Review Article

Radical cystectomy and urinary diversion in women: techniques, outcomes, and challenges—a narrative review

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Background and Objective: Standard radical cystectomy (RC) in women includes the removal of the bladder, urethra, uterus with the adnexa, and the anterior vaginal wall, thereby severely affecting the urinary, sexual, and reproductive system. To limit these detrimental effects, organ-sparing, including nerve-sparing approaches, have been developed. Health-related quality of life (HRQOL) and functional outcomes are, indeed, becoming increasingly central to the shared decision-making with the patient. The objectives of this narrative review are: (I) to review the current status of RC in women, including the use of different urinary diversions (UDs); (II) to discuss organ-sparing approaches and their impact on oncological and functional outcomes in women; (III) to discuss the impact of RC on HRQOL and sexual function in women.

Methods: We performed a non-systematic literature review of the available publications in the PubMed database.

Key Content and Findings: Over the past years, gender differences in oncological and functional outcomes after RC have received increased attention. According to the currently available literature, organ-sparing approaches can be safely performed in well-selected women without negatively impacting oncological outcomes. The orthotopic neobladder is feasible and oncologically safe in well-selected and informed women. The choice of the UD should be based on comprehensive counseling and the patient's comorbidities and preferences. There still is a lack of data on sexual recovery after the different surgical approaches aimed to mitigate sexual dysfunction in women undergoing RC.

Conclusions: Pre-and post-operative counseling and support of females undergoing RC regarding their expectations and experiences in terms of quality of life and functional and sexual outcomes are currently insufficient. Well-designed studies in this field are necessary to further improve outcomes of women treated with RC with an overarching aim to close the gender gap in managing women with bladder cancer.

Keywords: Radical cystectomy (RC); nerve-sparing; organ-sparing; women; functional outcomes

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Introduction

Radical cystectomy (RC), including pelvic lymph node dissection with neoadjuvant cisplatin-based therapy when possible, is the standard treatment of localized muscle-invasive bladder cancer (MIBC) and very high-risk non-muscle-invasive bladder cancer (1,2). Approximately one-fourth of MIBC patients will undergo RC, which is a complex procedure that differs between genders and is associated with high perioperative morbidity (3-5). Counseling women with bladder cancer requires discussion, regarding the surgical approach and its oncological safety, choice of urinary diversion (UD), and expected and desired postoperative functional outcomes. This review aims to discuss the most important aspects of organ sparing RC, the different types of UD, as well as functional and sexual outcomes after RC in females. We present the following article in accordance with the Narrative Review reporting checklist (available at https://tau.amegroups.com/article/view/10.21037/tau-22-463/rc).

Methods

We performed a non-systematic literature review of available publications using the US National Institutes of Health's PubMed Database. Combinations of the search terms displayed in *Table 1* were used (radical cystectomy AND female* AND sexual function; radical cystectomy AND women AND sexual function; organ sparing radical cystectomy AND female*; nerve sparing radical cystectomy AND female*; radical cystectomy AND female* AND urinary diversion AND functional outcome*) to identify studies that specifically reported outcomes of women undergoing RC published between 1995 and 2022. Articles that were not identified during the search but thought to be of interest to the reader were added by the authors. Additional information on the search strategy is displayed in *Table 1*.

Gender differences in oncological outcomes

Despite higher bladder cancer incidence rates and higher lifetime risks of developing bladder cancer in men, women are more likely to present with advanced disease stages and non-organ-confined disease (6-9). As a result, the oncological outcomes for bladder cancer in women are reported to be worse than in men (10-16). Interestingly, there is evidence that the gender gap after diagnosis of MIBC may be time-dependent and narrows or eventually disappears after adjusting for the effects of clinicopathological features (17-21).

Several contributing factors to the gender disparity have been extensively studied in the past years, but the underlying mechanisms are not yet fully understood (6). One possible explanation is differences in the referral patterns. As one of the first symptoms of bladder cancer, hematuria may be misinterpreted in females as part of a urinary tract infection, thus resulting in a prolonged time between symptoms and diagnosis (22,23). Aside from that, differences in hormonal and genetic factors, tumor biology, smoking habits, and occupational risk factors as well as postoperative complication rates have been investigated (8,12,24). Moreover, women were more likely to present with squamous cell carcinoma, which was associated with a worse oncologic outcome (20,25,26). However, differences in treatment patterns did not seem to influence survival rates (20).

