



# Are bladder cancer patients set at risk by minimally invasive approaches to radical cystectomy?

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Comment on: Albisinni S, Fossion L, Oderda M, *et al.* Critical Analysis of Early Recurrence after Laparoscopic Radical Cystectomy in a Large Cohort by the ESUT. *J Urol* 2016;195:1710-7.

**Abstract:** Radical cystectomy is the mainstay of surgical treatment in muscle invasive bladder cancer (BC). With the advent of minimally invasive surgical approaches during the last decades an increasing number of patients has been treated by minimally invasive surgical approaches, namely conventional laparoscopic (LRC) and robotic assisted radical cystectomy (RARC). Despite comparable results to open radical cystectomy regarding perioperative outcomes, oncological surrogate parameters (margin status, lymph node yield) and early oncological outcomes these novel techniques are under debate. A controversial issue beyond cost effectiveness and short term clinical benefit is especially oncological safety. In this context a recent study on LRC report on early recurrences and unexpected patterns of metastases in bladder cancer patients with favourable tumor characteristics. This perspective article will detail and discuss the relevance of the findings of this controversial article regarding further advancement of minimally invasive approaches in radical cystectomy.

**Keywords:** Bladder cancer; robotic radical cystectomy; laparoscopic radical cystectomy; radical cystectomy

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## Introduction

With about 480,000 newly diagnosed cases every year, bladder cancer (BC) is the seventh most common cancer worldwide (1). Two thirds of patients present at the clinic with non-muscle invasive disease (NMIBC) exhibiting a more or less unproblematic clinical course (5-year survival >95%, metastatic disease very rare). In contrast, patients with muscle-invasive disease (MIBC) may suffer from rapid local progression and distant metastasis and have a poor prognosis (5-year survival 50% or less).

Treatment of choice in non-metastatic MIBC is radical cystectomy including bilateral pelvic lymphadenectomy (RC) (2-5). However, even with RC, long-term disease free survival is below 65% in this patient group (2,6).

As MIBC usually recurs after RC presenting distant metastases, suggesting the presence of occult metastases (micrometastases) already at the time of extirpative treatment in a substantive number of patients, platin-based perioperative chemotherapy, either in neoadjuvant (neoadjuvant chemotherapy, NAC) or adjuvant (adjuvant chemotherapy, AC, USA) intention, is recommended in a multimodal curative approach. However, both NAC and AC do not improve oncological outcome sufficiently (<10% improvement in 5-year overall survival) (7,8). Once distant metastases are present, BC is incurable and despite aggressive platin-based chemotherapeutic treatment, long-term remissions are rarely observed and survival commonly does not exceed 2 years (9,10).

Traditionally, RC has been performed by an open surgical approach, first described by Marshall and Withmore in the midst of the last century (ORC) (11). Apart from surgical modifications of the technique enabling nerve-sparing which may conserve sexual function and, in case of orthotopic bladder substitutes, continence (12), the most important improvement regarding patient outcome has been the amelioration of perioperative morbidity and mortality due to advances in multidisciplinary perioperative patient care (13).

With the advent of minimally invasive surgical approaches during the last decades these novel techniques have also been used for RC and standardized protocols for laparoscopic radical cystectomies (LRC) and robot-assisted radical cystectomies (RARC) have been published (14,15). Regarding short-term perioperative outcomes, non-inferiority of both minimally-invasive approaches compared to ORC have been shown in a number of retrospective and prospective analyses. Also regarding general oncological outcome, first data point towards comparable results of LRC/RARC and ORC (16-19).

However, a recent publications raised concerns about the safety of LRC in patients suffering from MIBC, especially regarding early recurrences in patients with favourable stage II disease.

This perspective article will detail and discuss the relevance of the findings of this controversial article regarding further advancement of minimally invasive approaches in radical cystectomy.

### **Unexpected early recurrences following laparoscopic radical cystectomy**

In their retrospective study Albisinni *et al.* from the European Association of Urology, Section of Uro-Technology (ESUT) analysed 627 patients who underwent LRC and whose data have been included in a prospective multicentric database. Median follow-up of the study population was 46 months. Recurrences were observed in 31% of patients (11% local recurrences, 89% distant recurrences).

