis on multivariable competing risk analysis. The cumulative incidence of non-cancer death exceeded that of death from BCa after approximately ten years after RARC. We provided relevant data on oncologic outcomes of RARC at a high-volume robotic center, with acceptable rates of clinical recurrence and cancer-specific survival at long-term. In patients treated with RARC, the cumulative incidence of death from causes other than BCa is non-negligible, and should be taken into consideration for post-operative follow-up.

Keywords Bladder cancer · Robot-assisted radical cystectomy · Long-term oncologic outcomes · Clinical recurrence · Competing-risk mortality outcomes · Other-cause mortality

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Introduction

Radical cystectomy represents the standard of care for the surgical treatment of patients with muscle-invasive bladder cancer (BCa) and high-risk nonmuscle-invasive bladder cancer [1]. While open radical cystectomy is accepted as the gold standard because its long-term oncological outcomes are well established [2], minimally invasive techniques such as robotic-assisted radical cystectomy (RARC) have been developed. Although this approach might confer substantial advantages in terms of peri-operative morbidity as compared to open surgery [3–5], data on long-term cancer control after RARC are still limited [6], and a common limitation of papers on this topic is small sample size [7]. In fact, a recent systematic review on 87 studies showed that only 33% of studies reported a follow-up longer than three years after surgery [6]. Moreover, the series with the longest follow-up has only 14 patients with more than five years of follow-up [8].

Previous studies evaluating the oncologic efficacy of RARC in patients with bladder cancer reported acceptable results [9–11], and the latest European Association of Urology guidelines recognized that most endpoints, including intermediate-term oncologic outcomes, are not different between open and robotic cystectomy [1]. Still, besides a clear need for series on robotic cystectomy with longer follow-up to evaluate the long-term oncologic safety of this technique, there are other potential criticisms in the literature on RARC available to date. For instance, the evaluation of small highly selected cohorts suggests that results, especially those regarding oncologic endpoints, should be interpreted with caution [8, 9]. On the other hand, the inclusion of patients with heterogeneous characteristics coming from several centers across the world might, in part, preclude the applicability of results reported by multi-institutional investigations [12]. For these reasons, we previously described recurrence patterns and oncologic outcomes of RARC at our tertiary referral center [13]. Now, after almost two decades of experience in robotic radical cystectomy, we aimed at updating our results at longer follow-up to provide more comprehensive data on oncologic outcomes of RARC.

Materials and methods

Patient population

We analyzed data of 113 consecutive patients who underwent robotic radical cystectomy for non-metastatic urothelial BCa at Onze-Lieve-Vrouw Hospital (Aalst, Belgium) from 2003 to 2012. We excluded patients who received salvage surgery ($n=6$), resulting in a final cohort of 107 patients with complete clinical and follow-up data eligible for the analyses.

The surgical technique performed in our center has been previously described [14–17] and consists of ureteral dissection and ligation, retrovesical dissection, development of the rectovesical space, lateral dissection, division of the ovarian pedicles, and dissection of the uterine support (in female), identification and isolation of the bladder pedicles, vaginal dissection (in female), anterior dissection, incision of the endopelvic fascia, incision of the dorsal venous complex and apical dissection (in male), transection of the urethra, and re- construction of the vagina (in female). An anatomically defined extended pelvic lymph node dissection that included common, external, and internal iliac, presacral, and obturator nodes was performed according to the clinical judgment of the treating physician on the basis of disease characteristics and comorbidity status [18]. All surgeries were performed by two high-volume surgeons. Neoadjuvant chemotherapy was selectively adopted according to the treating physicians' preference, and consisted of at least three cycles of Cisplatin plus Gemcitabine.

Clinical stage was based on the histological report of the transurethral resection specimen, chest X-rays, and abdominal CT. Concomitant upper urinary tract urothelial carcinoma was evaluated by excretory urography or abdominal CT. Bone scans and brain CT were performed when suggested by signs and symptoms.