In summary, differences in oncologic outcomes across genders have been extensively studied over the past decades. It is established that women often present with advanced disease stages and non-organ-confined disease. However, there is still some uncertainty about the underlying mechanisms and whether there is a difference in long-term survival.

Standard RC

The female pelvis contains gastrointestinal, reproductive, and urinary tract organs and a complex interplay of pelvic floor muscles, ligaments, and nerve fibers orchestrates their simultaneous functioning. Standard RC fundamentally changes the anatomy and functionality of the female pelvis. In addition to bladder resection, the usual anterior pelvic exenteration includes the removal of the urethra, uterus with the adnexa, and the anterior vaginal wall. Therefore, pudendal, pelvic, and hypogastric nerve fibers that run beside the lateral walls of the vagina to the bladder neck

Table 1 The search strategy summary

Items	Specification
Date of search	February 11th, 2022
Databases and other sources searched	PubMed
Search terms used	"radical cystectomy", "female*", "women", "sexual function", "functional outcome", "urinary diversion", "organ sparing radical cystectomy", "nerve sparing radical cystectomy"
Timeframe	1995–2022
Inclusion and exclusion criteria	Inclusion criteria: relevance to the topic; English articles only
	Exclusion criteria: editorials/author replies
Selection process	One person assessed the relevance of the articles
Any additional consideration	Additional articles that the authors considered to be of interest to the reader were added

and urethra are at particular risk during standard RC (27). Regarding the proximal urethra, fibers from the pelvic plexus are particularly important and their removal can result in reduced sensitivity (28). Aside from the complete resection of the lower urinary tract and reproductive organs (RO), damage to the neurovascular bundles and the vascularization of the clitoris from the internal iliac artery are among the main reasons for impaired functional outcomes.

Organ-sparing RC

To mitigate the negative functional impact of surgery on urinary and sexual outcomes, the concept of RO-preserving RC (ROPRC), including pelvic nerve-sparing techniques, was developed. These techniques focus on preserving the neurovascular bundle, vagina, uterus, fallopian tubes, and ovaries or any variation of the stated techniques to increase continence rates, decrease sexual dysfunction and maintain postoperative hormonal homeostasis in premenopausal women.

Oncological safety of ROPRC

The main concern of organ-preserving RC is its oncological safety. Several studies demonstrated the technical feasibility of ROPRC without compromising oncological outcomes compared to standard RC (24,29). However, due to a lack of high-quality data, there is no recommendation for ROPRC as a standard alternative to standard RC for women (2,29). According to major guidelines, ROPRC may be offered to highly selected patients (e.g., absence of pT4 urothelial carcinoma, absence of tumor in the area to be preserved, desire for organ preservation) using an open (ORC), laparoscopic (LRC) or robot-assisted approach (2,30). Current data show favorable recurrence-free survival (RFS) and cancer-specific survival (CSS) rates for ROPRC when compared to standard RC in the general population, which is highly likely due to a selection bias (29,31,32). According to a systematic review, up to one-fourth of the women are affected by metastatic recurrence after an organ-preserving approach, similar to ORC and LRC (29). On the other hand, a recent retrospective study did not find any differences in survival outcomes for ROPRC compared to non-ROPRC in women with variant histology and it was suggested, also by other studies, that presence of advanced disease does not preclude ROPRC (33,34).

Considerations regarding patient selection for ROPRC

Clinically, several critical factors ought to be considered regarding the oncological outcome after ROPRC. Of those, a potentially higher risk for positive surgical margins, local recurrences in the remnant urethra and RO, as well as secondary malignancies, and possible invasion in the RO were recently studied (see *Table 2* for further criteria).

