



The current role of pentafecta in the reporting of radical cystectomy outcomes: a scoping review

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Background: Pentafecta has recently been validated for reporting radical cystectomy (RC) outcomes in open, laparoscopic and robotic series. We aim in this review to explore the current role of pentafecta in the reporting of RC outcomes.

Methods: A comprehensive literature search was performed in the PubMed database to identify relevant articles. The pentafecta achievement (PA) was defined originally as negative soft tissue surgical margin (NSTSM), lymph node (LN) dissection (LND) with removal of ≥ 16 LNs, absence of 90-days grade ≥ 3 Clavien-Dindo (CD) complications, a time interval of less than 3 months between the last transurethral resection of bladder tumor (TURBT) with evidence of muscle invasive bladder cancer (MIBC) and RC, and absence of local pelvic recurrence within 1 year. The definition was later modified and the last two criteria were replaced by absence of urinary diversion (UD) related complications and any clinical recurrence at one year.

Results: Twelve studies with 4,946 patients were enrolled in the present review. All the studies were retrospective except one recently published randomized study comparing open and robotic-assisted RC. Pentafecta was totally achieved in 34% and main causes of missing pentafecta were the number of resected LNs and 90-days major complications. Type of UD, increasing age, advanced tumor stage, and decreasing surgical experience were the factors most commonly associated with a lower likelihood of PA. A positive correlation was seen between PA and long-term oncological outcome and quality of life. The main limitations in the present studies are their retrospective nature, relatively small sample size, and short median follow-up, most of which was less than 3 years.

Conclusions: The new pentafecta definition provides a comprehensive tool for reporting RC outcomes by including measures of postoperative morbidity, functional outcomes and local cancer control. Pentafecta include standards that could be useful for improving surgical quality, surgical education and comparing different techniques. However, pentafecta is not yet suitable for perioperative risk stratification and patient counseling.

Keywords: Bladder cancer; radical cystectomy (RC); urinary diversion (UD); trifecta; pentafecta

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Introduction

Radical cystectomy (RC) is one of the most critical urological procedures with up to 35% early postoperative major complications and up to 7% perioperative mortality risk (1-3). Moreover, a considerable number of patients develop complications related to urinary diversion (UD) many years after surgery (4,5). Surgical quality has a direct impact on early postoperative complications and long-term functional outcome. In addition, adequate RC and lymph node dissection (LND) with en bloc tumor removal determine the oncological outcomes (6-8). Standardized reporting of such complex outcomes is necessary to accurately define predictors of outcome and guide surgical training, especially after the widespread use of robotic-assisted surgery and the need to evaluate and improve the surgical quality of the new technology.

Trifecta and pentafecta are terms introduced in the last two decades to describe the outcome of partial nephrectomy

(PN) and radical prostatectomy (RP). Achieving trifecta and pentafecta requires optimal cancer control, perioperative and functional outcome, e.g., continence and potency in RP and renal function in PN without serious surgical complications (9-11). Aziz *et al.* first proposed the concept of pentafecta in RC in 2015, using five standards based on expert opinions from the Prospective Multicenter Radical Cystectomy series (PROMETRIC) group (12). Pentafecta includes achievement of: (I) a negative soft tissue surgical margin (NSTSM); (II) LND with collection of ≥ 16 lymph nodes (LNs); (III) absence of 90-days grade ≥ 3 Clavien-Dindo (CD) complications; (IV) a time interval of less than 3 months between the last transurethral resection of bladder tumor (TURBT) with evidence of muscle invasive bladder cancer (MIBC) and RC; and (V) absence of local pelvic recurrence within 1 year. In 2020, the University of Southern California (USC) group modified the definition to be applied for both MIBC and Non-MIBC (13). They replaced the interval between the last TURBT and RC with the absence of long-term sequelae related to UD ≤ 12 months, and also changed the last measure to take into account the absence of clinical recurrence and not only local pelvic recurrence. The pentafecta was validated in further studies including different techniques of RC. In this review we summarize the available evidence related to this new concept in reporting the outcome after RC (12-23). We present this article in accordance with the PRISMA-ScR reporting checklist (available at <https://tau.amegroups.com/article/view/10.21037/tau-23-593/rc>).