Variables definition

Available data consisted of variables related to:

(i) pre-operative age, Body Mass Index, gender, ASA score (2 vs. 3 vs. 4), Charlson Comorbidity Index [19], neoadjuvant therapies, TUR histology (urothelial vs. squamous vs. other).

(ii) *intra- and peri-operative* type of urinary diversion (ileal conduit vs. neobladder), approach to urinary diversion (intra- vs. extra-corporeal), pelvic lymphadenectomy (performed vs. not performed).

(iii) *post-operative* pathologic T stage (pT0 vs. pTa/pT1/pTis vs. pT2 vs. pT3-4), pathologic N stage (pN0 vs. pN1 vs. pN2), histology type, positive soft tissue surgical margins, number of lymph nodes removed, number of positive nodes (0 vs. 1 vs. 2 vs. ≥ 3), incidental prostate cancer, stage of incidental prostate cancer (T1 vs. T2 vs. T3), ISUP group of incidental prostate cancer (1 vs. ≥ 2), post-operative complications according to Clavien–Dindo classification [20, 21] (0 vs. 1–2 vs. ≥ 3), and additional therapies after RARC.

Follow-up and outcome parameters

Patients were evaluated 2 months after discharge and then at least every 4 months for the first year, semi-annually for the second year, and annually thereafter [1]. Follow-up visits consisted of a physical examination, serum chemistry evaluation, and diagnostic imaging. Computed tomography of the chest, abdomen and pelvis was performed at least annually or when clinically indicated. Additional radiographic evaluations were performed at the discretion of the treating physician.

Outcome definition

Our primary goal was to describe long-term oncologic outcomes after robotic radical cystectomy, namely cancer-specific mortality (CSM)-free survival and clinical recurrence (CR)-free survival after RARC. CR-free survival was defined as time from surgery to local and/or metastatic recurrence based on histologic and/or radiologic evidence. Local recurrence was defined as evidence of disease in the true pelvis. Systemic recurrence was defined as evidence of metastatic disease outside the pelvis. Vital status and cause of death were identified from death certificates and physician correspondence.

Statistical analyses

Our statistical analyses involved several steps. First, the probability of freedom from each outcome of interest and corresponding 95% confidence interval were calculated using Kaplan–Meier analyses. For non-mortality outcomes (i.e., CR-free survival), patients were censored on the date of last evidence of freedom from CR. Second, multivariable competing risk regression models investigated predictors of clinical recurrence and cancer death after RARC with death from other causes as the competing event. The adjustment for case-mix included the following variables that were selected a priori: age, pathologic stage (pT0 vs. pT1–pT2 vs. pT3–pT4), nodal stage (pN*x* vs. pN0 vs. pN1–2), positive surgical margins (no vs. yes), and the administration of adjuvant treatments (no vs. yes). Since data from different surgeons are correlated[22], we incorporated surgeon clustering in our analysis using the *cluster* option in Stata statistical software. Third, the estimated cumulative incidence of cancer death was derived from the competing risk regression model with death from other causes as competing event. In separate analyses, we calculated the cumulative incidence of death from other causes with cancer death as competing event. Finally, cumulative incidences of cancer death and death from other causes were then depicted, along with the incidence of the composite outcome of all-cause mortality.

Table 1 Patients demographics. All numbers are medians (interquartile range) and frequencies (proportions)

	Overall population ($n = 107$; 100%)
Age at RARC, years	70 (60, 76)
Body Mass Index	26 (23, 29)
Gender	
Female	20 (19%)
Male	87 (81%)
ASA score	
2	55 (51%)
3	51 (48%)
4	1 (1%)
Age-adjusted CCI	
0–1	25 (23%)
2–4	54 (51%)
> 4	28 (26%)
Neoadjuvant therapies	
None	88 (82%)
Chemotherapy	18 (17%)
Radiotherapy	1 (1%)
TUR Histology	
Urothelial	101 (94%)
Squamous	3 (3%)
Other	3 (3%)

RARC, robot-assisted radical cystectomy; *CCI*, Charlson Comorbidity Index

All statistical analyses were performed using Stata version 14.0 (StataCorp LP, College Station, TX, USA) and R statistical software v.3.5.1.

