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UROLOGY - REVIEW

Organ-sparing procedures in GU cancer: part 3-organ-sparing procedures in urothelial cancer of upper tract, bladder and urethra

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Abstract

Purpose The impact of radical surgery for urothelial carcinoma is significant on patient's quality of life. Organ-sparing surgery (OSS) can provide comparable oncological outcomes and with improved quality of life. In this review, we summarize the indications, techniques and outcomes of OSS for these tumors.

Methods PubMed® was searched for relevant articles. Keywords used were: for upper tract urothelial carcinoma (UTUC): endoscopic, ureteroscopic/percutaneous management, laser ablation; for urothelial bladder cancer: bladder preservation, trimodal therapy, muscle invasive bladder cancer (MIBC); for urethral cancer: urethra/penile-sparing, urethral carcinoma.

Results Kidney-sparing surgery is an option in patients with low-risk UTUC with better renal function preservation and comparable oncological control to radical nephroureterectomy. In select patients with MIBC, trimodal therapy has better quality of life and comparable oncological control to radical cystectomy. In distal male urethral cancer, penile conserving surgery is feasible and offers acceptable survival outcomes. In female urethral cancer, organ preservation can be achieved, in addition to OSS, through radiation.

Conclusions In the appropriately selected patient, OSS in upper tract, bladder and urethral carcinoma has comparable oncological outcomes to radical surgery and with the additional benefit of improved quality of life.

Keywords Upper tract urothelial cancer · Ureteroscopic management · Percutaneous management · Muscle invasive bladder cancer · Bladder preservation · Trimodal therapy · Urethra sparing · Penile sparing · Urethral carcinoma

Abbreviations

5-FU	Fluorouracil
BC	Bladder cancer
BCG	Bacillus Calmette–Guérin
BPT	Bladder preservation techniques
CIS	Carcinoma in situ
CRT	Chemoradiation therapy
MIBC	Muscle invasive bladder cancer
MMC	Mitomycin-C
MVAC	Methotrexate, vinblastine, doxorubicin and cisplatin
NAC	Neoadjuvant chemotherapy
OSS	Organ-sparing surgery
RC	Radical cystectomy
RNU	Radical nephroureterectomy
RT	Radiotherapy
TMT	Trimodal therapy
TUR	Transurethral resection
TURBT	Transurethral resection of bladder tumor
UTUC	Upper tract urothelial carcinoma

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Kidney-sparing procedures for upper tract urothelial carcinoma

Introduction

Upper tract urothelial carcinoma (UTUC) is a rare malignancy with a reported incidence of two new cases per 100,000 people per annum in the United States [1]. UTUC is located in the renal pelvis in two-thirds of cases; however, it may occur anywhere in the ureter. Radical nephroureterectomy (RNU) with excision of ipsilateral bladder cuff is the gold-standard treatment for high-grade UTUC; however, it affects the overall kidney function.

Patient selection for kidney-sparing procedures

Imaging by computed tomography urography (CTU), magnetic resonance urography (MRU) and endoscopy are helpful in patient selection. Biopsy for UTUC tumors commonly has the problem of insufficient volume with difficulty in tumor stage and grade assessment. Novel imaging techniques as endoluminal ultrasound and optical coherence tomography may have a role in better tissue depth assessment. Commonly, the absence of hydronephrosis, low-grade histology, and negative cytology are predictive for non-muscle invasive disease in almost all patients and consequently are good candidates for kidney-sparing procedures [2].

Techniques for kidney-sparing procedures

(A) Endoscopic procedures

Retrograde ureteroscopic management

Advantages Low risk of tumor spillage, outpatient setting and visualization of the entire urinary tract. However, limitations include difficulty to obtain adequate specimen and narrow caliber working channels which poses instruments limitation. Usually ureteroscopic techniques start with cystoscopy to rule out bladder tumors, followed by collection of urine cytology for both sides of the urinary tract, preferably prior to contrast injection or manipulation. Tumor base ablation can be performed after initial debulking using a basket, laser or electrocautery. Owing to the higher rates of delayed stricture formation with the mono-polar electrocautery, lasers have been advocated in the UTUC tumor ablation. The Holmium Yttrium Aluminum Garnet (Ho:YAG) is a pulsatile laser with a depth of penetration of 0.4 mm and is ideal for UTUC ablation [3] The Neodymium Yttrium Aluminum Garnet (Nd:YAG) is a continuous beam laser with a 5–10 mm penetration depth and its use is limited to larger renal pelvic tumors [3]. Thulium laser has fine hemostatic properties and has been tried in UTUC. Musi et al. described their experience with 42 patients treated by Thulium laser and reported a recurrence-free survival of 44 months, most of the complications were minor (Clavien–Dindo grade 1) and only four patients required RNU [4].