Methods

Search strategy

A comprehensive search of the PubMed database was conducted to find original studies that addressed the use of pentafecta in describing RC outcomes. Aziz *et al.* first introduced the concept of trifecta and pentafecta after RC in 2015 (12). Accordingly, the computer search was performed between May 2015 and August 2023 to find relevant published studies. The search was performed using different combinations of the following keywords: ‘cancer, bladder’, ‘radical cystectomy’ and pentafecta. In addition, a second search was conducted using only the term “pentafecta” to ensure a comprehensive review. The titles were screened to identify the relevant articles. Results were deduplicated using EndNote program. For the relevant titles, the abstracts then the articles were inspected to be

Highlight box

Key findings

- Pentafecta include standards that could be useful for improving surgical quality, surgical education and comparing different techniques. However, the current concept is not yet suitable for perioperative risk stratification and patient counseling.

What is known and what is new?

- The new pentafecta definition provides a comprehensive tool for reporting radical cystectomy outcomes by including measures of postoperative morbidity, functional outcomes and local cancer control. The current definition was validated and showed a positive correlation with long-term oncologic outcome and quality of life.
- In the current review, we found many limitations regarding the available studies and pentafecta components. The observed overlaps between the different pentafecta components should be further explored and it might be necessary to combine some measures or even replace some of them. Some measures could still be added in subgroups of patients, e.g., continence in orthotopic bladder substitution or use of nerve-sparing techniques and minimally invasive procedures in appropriate patients, as these measures correlate strongly with patients’ quality of life.

What is the implication, and what should change now?

- Pentafecta could be used to improve individual surgical quality and to evaluate new techniques or treatment regimens compared to the known standards. There is still a need for prospective, large and long-term follow-up studies. In addition, further discussion and modifications to the pentafecta components should be carried out to reduce the overlap between the components with possibility of including other measures.

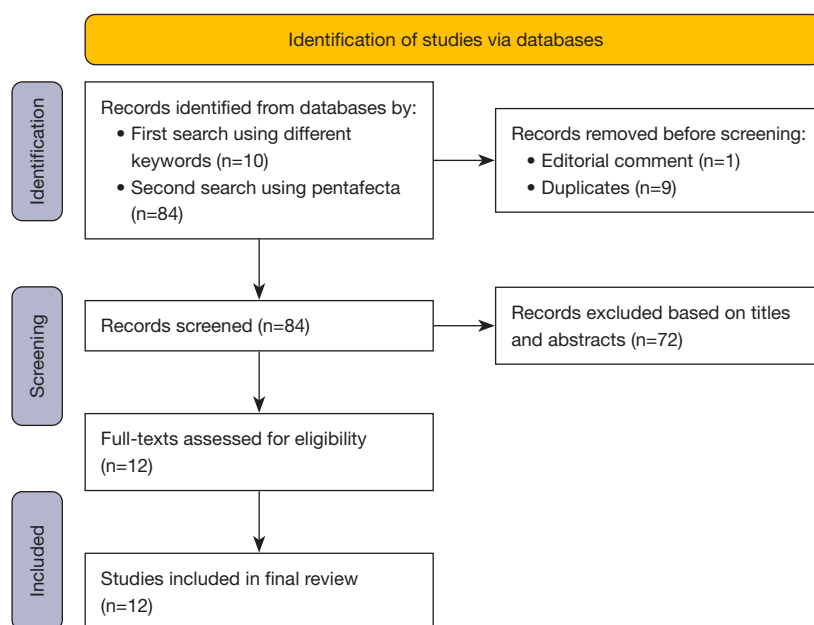


Figure 1 PRISMA flow diagram.

included. The list of references in the finally selected papers were also evaluated for potentially relevant studies. Only papers that were written in English were included.

Data extraction

The following information were extracted from each eligible study: publication details (title, first author and publication year), number of the patients, operative parameters (approach, and type of diversion), pathological and nodal staging, rates of pentafecta achievement (PA) and its criteria, predictors of PA and the correlation with oncological outcome or quality of life.