Results

Descriptive characteristics of our cohort are described in Table 1. Median (interquartile range [IQR]) age at RARC was 70 (60, 76) years, and 87 (81%) patients were males. Neoadjuvant chemotherapy was administered in 18 (17%) patients.

Overall, 26% of urinary diversions was performed with an intra-corporeal approach ($n = 28$), and 89 (83%) patients received an ileal conduit (Table 2). A total of 76 (71%) patients received a pelvic lymphadenectomy, with a median (IQR) number of lymph nodes removed of 11 (6, 14). After 30 days from RARC, 54 (50%) patients have experienced at least one complication. Among them, 13 (24%) patients had a Clavien–Dindo ≥ 3 complication.

Table 2 Intra- and post-operative characteristics

Overall population ($n=107$; 100%)	
Diversion type	
Ileal conduit	89 (83%)
Neobladder	18 (17%)
Diversion–Approach	
Extra-corporeal	79 (74%)
Intra-corporeal	28 (26%)
Pelvic LND	
Not performed	31 (29%)
Performed	76 (71%)
pT stage	
pT0	13 (12%)
pTa/T1/Tis	26 (24%)
pT2	25 (23%)
pT3-T4	43 (41%)
Number of nodes removed	11 (6, 14)
pN stage	
pN0	56 (74%)
pN1	12 (15%)
pN2	8 (11%)
Histology type	
Negative	13 (12%)
Urothelial	87 (81%)
Squamous	5 (5%)
Adenocarcinoma	1 (1%)
Unknown	1 (1%)
Positive soft tissue surgical margins	
No	100 (93%)
Yes	7 (7%)
Incidental PCa	
No	53 (61%)
Yes	34 (39%)
Incidental PCa stage	
T1–T2	32 (94%)
T3–T4	2 (6%)
Incidental PCa ISUP group	
1	31 (91%)
2+	3 (9%)
30-day complications	
No	53 (50%)
Yes	54 (50%)
Clavien–Dindo grade of 30-day complications	
1–2	41 (76%)
3+	13 (24%)
Adjuvant treatments	
None	95 (89%)
Radiotherapy	12 (11%)

All numbers are medians (interquartile range) and frequencies (proportions)

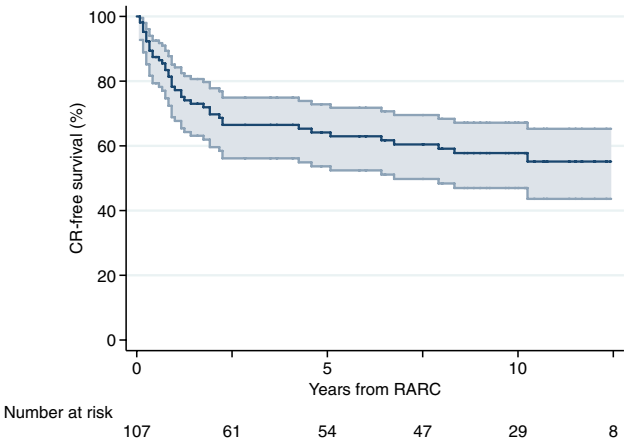

Fig. 1 Kaplan–Meier curves depicting clinical recurrence-free survival after robotic radical cystectomy

Clinical recurrence-free survival

A total of 41 patients developed CR, and recurrences were multiple in 61% of cases ($n=25$). Most common locations of recurrences were in the liver ($n=12$, 29%), lung ($n=11$, 27%), bone ($n=10$, 24%), lymph nodes ($n=7$, 17%), pelvis ($n=1$, 2%), and other location ($n=12$, 29%; including one patient with port-site metastasis and three patients with peritoneal carcinosis). Median (IQR) follow-up for patients who did not experience clinical recurrence was 117 (49, 129) months. The 10- and 12-year probabilities of freedom from clinical recurrence were 58% (95% confidence interval [CI] 47%, 67%) and 55% (95% CI 44%, 65%), respectively (Fig. 1). Most patients recurred within 3 years after surgery. However, if a patient did not recur within the first 3 years, the probability of remaining free from CR at 12 years was 83% (95% CI 68%, 91%; Table 3).