A special focus of this study was the analysis of patients with “favourable pathological characteristics” ( $\leq$ pT2 N0 R0). In this cohort, 27/311 (8.7%) patients had recurrent disease within the first 2 years after LRC. In one of these patients, surgical negligence (ruptured endobag) was observed. Following the authors, most these patients had

“progression to high tumor volume metastatic disease” and in some patients “unusual metastatic landing sites” were reported. In a multivariate analysis, early progression was dependent on tumor stage (more frequent in pT2 than in pT0-1 patients).

The authors conclude that their findings “raise some doubts about the safety of the laparoscopic approach”.

### **Discussion**

While the authors should be commended for the objective and straightforward analysis of this large patient cohort (especially regarding the detailed information on the patients of interest), in my opinion their findings do not raise doubts but do rather underline non-inferiority of minimally invasive approaches to RC regarding oncological safety.

General oncological outcome of the total patient cohort [recurrence free survival (RFS) 69% after 46 months] is comparable to data of former large ORC cohorts. For example, in the Hautmann series, recurrence free survival after 48 months has been reported with 70% (2). Also other large ORC series report comparable outcome data (5,20). Distribution of recurrences (local 11%, distant 89%) is in line with the data of the ORC series as well and does neither raise concerns about a negative impact of LRC on oncological safety. Also oncological surrogate parameters (lymph node yield, margin status) are comparable to data reported on ORC (21). The question on oncological outcome following LRC compared to ORC has also been stressed by a number of recent meta analyses, a randomised-controlled trial and several retrospective comparative analyses (22-27). In summary, despite limited follow up, profound differences comparing LRC and ORC have not yet been observed.

Focussing on the concurring minimally invasive approach, RARC, recent investigation support non-inferiority of oncological safety compared to ORC as well. For example, in a retrospective analysis, Nguyen and co-workers from the Weill Cornell Medical College compared two consecutive cohorts of patients undergoing either open (ORC, n=120) or robot-assisted radical cystectomy (RARC, n=263) at a single academic institution regarding their oncological outcome. Median follow-up of the ORC and RARC cohort was 30 and 23 months. Recurrence free survival did not differ substantially and was 23% in the

ORC and 18% in the RARC cohort after 2 years (which mirrors the data presented by Albisinni in LRC patients). Local (ORC: 23%, RARC: 18%) and distant recurrence rate (ORC: 36%, RARC: 29%) were similar in ORC and RARC patients as well. Lymph node yield and margin status was also comparable between both groups. In an adjusted multivariable analysis, RARC could not be delineated as a predictor of recurrence (28). Comparable results have also been reported, despite known limitations regarding follow-up, by further retrospective comparative analyses and meta-analyses (19,29-35).

Regarding early oncological failures in  $\leq$  pT2 N0 R0 patients, results of the ESUT analysis should not be misinterpreted as well. Though recurrence in patients with such “favourable pathologic characteristics” which, from the urologic surgeon’s view, should be “cured” by RC, are not really unexpected. In the large ORC series, RFS after 24 months has been reported 85-95% in  $\leq$ pT2 N0 R0 patients (2,5,20). Especially in pT2b patients, expected 2-year PFS may even be much worse (36). Accordingly, a recurrence of 8.7% after two years of follow-up in these patients is rather not unexpected but mirrors reality in patients suffering from muscle-invasive bladder cancer quite well.

Interestingly, Albisinni *et al.* report on unexpected metastatic sites (scapula, corpora cavernosa and axillary lymph nodes) in recurrent patients. According data have also been reported by the Nguyen *et al.* from Weill Cornell Medical College only recently (28). In this study, differences in the pattern of distant recurrences comparing ORC and RARC were observed as extrapelvic lymphatic and peritoneal metastases were more frequently in the RARC group (23 *vs.* 15%, 21% *vs.* 8%). However, in a follow-up study on 310 RARC patients, Nguyen found that rather tumor biology is impacting recurrence patterns than surgical factors.

## Conclusions

In summary, current knowledge on minimally invasive approaches to radical cystectomy like LRC or RARC does not suggest any additional risk regarding oncological outcome of bladder cancer patients. However, given the lack of prospective comparative data and mature long-term follow-up data, uro-oncological surgeons should remain vigilant and assess their patient outcomes precisely and constantly.

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