Results

The PRISMA flowchart is shown in *Figure 1*. The first search using the previous mentioned keywords phrases yielded ten articles in total. The abstracts of these studies were reviewed for possible inclusion, which results in exclusion of one editorial comment and nine original articles to be included in our review. The search with the term of pentafecta alone resulted in 84 articles, from which 3 more articles were added to the current review. Finally, 12 were included in the present paper.

Table 1 provides detailed information on the study

characteristics and their results. Of 12 studies, four were based on a multi-institutional database (12,15,16,19), while eight were single center-studies (13,14,17,18,20-23). The included studies were retrospective except for one randomized study comparing open RC (ORC) and robotic-assisted RC (RARC) regarding PA. Of the 11 observational studies articles, 3 were ORC series, 6 were RARC, 1 was laparoscopic RC (LRC) and 1 contained both ORC and LRC. The PROMETRICS and USC definitions of pentafecta were externally validated by Brassetti *et al.* in 2019 (14). Thereafter, the PROMETRICS definition was used in one other study, but the authors replaced 90 days reported postoperative complications by only 30 days and one-year local pelvic recurrence by any clinical recurrence (22). On the other hand, the USC pentafecta was validated in 8 articles, but some changes in the definition were seen. A threshold of 10 dissected LNs instead of 16 was used in one study (19). While in 2 series, ureteroenteric stricture (UES) was used as the only element to describe the one-year UD associated complications, and one of them used complications reported at 30 days instead of 90 days (15,21).

The sample size of the studies ranged from 104 to 1,624 and included a total of 4,946 patients. In the 12 studies, the rate PA ranged widely from 15% and 60%. Overall, pentafecta was achieved in 1,627 (34.6%) and 1,606 (32.5%)

Table 1 Studies discussed pentapecta

Authors, year	Patient No.	Technique	UD	Pathological staging	Nodal positivity	PA	Predictors of missing pentapecta	Median follow-up (mo.)	Prognostic significance of pentapecta
Aziz <i>et al.</i> 2015 (12)	334	ORC	NR	NR	NR	29% (PRO.) • LN ≥16: NR • Negative STSM: NR • Absence of 90 days major complications: NR • Time between TURBT and cystectomy ≤3 mo.: NR • Absence of local recurrence ≤12 mo.: NR	Increasing age	25	NR
Cacciamani <i>et al.</i> 2020 (13)	270	RARC + ICUD	IC: 65.6%; OBS: 34.4%	OC: 84.8%; LA: 15.2%	9.6%	53.3% (USC) • LN ≥16: 93% • Negative STSM: 98.9% • Absence of 90 days major complications: 76.6% • Absence of 1-year UD-related sequelae: 81.5% • Absence of clinical recurrence ≤12 mo.: 92.2%	• Increasing age • UD (OBS vs. IC) • pN+ disease	22.3	Pentapecta correlated with OS (P<0.001)
Braschetti <i>et al.</i> 2019 (14)	137	RARC + ICUD	OBS	OC: 63%; LA: 37%	NR	62% (USC)/47% (PRO.) • LN ≥16: 93%/93% • Negative STSM: 97%/97% • Absence of 90 days major complication: 86%/86% • Absence of 1-year UD-related sequelae: 87%/– • Absence of clinical recurrence ≤12 months: 93%/93% • Time between TURBT and cystectomy ≤3 months: –/65%	NR	NR	Pentapecta not correlated with 3-years OS
Oh <i>et al.</i> 2021 (15)	730	RARC + ICUD or ECUD	IC: 53.6%; OBS: 37.7%; UC: 3.6%	OC: 62.3%; LA: 37.7%	21.6%	28.5% (USC) • LN ≥16: NR • Negative STSM: 97% • Absence of 90 days major complications: 78.9% • Absence UES ≤12 mo.: 91.1% • Absence of clinical recurrence ≤12 mo.: NR	NR	19.8	PA vs. non-PA (5-year OS 84.4% vs. 76.2%; 10-year OS 70.4% vs. 58.1%; P=0.016) PA vs. non-PA (5-year CSS 92.1% vs. 85.9%; 10-year CSS 87.8% vs. 70.0%; P=0.036)
Baron <i>et al.</i> 2021 (16)	104	RARC + ICUD	IC: 27.8%; OBS: 72.2%	OC: 78.8%; LA: 21.2%	14.5%	39.4% (USC) • LN ≥16: 56% • Negative STSM: 96% • Absence of 90 days major complications: 85% • Absence of 1-year UD-related sequelae: 81% • Absence of clinical recurrence ≤12 mo.: 91%	• Increasing age • Decreasing surgeon experience	18	Pentapecta not correlated with OS (5 years OS 73.8% vs. 93.2%; P=0.78)