Urethral recurrence (UR)

UR rates of up to 13% were reported after ROPRC instead of rates around 5% after standard RC (29,35-40). To what extent, however, UR affects long-term survival is currently unclear, as some studies found a difference in overall survival (OS) and CSS, while others did not (35,36). UR

Table 2 Aspects for pre-and intraoperative evaluation of candidates for ROPRC

Functional aspects prior to ROPRC	Oncological contraindications for ROPRC
Age	Bladder neck and trigonum involving bladder cancer
Performance status	Presence of preoperative hydronephrosis
Gynecological examination	Presence of CIS
History of abnormal vaginal bleeding	Clinical tumor stage ≥ cT3
Preoperative continence status	Suspected nodal-positive disease
Preoperative sexual function	Intraoperative positive urethral margins
Menopausal status	Intraoperative positive ureteral margins
Fertility goal	Family history for gynecological malignancies
Previous pelvic surgeries	Genetic predisposition for gynecological malignancies (*BRCA1/2* mutations)

ROPRC, reproductive organ-preserving radical cystectomy; CIS, carcinoma in situ.

is, however, a highly problematic event as interventions in female patients can be difficult and may lead to incontinence. In general, tumor multifocality, carcinoma in situ (CIS), and bladder neck invasion were associated with an increased risk for UR or urethra tumor involvement at RC in women (35,36,41). Orthotopic UD was associated with a decreased risk for UR compared to other types of UD; here as well likely secondary to a selection bias (36).

Involvement of RO

RO involvement occurred in up to 23% of females undergoing standard RC, with vaginal and uterus involvement being the most common (42-46). This is likely due to the generally late diagnosis of bladder cancer in females. Regarding ROPRC, two studies found that RO involvement rates were equal or lower compared to standard RC (33,34). Most women with RO involvement have locally advanced bladder cancer with lymphovascular invasion, trigonal tumors, or concomitant non-bladder primary malignancies, however, intraoperative findings of primary malignancies of the RO are rare (34,44,45). Variant histology, tumor in the trigone or bladder neck, a palpable mass, hydronephrosis, and lymph node-positive disease were identified as risk factors for RO involvement (42,45,47). If present, RO involvement significantly impairs OS (34,42). Interestingly, neoadjuvant chemotherapy (NAC) did not influence the rate of RO involvement, as it was as frequent in women who did and those who did not receive NAC (34).

In summary, there is growing evidence that ROPRC can be safely performed in well-selected patients without negatively impacting oncological outcomes. Better-designed studies are necessary to truly estimate the risk, benefit, and selection criteria for ROPRC.

RC and the growing influence of robotic surgery

Historically, RC was performed using an open approach. With the advent of robot-assisted surgery, robot-assisted RC (RARC) has been increasingly utilized in both males and females (48-52). A critical preoperative assessment of patient characteristics is vital to choosing the appropriate surgical approach. Patient characteristics to guide decision-making include previous abdominal surgery, the body mass index, history of pelvic radiation, presence of bulky, cardiovascular, or pulmonary disease, and performance status (52). When critical patient selection is performed, ORC and RARC are feasible therapeutic options independent of patients' age (53,54). Nowadays, RARC is already the method of choice in many large centers, but based on survival outcomes, no surgical approach appears superior (50,55,56). Overall, complication rates have been suspected to be more favorable for RARC in retrospective but not prospective studies; on the other hand, RARC is still associated with a significantly longer operative time (55-58). Women undergoing ORC are prone to having higher intraoperative blood loss and receiving more blood transfusions than their male counterparts (57).

Regarding robot-assisted ROPRC, several studies recently showed the feasibility, but solid survival data are still scarce (32,59-62). Current studies are limited to case reports or small retrospective series. Further well-designed

studies are necessary to fully understand its impact on short- and long-term oncological outcomes.

UD

Today, the ileal conduit (IC) represents the most common incontinent UD across genders, while the orthotopic neobladder (ONB) is the most common continent procedure (63-65). Certain oncological aspects preclude ONB reconstruction, such as tumor localization in the trigonum or bladder neck and positive surgical urethral margins intraoperatively. Several studies showed that ONB reconstruction is oncologically safe in well-selected females, even for limited lymph node-positive disease in certain cases (37,38,66-68). Nonetheless, ONB has been less frequently used in women and women are less likely to receive a continent UD than males (64,65,69).

Current rates for continent UD in females range around 4–15% (65,69-71). Across all patients with bladder cancer, there has been a decreasing use of ONB reconstruction (10–30%), with only single centers exceeding this range (63-65,69,72,73). This trend does not dependent on the surgical approach [ORC *vs.* RARC ± intracorporeal UD (ICUD)]. Although the feasibility of ONB as ICUD was confirmed by several studies, IC remains the most popular ICUD regardless of patient's age (54,74-76). Keeping that in mind, despite being intraoperative technically less demanding, it is well known that IC is associated with a significant burden of long-term complications, including impaired renal function, urinary tract infections, and parastomal hernia (77).