Cancer-specific survival

Overall, 68 patients died during follow-up, 34 of them from bladder cancer. The median follow-up for survivors was 123 (IQR: 117, 149) months. The predicted 10- and 12-year cancer-specific survival was 65% (95% CI 54%, 74%) and 62% (95% CI 50%, 72%), respectively (Fig. 2). The predicted 10- and 12-year overall survival was 41% (95% CI 32%, 51%) and 34% (95% CI 24%, 44%), respectively (Fig. 3). Median (95% CI) time to death from all causes after RARC was 86 (44, 125) months.

Predictors of clinical recurrence and cancer death after robotic radical cystectomy

On multivariable competing risk regression analyses, the presence of nodal involvement at final pathology was

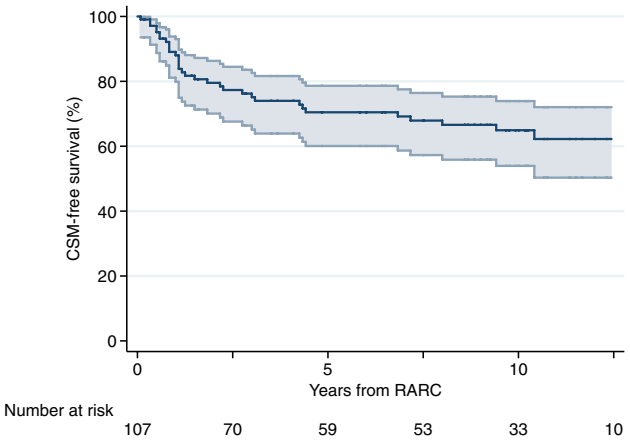

Fig. 2 Kaplan–Meier curves depicting cancer-specific mortality-free survival after robotic radical cystectomy

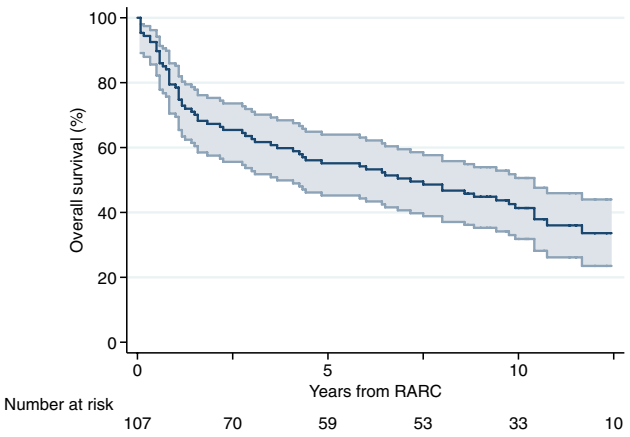

Fig. 3 Kaplan–Meier curves depicting overall survival after robotic radical cystectomy

associated with higher probability of clinical recurrence (HR 1.82; 95% CI 1.06, 3.13, $p = 0.030$) and CSM after RARC (HR 1.70, 95% CI 1.30, 2.22; $p < 0.0001$; Table 4). The 10-year cumulative incidences of death from BCa and from other causes after RARC were 30% (95% CI 22%, 39%) and 29% (95%: 20%, 37%; Supplementary Fig. 1), respectively. The 12-year cumulative incidences of cancer death and other-cause mortality were 32% (95%: 23%, 41%), and 35% (95%: 24%, 45%), respectively. Cumulative incidences of cancer and non-cancer death are described in Fig. 4, along with the incidence of the composite outcome of all-cause mortality. As can be seen, the cumulative incidence of non-cancer death exceeded that of death from bladder cancer after approximately ten years from surgery.

Discussion

In this study, we described the long-term outcomes of patients treated with robotic radical cystectomy for bladder cancer, with the longest follow-up available in urologic literature. Moreover, assessing cause-specific death rates long-term after RARC, we found that the risk of death from causes other than BCa after RARC overcame the risk of cancer death after approximately ten years from surgery.