Table 1 (continued)

Table 1 (continued)

Authors, year	Patient No.	Technique	UD	Pathological staging	Nodal positivity	PA	Predictors of missing pentafecta	Median follow-up (mo.)	Prognostic significance of pentafecta
Laymon <i>et al.</i> 2022 (17)	1,624	ORC	IC: 34%; OBS: 66%	OC: 55.7%; LA: 44.3%	23.5%	33.6% (USC) <ul style="list-style-type: none"> • LN ≥16: 50.5% • Negative STSM: 98.8% • Absence of 90 days major complications: 80.2% • Absence of 1-year UD-related sequelae: 95.6% • Absence of clinical recurrence ≤12 mo.: 88.7% 	(Univariate) <ul style="list-style-type: none"> • Higher ASA score • Body mass index • Blood transfusion • UD (IC vs. OBS) 	32	PA vs. non-PA (5 years RFS 81.7% vs. 62.5%; P<0.0001)
Piazza <i>et al.</i> 2022 (18)	366	RARC + ICUD	IC: 78%; OBS: 22%	OC: 64.2%; LA: 35.8%	14%	52.2% (USC) <ul style="list-style-type: none"> • LN ≥16: 75.7% • Negative STSM: 93.7% • Absence of 90 days major complications: 85.2% • Absence of 1-year UD-related sequelae: 88% • Absence of clinical recurrence ≤12 mo.: 92.1% 	<ul style="list-style-type: none"> • Increasing age • Decreasing surgeon experience • Previous prostatic surgery • UD (IC vs. OBS) • LA disease 	29	PA vs. non-PA (5 years OS 71.8% vs. 59.6%; P<0.001) and 5-year CSS (84% vs. 71%, P<0.001)
Zapala <i>et al.</i> 2022 (19)	304	ORC: 14.8%; LRC: 85.2%	IC: 42.4%; OBS: 2.6%; UC: 44.7%; others: 8.9%	OC: 60.6%; LA: 39.4%	24.3%	22% (USC) <ul style="list-style-type: none"> • LN ≥10: 47% • Negative STSM: 87.5% • Absence of 90 days major complications: 81.3% • Absence of 1-year UD-related sequelae: 88.2% • Absence of clinical recurrence ≤12 months: 64.8% 	<ul style="list-style-type: none"> • Technique (open vs. lap) • UD (OBS vs. IC vs. others) • LA disease • Pure urothelial carcinoma vs. variant histology • Higher preoperative creatinine 	18.5	At the median follow-up: OM and CSS were 2.99% and 1.49%, respectively, in PA vs. 43.6% and 33.7% for non-PA
Li <i>et al.</i> 2022 (20)	340	LRC	IC: 31.5%; OBS: 17.6%; UC: 50.9%	OC: 68.5%; LA: 31.5%	8.2%	14.7% (USC) <ul style="list-style-type: none"> • LN ≥16: 30.3% • Negative STSM: 95.3% • Absence of 90 days major complications: 83.8% • Absence of 1-year UD-related sequelae: 75% • Absence of clinical recurrence ≤12 months: 85.6% 	<ul style="list-style-type: none"> • UD (UC vs. IC and OBS) • Decreasing surgical experience 	23	PA vs. non-PA (5-year OS: 72.7% vs. 63.8% P=0.027)
Noh <i>et al.</i> 2022 (21)	203	RARC + ICUD	IC: 41.8%; OBS: 58.2%	OC: 64.2%; LA: 35.8%	21.2%	53.7% (USC) <ul style="list-style-type: none"> • LN ≥16: 83% • Negative STSM: 95.5% • Absence of 30 days major complications: 79.5% • Absence of UES ≤ 12 mo.: 91.5% • Absence of clinical recurrence ≤12 mo.: 85% 	NR	Mean: 44	NR