In patients that cannot undergo ONB reconstruction but desire a continent UD, surpravesical continent cutaneous pouches such as the MAINZ-I, the Indiana-, the Miami- or the ileal Kock-pouch may provide an alternative to the IC (77,78). Continent cutaneous pouches generally consist of some sort of continent catheterizable stoma, but its construction remains one of the main surgical difficulties and only a few centers are capable of performing continent cutaneous UD (79). Small, retrospective single-center series suggest that continent cutaneous UD are performed more frequently in women than in men (80,81). As with all continent UD, sufficient renal function and adequate handling of catheterization are paramount for patient selection.

As RARC is more widely available nowadays, ICUD entered the stage and has become increasingly popular (74,75,82,83). Systematic reviews and meta-analyses showed equivalent complication rates for ICUD compared to extracorporeal UD (ECUD) (84). In experienced hands, ICUD has been reported to be associated with a reduced risk for major complications (84), similar to all procedures performed by high-volume surgeons in high-volume centers. Estimated blood loss and blood transfusion rates are significantly lower in patients with ICUD than in patients with ECUD, but readmission rates were reported to be higher for ICUD (75,84). Because ICUD is still in its infancy, prospective studies with long-term oncologic and functional outcomes specifically designed to assess outcomes in females are still lacking (85). To conclude, IC, ONB, and continent cutaneous UD are feasible forms of UD in women, but ONB and continent cutaneous pouches are performed only in the minority of females. Current studies provide evidence for the feasibility of performing ICUD with a robot-assisted approach. However, long-term results in women are still pending.

Postoperative functional outcomes

In addition to oncological aspects, the patient's requirements regarding the quality of life and handling of the UD should be the main focus of decision-making. It is primarily the technical aspects and the often limited functional outcomes of surgery that stand in the way of more widespread use of continent UD. In that regard, postoperative incontinence and/or hypercontinence are two major issues after ONB and heterotopic reconstruction (86). Therefore, thorough education on incontinence and hypercontinence rates and the possible need for intermittent self-catheterization (ISC) should be provided preoperatively. However, as not all studies adhered to the same definitions of outcome measurements, systematic comparisons to guide health care providers and payers in counseling and reimbursement, respectively, are difficult (29,87).

A significant proportion of women undergoing ONB reconstruction are affected by postoperative incontinence, which occurs when the reservoir pressure exceeds the outlet pressure. Therefore, the functional integrity of the urethral rhabdosphincter is crucial for maintaining postoperative continence. In women undergoing ONB reconstruction, daytime incontinence rates up to 69% have been reported, while nighttime incontinence may affect up to 85% of the patients (87). In addition, preexisting stress incontinence may worsen upon RC with ONB reconstruction (88). In comparison, day- and night-time continence rates for continent cutaneous UD ranged around 90%, depending

on the tissue (appendix, intussuscepted ileal nipple) used for the continence mechanism (77,79,89,90).

After RC, the absence of the detrusor-sphincter reflex, which normally increases outlet pressure, is one mechanism that confers higher nocturnal incontinence rates (91). Conversely, longer functional urethra length and higher preoperative urethral closing pressure at rest were associated with lower postoperative incontinence rates (92). In detail, it was hypothesized that due to denervation and consecutive atrophy of the proximal part of the urethra, the urethral walls might collapse during voiding resulting in incontinence and postvoid residual (PVR) urine formation (28,92). Therefore, nerve-sparing surgical approaches and uterus preservation may improve postoperative functional outcomes (29,93,94) by preserving the innervation of the proximal urethra (28).

Hypercontinence rates varied widely and incidence rates as high as 69% were described (87). Accordingly, data on the need for additional ISC vary widely (37,66-68,95,96). Of note, even high-volume centers with experienced surgeons reported ISC rates greater than 60% (37,96,97). It has been suggested that intraoperative damage of parasympathetic pelvic nerve fibers may lead to a hypertonic urethra due to sympathetic overstimulation. This hypothesis was supported by functional studies on hypercontinent women who had increased urethral closing pressures with PVR after RC requiring ISC (92). Given that females appeared comparatively less bothered by ISC (37,97), a continent cutaneous UD may be an alternative for these women. ISC is much easier in such a setting, despite reported rates of stomal stenosis and difficulty catheterizing the stoma up to 31% (77,90,98).