Our findings provide relevant insights into the natural history of bladder cancer following RARC and, thus, have relevant implications for clinical practice. To date, there are only few studies describing long-term outcomes after RARC, often limited by the limited follow-up or small sample size. For example, oncologic outcomes of CORAL trial were recently published, but survival rates after RARC should be interpreted with caution as only 20 patients were included in the robotic arm [9]. A larger

Table 3 Number of patients who experienced clinical recurrence after robotic cystectomy at each timepoint of interest

Years after RARC		Number of clinical recurrences[a]
1		23 (56%)
3		33 (81%)
5		35 (85%)
Conditioning year[b]	12-year conditional probability of freedom from each endpoint of interest	
	Clinical recurrence	Cancer-specific mortality
1	70% (57%, 81%)	70% (57%, 80%)
3	83% (68%, 91%)	82% (67%, 90%)
5	86% (70%, 94%)	88% (73%, 95%)

[a]All percentages are calculated over the total number of recurrences ($n = 41$)

[b]Conditional freedom from each endpoint of interest at 1, 3, and 5 years of follow-up after robotic cystectomy. 95% confidence interval is reported in parentheses

RARC, robot-assisted radical cystectomy

Table 4 Multivariable competing risk regressions to predict (a) clinical recurrence and (b) cancer-specific mortality for 107 patients treated with robotic radical cystectomy

	Subhazard Ratio	95% Confidence Interval	p-value
(a) Clinical recurrence			
Age	1	0.98, 1.02	0.9
pT stage			
pT0	Ref.	–	
pT1–2	0.9	0.26, 3.10	0.9
pT3–4	1.84	0.47, 7.13	0.4
pN stage			
pN0	Ref.	–	
pN1–2	1.82	1.06, 3.13	0.03
pN*x*	1.28	1.05, 1.56	0.013
Positive surgical margins			
No	Ref.	–	
Yes	2.62	0.72, 9.58	0.14
Adjuvant treatments			
No	Ref.	–	
Yes	1.39	0.72, 2.68	0.3
(b) Cancer-specific mortality			
Age	1.01	0.99, 1.04	0.3
pT stage			
pT0	Ref.	–	
pT1–2	1.19	0.30, 4.63	0.8
pT3–4	2.35	0.56, 9.96	0.2
pN stage			
pN0	Ref.	–	
pN1–2	1.7	1.30, 2.22	< 0.0001
pN*x*	1.11	0.94, 1.32	0.2
Positive surgical margins			
No	Ref.	–	
Yes	2.66	0.63, 11.11	0.2
Adjuvant treatments			
No	Ref.	–	
Yes	1.49	1.03, 2.17	0.034

Death from other causes was used as competing event in both models

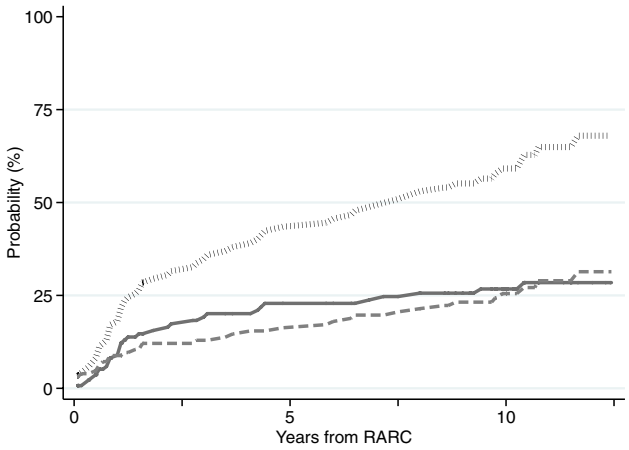

Fig. 4 Cumulative incidence functions of death from bladder cancer (solid line), death from other causes (dashed), and all-cause mortality (dotted) after robotic radical cystectomy

population of 702 patients was analyzed by the International Robotic Cystectomy Consortium, with a 5-year cancer-specific survival of 75% [12] that is consistent with our data, and other prior investigators described similar rates of clinical recurrence [7] and cancer death [23]. However, considering the much shorter follow-up of these studies, definitive conclusions on long-term survival rates after RARC could not be drawn. In this regard, we here provided the longest oncologic follow-up available on RARC, which included a median follow-up of > 10 years for survivors. Therefore, the large population included in our study and the adequate length of follow-up make us confident that our results provide solid evidence on long-term outcomes of RARC.