Table 1 (continued)

Table 1 (continued)

Authors, year	Patient No.	Technique	UD	Pathological staging	Nodal positivity	PA	Predictors of missing pentafecta	Median follow-up (mo.)	Prognostic significance of pentafecta
von Deimling et al. 2023 (22)	420	ORC	Incontinent: 71%; continent: 29%	OC: 59%; LA: 41%	29%	26% (PRO.) • LN \geq 16: 42% • Negative STSM: 88% • Absence of 30 days major complications: 85% • Time between TURBT and cystectomy \leq 3 mo.: 87% • Absence of clinical recurrence \leq 12 mo.: 85%	• CCI • UD (incontinent vs. continent)	73	Pentafecta correlated with OM (HR 0.59, P=0.028)
Mastroianni et al. 2023 (23)	114	ORC: 58; RARC + ICUD: 58	IC: 24%; OBS: 76%	NR	NR	58.7% (USC) (RARC: 58% vs. ORC: 60%, P=0.85) • LN \geq 16: (RARC: 95% vs. ORC: 95%) • Negative STSM: (RARC: 100% vs. ORC: 100%) • Absence of 90 days (RARC: 84% vs. ORC: 89%) • Absence of 1-year UD-related sequelae (RARC: 65% vs. ORC: 72%) • Absence of clinical recurrence \leq 12 mo.: (RARC: 88% vs. ORC: 84%)	NR	NR	PA was the only predictors of 2-year unmodified HRQoL (OR; 4.35, 95% CI: 1.67–11.34; P=0.003)

UD, urinary diversion; PA, pentafecta achievement; ORC, open radical cystectomy; NR, not reported; PRO., PROMETRICS; LN, lymph nodes; STSM, soft tissue surgical margin; TURBT, transurethral resection of bladder tumor; mo., months; RARC, robotic-assisted radical cystectomy; ICUD, intracorporeal UD; IC, ileal conduit; OBS, orthotopic bladder substitution; OC, organ confined; LA, local advanced; USC, University of South California; OS, overall survival; ECUD, extracorporeal UD; UC, ureterocutaneous anastomosis; UES, ureteroenteric stricture; CSS, cancer specific survival; ASA, American Society of Anesthesiologists; LRC, laparoscopic radical cystectomy; CCI, Charlson comorbidity index; OM, overall mortality; RFS, recurrence free survival; HR, hazard ratio; HRQoL, health-related quality of life; OR, odds ratio; CI, confidence interval.

patients using the USC and PROMETRIC definitions in the Brassetti series, respectively. The ranges in which the various components of USC pentapecta were achieved, including NSTSM, resection of ≥ 16 LNs, and absence of postoperative major complications, one-year UD-related complications, and one-year RFS were 88–100%, 30–93%, 75–90%, 65–95%, and 65–93%, respectively (Table 1).

Aziz *et al.* in the original study did not mention causes of missing pentapecta. In subsequent reports, the leading cause of missing pentapecta was the number of resected LNs (six studies), followed by postoperative major complications (four studies). Long-term complications related to UD and a time interval between TURBT and RC of less than 3 months were seen as the most common reason in one study each. Predictors of missing pentapecta were analysed in seven studies using a multivariable analysis; type of diversion, age, surgeon experience and tumor staging were most frequently reported factors that affect PA. The prognostic significance of PA was reported in ten studies, from which nine studied the correlation between PA and oncological outcome and one study tested the 2-year health-related quality of life (HRQoL). A positive correlation between oncological outcome either overall survival (OS), cancer specific survival (CSS) or recurrence free survival (RFS) was seen in seven reports, while in two studies PA failed to show any association. Mastroianni *et al.* found in a randomized study including ORC and RARC groups that PA was the only predictor of 2-year HRQoL (23) (Table 1).