Again, organ-sparing approaches may improve postoperative hypercontinence rates, but current data is based on small series of low quality (29). Considering the pelvic anatomy after ROPRC, it is plausible that preservation of the uterus and adnexa with its suspensory apparatus stabilizes the ONB and helps avoid dorsal kinking. This is thought to promote complete bladder emptying, thereby preventing PVR formation (99). In addition, wrapping the ONB circumferentially with omentum or round ligament suspension may as well improve ONB filling and emptying (86,100).

Perioperative morbidity in females

Compared with men, women that underwent standard RC had higher odds of receiving more postoperative transfusions, being readmitted to the hospital, and suffering from surgical site infections (24). In females alone, there was no difference in complication rates between surgical techniques (standard RC *vs.* ROPRC) (24). A retrospective study in females aged ≥75 years reported even lower long- and short-term complication rates than for standard RC, probably primarily due to a selection bias (101). Moreover, this study included only women with cutaneous ureterostomy (101).

Altogether, the often limited functional outcomes of surgery stand in the way of a more widespread use of ONB. In that regard, most women undergoing ONB reconstruction may be affected by postoperative incontinence and hypercontinence, but systematic comparisons are difficult due to a lack of uniformity in outcome variables' definitions. The need for additional ISC varied widely and even experienced centers reported rates greater than 60%. Continent cutaneous UD may be an alternative in women ineligible for ONB reconstruction but capable of performing ISC. Despite continence rates that range around 90%, continent cutaneous pouches are rarely utilized.

Postoperative health-related quality of life (HRQOL)

High-quality evidence for HRQOL after RC with UD is indeed scarce, and it is especially poorly assessed in IC patients, in patients with continent cutaneous pouches, and after ROPRC (29,87). Most studies show a large heterogeneity in data acquisition and questionnaires employed. The most commonly used questionnaires comprise the European Organization for Research and Treatment of Cancer (EORTC)-Quality of Life Questionnaire-Cancer 30 and Bladder Cancer-Muscle Invasive 30 (EORTC-QLQ-C30/-BLM30), the Functional Assessment of Cancer Therapy (FACT)-General and Bladder Cancer (FACT-G/-Bl), and different versions of the short form (SF) health survey. Of note, the EORTC-QLQ-BLM30 and the FACT-Bl-Cystectomy are particularly designed to assess HRQOL in patients after surgery for MIBC (102,103). In addition, some studies employed individual interviews as well as self-derived questionnaires.

Generally speaking, postoperative urinary or sexual function issues leading to impaired HRQOL are common regardless of UD type (104). Overall, no UD type is significantly superior to the others concerning HRQOL irrespective of gender and in women alone (87,105-109). In light of this, selecting the ideal UD for each patient

in a shared decision-making process with the patient herself remains crucial. ONB is mainly tailored towards younger patients even though previous studies have proved the feasibility in well-selected elderly patients (53,110). In patients with postoperatively preserved continence, ONB is associated with a good HRQOL, partly due to its orthotopic nature and conservation of voiding through the via naturalis (108,111,112). Similarly, the HRQOL of patients with a cutaneous continent UD may not differ from that of patients with an ONB or an IC, but the overall evidence is conflicting (79,106). A more recent study with long-term follow-up found that females older than 65 with a continent cutaneous UD had worse bowel bother than patients with an IC (113). In other studies, ONB patients had significantly better global health status, physical functioning, and role functioning after 2 years of follow-up than IC patients (112).

Summing up, using different definitions and questionnaires to assess postoperative functional outcomes reduces comparability between studies. Ultimately, there is no one best UD regarding functional outcomes and HRQOL. However, satisfactory levels of HRQOL can be achieved only when the choice of UD in each individual is based on shared decision-making, the patient's comorbidities as well as the surgeon's or center's experience, team, and volume.