Our data entail a second relevant point for the management of patients treated with robotic radical cystectomy for bladder cancer, providing relevant data on the relative contribution of cancer-specific and other-cause mortality to overall survival after RARC. Prior series have tried to address the same topic. For instance, using the Surveillance, Epidemiology, and End Results (SEER) registries, Lughezzani et al. described survival outcomes of 11,260 patients treated with radical cystectomy between 1988 and 2006. They found cancer-specific mortality to be the main cause of mortality regardless of disease stage and age, with a CSM-free survival ranging from 18 to 67% five years after surgery [24], a finding that was confirmed by a subsequent investigations [25]. However, population-based registries may suffer from inherent limitations that may include a lack of data on indications for neoadjuvant and/or adjuvant therapies, variables that are not included in the SEER database. Moreover, the SEER database only includes North American patients and as such, these findings are only may not be generalizable to other parts of the world or to single-center series. Moschini et al. described the first single-center experience including 1222 patients treated with radical cystectomy between 1990 and 2012 at an high-volume European center [26]. After a median follow-up of 6 years, they showed a 10-year cumulative incidence of cancer-specific and other-cause mortality of 52% and 23%, respectively. Other series described similar survival rates [8], but were somewhat limited but their design (i.e., population-based registries [24, 25]), limited follow-up after surgery [26] or small sample size [8]. By contrast, we here provided the largest series on RARC with mature follow-up, including detailed analyses of cause-specific

mortality rates. If replicated, our findings may have important implications for follow-up after robotic radical cystectomy, as they could suggest that comorbidities and performance status may be important contributors to overall mortality after RARC. In this regard, a recent systematic review assessed the risk assessment tools for pre-operative comorbidities in patients with bladder cancer, and the inclusion of comorbidity risk assessment tools both in pre- and post-operative counseling [27]. Also, our data on the timing of recurrences may help physicians to optimize follow-up after surgery, allowing for a schedule that may vary over time based on individual risk, especially after five years from radical cystectomy.

Our study is not devoid of limitations. First, the retrospective study may be subject to selection bias and uncontrolled confounding factors, even with the use of competing risks regression models. For instance, while there is evidence that positive surgical margins affect oncologic outcomes after RARC [28], we did not find evidence of such an association in our cohort. Moreover, our data derive from highly experienced surgeons with high annual caseload and as such, the generalizability of our findings may be limited to centers with similar caseload and experience. We also have to acknowledge that, given the historical nature of our cohort, only few patients received neoadjuvant treatments and as such, our findings may be different in a more contemporary population. In addition, the number of lymph nodes removed in our cohort was lower than that of other series, and some patients did not receive a lymphadenectomy. Since there is evidence that a more extended pelvic lymph node dissection is associated with better survival after RARC [29], it may be postulated that this selection bias might be responsible for our results. However, we found relatively better cancer-specific survival as compared to other prior series. For this reason, if we assume that unmeasured confounders are correlated with measured covariates, then any selection bias in the study would operate in the opposite direction to our findings and as such, we are confident that our findings were not related to selection bias. Despite these limitations, our study represents the largest and only series on robot-assisted radical cystectomy with mature follow-up after surgery.

Conclusions

We described long-term oncologic outcomes of robotic radical cystectomy at a high-volume center, with the longest available follow-up. RARC provides acceptable rates of cancer-specific survival at long-term follow-up. At the same time, we found a non-negligible risk of death from other causes in patients treated with RARC, which overcame the risk of cancer death approximately ten years after surgery.

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Declarations

Competing interests The authors declare no competing interests.

Conflict of interest The authors declare no conflicts of interest in preparing this article.

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