Discussion

Standardized reporting of outcomes after RC using measures of perioperative morbidity, functional outcome and oncological adequacy is necessary to monitor surgical quality and improve performance. Trifecta and pentapecta have been proposed for the first time in 2015 by Aziz *et al.* (12). The authors surveyed 50 experienced urologists from the PROMETRICS group and asked them to assign points from 1 to 5 for 10 criteria of oncologic and functional importance related to RC. The three most important criteria in the final ranking were NSTSM, resection of ≥ 16 LNs, and the absence of 90-days \geq grade 3 CD complications. The previous three factors formed the trifecta, while the next two factors in the ranking were added to the trifecta to form the pentapecta, namely a time interval of less than 3 months between the last TURBT with evidence of MIBC and RC, and the absence of local pelvic recurrence within 1 year. The authors applied the previous

definition to 334 patients from the prospective multicenter RC series and reported 35.3% achievement of trifecta and 29% pentapecta. The previous definition of pentapecta was not popularized as it was limited only to patients with MIBC undergoing RC. In 2019, Cacciamani *et al.* from USC modified the definition to be applied for both MIBC and non-MIBC by replacing the last 2 criteria proposed by Aziz *et al.* by absence of long-term sequelae related to UD and any clinical recurrence within one year (13). Many following studies validated the USC pentapecta in open and robotic series. In the available 12 articles, PA varied between 15% and 60% with an overall result of almost 34% in all studies. Comparison of rates between studies is difficult because of the retrospective nature, heterogeneous patient population, surgical experience, and techniques. Therefore, pentapecta should be used primarily to improve individual surgical outcomes or to explore new techniques and not to compare with the results of others.

The leading cause of missing pentapecta in the current review was the number of LNs resected. The therapeutic role of LND in either patients with nodal-negative or positive disease is currently well established (24). Up to 20% of patients with regional LN metastasis could be cured with surgery alone (25). However, the adequate template of LND remains controversial (26,27). Furthermore, the template alone is not sufficient to determine surgical quality, as LN retrieval within the same template is highly dependent on the surgeon. Careful dissection with skeletonization of the pelvic vessels and en bloc LNs removal are important prerequisites for adequate surgery. Thus, Aziz and his colleagues for better standardization used the number of removed LNs as a measure of adequate LND (12). A cut-off of 16 LNs was used based on previous studies that showed a better oncological outcome for dissection of ≥ 16 LNs (28,29). The retrospective nature of most of the included studies and the lack of consensus on the optimal template or the number of LNs that should be removed may be the main factors that influenced the optimal LND in the current review. Moreover, the LN count is affected by many factors including the variability in surgical techniques, methods of LN collection, packing and pathological counting (30). Zehnder *et al.* for example reported a median 65 LNs retrieval by LN submission in 13 anatomical packets versus 32 LNs for en bloc submission ($P < 0.001$) (31). Further prospective studies using standards for LN dissection and counting could improve the results of pentapecta and accurately assess its prognostic significance.

Being one of the most morbid urologic procedures,

occurrence of 90-days \geq III CD complications were the second most common cause of missing pentafecta. However, the reporting of postoperative complications in the available series was not standardized, which is a major limitation that may affect the accuracy of the results. We believe that the use of pentafecta also requires a clear recommendation for the use of a validated methodology for reporting complications, as previously recommended by the European Association of Urology (32).

One of the controversial metrics for pentafecta is UD-related complications at one year, which, according to the USC group, includes complications requiring corrective surgery, such as UES, parastomal hernia, complications related to the stoma, fistula, etc. Some argue that some of these complications overlap with the 90-day \geq III CD complications; moreover, some of these complications may not be of great importance because they do not affect survival or even quality of life. In their multicenter study of the KORAC database, Oh *et al.* used only UES to describe long-term UD-related sequelae (15). They believe that UES is a late complication of UD that does not overlap with 90-day complications; moreover, it is the main cause of deterioration of renal function after RC, and treatment is difficult and affects quality of life. Nevertheless, it could be critically noted that UES is not the only factor that can cause deterioration of renal function. Many other UD-related sequelae can cause urinary tract obstruction and impaired renal function, including stomatal stenosis, parastomal hernia, nipple stricture, and neobladder outlet obstruction (33). Therefore, the use of the USC definition appears more inclusive.