Postoperative sexual recovery

Sexual dysfunction is a common problem after RC and affects almost two-thirds of all women (104,114,115). Despite this problem's urgency, existing data on this topic are inconclusive and heterogeneous, as there is a lack of standardized assessment and reporting across studies (87,116). The most commonly used questionnaire, the Female Sexual Function Index (FSFI), falls short in evaluating sexual function in women who are not sexually active postoperatively (117). Moreover, most studies did not assess baseline sexual function prior to RC. Since sexual recovery after surgery will likely not exceed baseline function, quantifying merely postoperative sexual activity is insufficient to demask an RC-induced decline of sexual function. Three studies comparing pre- and postoperative sexual function found that postoperative measures were inferior to baseline (62,93,118). Despite an initial worsening of sexual function in the early postoperative period, some women experienced recovery at 12 months follow-up (62). Of note, in one study, postoperative FSFI scores improved compared to baseline function in 12 women undergoing RC with ONB reconstruction (119). Therefore, longitudinal assessment of sexual function in women upon diagnosis of MIBC is necessary to provide accurate estimates regarding the possibility of long-term sexual recovery.

Overall, there is evidence that more than half of the women remain sexually active after RC (62,111,115). Among these, the most common problems are decreased desire, impaired ability to achieve orgasm, dyspareunia, and reduced satisfaction (93,99,114). A study by Volkmer *et al.* found that for patients aged <60 years, partnership at the time of surgery as well as current partnership, sexual intercourse within 4 weeks prior to surgery, and cystectomy for a benign disease had a positive impact on postoperative female sexuality (119). Further, the choice of UD may affect sexual function, as patients with ONB have been reported to be significantly more interested in sexual intercourse (120). In this context, less than 10% of patients after robot-assisted ROPRC and ONB reconstruction reported a high impact of the surgery on the body image (32).

Preservation of the uterus with the adnexa, the anterior vaginal wall, and the neurovascular bundle plays an important role in sexual functioning (27,116). Devascularization of the clitoris due to urethral resection poses an additional threat to postoperative sexual recovery. Some authors hypothesized that preservation of the integrity of the vagina is one of the critical reasons for preserved sexual function postoperatively (32,99). Thus, ROPRC and nerve-sparing techniques have gained more attention with promising outcomes regarding sexual function (29,32,87,93,99,121).

In direct gender comparison, women appeared to be associated with poorer quality of life after RC, particularly in assets such as cognitive functioning, future perspective, and sexual functioning (110,120,122). Adequate pre-and postoperative counseling sheds light on the patient's needs and facilitates the development of sexual rehabilitation strategies after RC. Partners should be included whenever possible. A study recently stressed the psychological and health concerns in women who undergo RC (123). Nevertheless, more than half of the women did not receive preoperative counseling regarding possible sexual function changes or reported that it was inadequately provided (123,124). In this regard, women were even less likely to be counseled regarding sexual function pre-and postoperatively compared to men (125). In support of this notion, nerve-sparing techniques were often not mentioned during women's counseling, despite their potential benefit for postoperative sexual function (125).

Indeed, there still is a significant need for studies exploring female sexual function before and after RC, and sexual recovery is insufficiently analyzed. At the current stage of low-level evidence, existing data show promising functional results for nerve- and organ-sparing techniques. ROPRC has been reported to reduce postoperative sexual dysfunction compared to standard RC, but this is highly likely due to selection bias (114). Adequate pre-and postoperative counseling regarding sexual function is an unmet need in female patients undergoing RC.

Conclusions

RC strongly affects the anatomy and functionality of the female pelvis, specifically, the urinary and reproductive tract. Several factors influence the choice of the UD, including the patient's needs and performance status, and with critical patient selection appropriate HRQOL may be achieved. Still, only a small proportion of women undergo ONB reconstruction or receive a continent cutaneous UD. Sexual function and its impact by RC is still understudied, specifically in women. Although robot-assisted and/or organ-sparing approaches bear great potential, their safety, benefits, and risks regarding oncologic and functional outcomes, especially sexual function, require further prospective investigation. Nonetheless, current studies increasingly support the benefits of organ-sparing treatment options for well-selected women. These treatment options together with patient satisfaction should be further studied systematically to refine tailoring future counseling and management strategies to the individual, especially in terms of postoperative functional recovery.

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Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://tau.amegroups.com/article/view/10.21037/tau-22-463/rc

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