Factors affecting achievement of pentafecta

Type of UD was the most frequent factor that affected PA in the literature; however, the results were contradictory regarding the type of UD that negatively impact the pentafecta. Orthotopic bladder substitution (OBS) is the most complex type of UD, associated with a higher risk of serious postoperative complications. Accordingly, the early learning curve may affect PA compared to other simple incontinent diversions. On the other hand, the choice of UD is usually biased and OBS is offered to young, fit patients with favorable pathological features. Piazza *et al.* for example found a higher PA in patients with OBS versus ileal conduit (IC) (69.5% *vs.* 47.2%, $P=0.004$); however, patients received OBS were significantly younger with less comorbidities (18). Finally, it is not possible to correlate any type of UD

with PA without controlling for the other surgical, patient, and tumor-related factors. Otherwise, age, advanced tumor stage, and surgeon experience were frequently seen to be important predictors of PA. The above factors are known to influence local tumor control and perioperative outcome, which are components of pentafecta. In their series of 366 patients undergoing RARC and ICUD treatment, Piazza *et al.* reported two phases of PA with an initial phase of lower achievement and a second phase of rapid improvement after 180 cases. Thereafter, a significant increase from 40% to 88% was observed for cases between 180 and 350. Remarkably, the plateau phase was not reached in this study indicating further improvement is still going (18). In another robot-assisted series, which included a small number of patients [104], the PA rate increased significantly from 31% for surgeons with less than 10 cases to 56% for more than 30 cases ($P=0.05$). In addition, the influence of the learning curve on the oncologic outcome was shown, as no patient in the group operated on by the experienced surgeons developed a recurrence (16). In laparoscopic series, surgeon experience was independent predictor of PA among 340 cases [odds ratio (OR) 1.05; 95% confidence interval (CI): 1.03–1.07, $P<0.001$] (20).

Some previous reports have found that female gender correlates with a less favorable oncologic outcome and higher perioperative morbidity compared to men (34,35). However, in the current review, no study found a difference in PA between the two genders; the overall PA in the nine studies was 34% in men and 31% in women. The available studies remain limited due to their heterogeneity and the low proportion of women; therefore, future comparative matched studies examining the difference in PA between men and women are still needed.

Applications of pentafecta

As already mentioned, PA is strongly correlated with the surgeon's experience. Hereby, one of the most important applications of pentafecta is certainly the evaluation of surgical quality and the guidance of surgical training. Moreover, pentafecta can be used in the comparative studies to investigate a new technique or approach, as they allow a comprehensive evaluation of surgical outcomes. Mastroianni *et al.* in the only randomised study in this review compared ORC and RARC and ICUD in 114 patients regarding PA. Both techniques were comparable in attainment of all items of pentafecta and the final PA was 58% and 60% for RARC and ORC, respectively ($P=0.85$). These results demonstrate

the safety, functional and oncological efficacy of RARC with ICUD (23).

Prognostic significance of pentafecta

In most studies, PA was shown to result in better oncologic outcomes compared with non-PA. Laymon *et al.* found significantly longer RFS in the PA-group compared to the non-PA group at a median follow-up of 32 months in the largest ORC series of 1624 patients (5-year RFS 81.7% *vs.* 62.5%, $P < 0.0001$). In multivariate analysis PA was an independent predictor of RFS (HR 0.3; 95% CI: 0.2–0.5; $P < 0.001$) (17). In studies assessing survival outcomes, PA correlated with survival in all except 2 articles; however, both were limited by small sample size. In the largest multicenter series examining survival in 730 patients, PA was associated with higher 5-year OS (84.4% *vs.* 76.2%, $P = 0.016$) and CSS (92.1% *vs.* 85.9%, $P = 0.036$) at a relatively short median follow-up of 20 months. Additionally, PA correlated with OS in the multivariable analysis (HR 0.561; 95% CI: 0.32–0.96; $P = 0.038$) (15). von Deimling *et al.* tried to assess the discriminative ability of pentafecta for prediction of oncological endpoints. Interestingly, at a long follow-up of 73 months in 420 patients, the achievement of 4 out of 5 measures in pentafecta (4/5) was comparable to full PA (5/5) in survival analysis, whereas a significant difference was found after classification of PA into 3 groups ($\geq 4/5$, $3/5$, and $\leq 2/5$) with increasing 5-year OM (22%, 71% and 86%, respectively) and 5-year CSM (16%, 47%, and 81%, respectively) with decreasing number of PA ($P \leq 0.005$) (22). These results suggest that attainment of at least 4/5 elements is required to ensure adequate outcome. Despite the encouraging results, previous studies were limited either by the short follow-up time or the small sample size, which of course affects the survival analysis.

Pentafecta and quality of life

The correlation between PA and quality of life was investigated once by Mastroianni *et al.* The HRQoL after 2 years was determined using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30). In the univariable regression analysis, PA was a predictor of unchanged HRQoL after 2 years (OR 4.35, 95% CI: 1.67–11.34; $P = 0.003$) (23).

Although continence is one of the functional outcomes of OBS that influences quality of life and reflects surgical

quality, it is not yet considered in pentafecta. Brassetti *et al.* introduced the trifecta definition rather than pentafecta to report the outcome of RC with OBS, they included for the first time the continence as a main functional result of OBS. The other two included factors in trifecta were absence of one-year \geq grade III complications and one-year RFS. Trifecta was achieved in 53% and was significantly associated with learning curve and overall survival (OS) in this study. Rates of trifecta showed improvement from 33% in the first tertile to 70% in the last one ($P = 0.011$). Patients achieved trifecta had a significantly higher 3-years OS (93% *vs.* 73%, $P = 0.032$) (14). Mastroianni *et al.* used the same trifecta definition to compare ORC and RARC in their randomized study and reported a comparable outcome. Achievement of trifecta in this study was a predictor of 2-year HRQoL (OR 3.53, 95% CI: 1.31–9.46; $P = 0.012$) (23).

Conclusions

Pentafecta provides a comprehensive tool for reporting RC outcomes. The new concept may be useful for improving surgical quality and comparing different techniques. However, pentafecta is not yet suitable for perioperative risk stratification and patient counseling, as some measures are only evaluated after one year. Moreover, pathological staging which is the main predictor of long-term oncological outcome is not considered in pentafecta. The overlap between some metrics in pentafecta remains a major limitation that requires further discussion and modifications. First, the number of LNs resected and marginal status directly affect tumor recurrence and, accordingly, directly correlate with another measure in pentafecta, which is one-year clinical recurrence. Second, the 90-day major complications may overlap with some long-term UD-related complications, e.g., early onset of UES. Third, clinical recurrence at one year and 90-day CD grade V complications (death) are considered endpoints rather than metrics and would directly impact the analysis of long-term oncologic endpoints, e.g., RFS, CSS, and OS. The above overlaps should be further explored and it may be necessary to combine some measures or even replace some of them. Some measures could still be added in subgroups of patients, e.g., continence in OBS or use of nerve-sparing techniques and minimally invasive procedures in appropriate patients, as these measures correlate strongly with patients' quality of life.

The main limitations with the studies in the present review are their retrospective nature, relatively small sample

size, and short median follow-up time, most of which was less than 3 years. Further prospective, large and long-term follow studies are still needed. Furthermore, it should be emphasized that comparison of results between different studies or institutions remains difficult because of wide variations not only in the included population but also in surgeon experience and techniques, pathologic evaluation, methods of recording complications, and follow-up regimens. Without standardization of most of the above factors, Pentafecta should therefore only be used to improve individual surgical quality and to evaluate new techniques or treatment regimens with the known standards.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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