Percutaneous endoscopic management

Advantages Larger working channels, improved visualization, easier access to lower pole tumors, and a useful option in patients with urinary diversions hindering ureteroscopic access. Tumor resection/ablation can be accomplished with the resectoscope or using the laser. However, limitations include invasiveness compared to retrograde ureteroscopy, violation of the closed urinary tract system and the potential risk of tumor seeding along the nephrostomy tract which is rarely reported. To minimize the risk of tumor seeding, it is advised to use single-stage percutaneous endoscopic procedure, percutaneous tract dilation and tumor resection, use of sterile water for irrigation for its cytolytic effects, reduce intrarenal pressure using a 30-F working sheath and keeping the irrigation fluid height at 40 cm above the patient level [5]. Similar to ureteroscopy, tumor debulking with subsequent ablation using electrocautery or laser is performed after the percutaneous access is obtained. In bulky tumors, second look nephroscopy can be performed in 4–14 days to eradicate any residual tumors, and surveillance in 3 months by retrograde ureteroscopy is performed [6]. Complications related to percutaneous access of the kidney include: bleeding, perforation of the collecting system and hemothorax/hydrothorax especially with supracostal access [7].

(B) Adjuvant intracavitary instillations

Intracavitary Bacillus Calmette–Guerin (BCG) or chemotherapy has been tried in UTUC, though large randomized controlled trials are lacking. Antegrade instillation via a percutaneous nephrostomy tube or retrograde instillation by an external ureteral catheter, or passive reflux via an indwelling ureteral stent with bladder catheterization has been tried [8].

Intracavitary BCG

Indications: Ta (non-invasive), T1 (invasion into lamina propria) or carcinoma in situ (CIS) through 6 weeks instillations; starting 4 weeks after tumor ablation. Contraindications to intracavitary BCG include: urine extravasation/obstruction, urinary tract infection, gross hematuria and history of BCG sepsis due to the risk of BCG infection/sepsis. Oncological

outcomes: a single study of 133 renal units with UTUC received adjuvant BCG after percutaneous resection of UTUC was shown to have no oncological benefit with regard to recurrence and progression of disease [9]. In patients with upper urinary tract CIS treated with BCG, a recent meta-analysis showed the pooled estimates for cytology response, upper tract recurrence, and progression were 84%, 34%, and 16%, respectively [10].

Intracavitary chemotherapy

Thiotepa, mitomycin-C (MMC) and epirubicin have been tried in the same manner as BCG with 6 weeks instillations. More recently, MMC has been tried in gel format (MitoGel®, UroGen Pharma Ltd, New York, NY, USA) in animal models and trial on human is underway (NCT02701023). MMC gel is in liquid format that solidifies at body temperatures and can stay in such state for up to 6 h, increasing contact time with upper tract urothelium [11].

(C) Segmental ureterectomy

Advantages Allows for definitive pathological stage and grade with preservation of ipsilateral renal unit. For distal ureteral tumors that are unifocal, <2 cm and $\leq$T2 disease, distal ureterectomy with ureteral reimplantation was tried with comparable oncological outcomes to RNU [12]. Other methods of reconstruction include psoas hitch, Boari flap and in long ureteral segments loss, an ileal ureter. Complications of ileal ureter include pyelonephritis, recurrent urolithiasis, anastomotic stricture, chronic renal failure, mucus obstruction and metabolic acidosis [13]. In tumors of mid ureter, segmental resection followed by a tension free, spatulated and stented end to end ureteral anastomosis can be utilized.

Surveillance

Following kidney-sparing procedures in UTUC, the reported recurrence rate is 51.2% and 81.3% at second-look ureteroscopy in previously negative and positive ureteroscopy, respectively [14]. Usually, a second-look ureteroscopy 6–8 weeks after initial ureteroscopic ablation is indicated with follow-up with ureteroscopic evaluation every 6 months in the first 1–2 years following resection [15]. Tumor detection rates are enhanced when using novel imaging techniques such as photodynamic and narrow band imaging with digital ureteroscopy.

Summary of recommendations on organ-sparing procedures in UTUC in urological guidelines

(A) European Association of Urology (EAU) guidelines recommendations

The EAU provides useful recommendations in relation to indications, intracavitary treatment and follow-up after kidney-sparing procedure in UTUC [16].

1. *Indications* Imperative indications include patients with (1) a functional or anatomic solitary kidney, (2) significant renal insufficiency, (3) bilateral tumors, and (4) significant comorbidities [17]. Elective indications are for the low-risk UTUC. In the EAU guidelines, low-risk UTUC is defined as: low grade on biopsy/cytology, unifocal disease, tumor size ≤ 2 cm, and no radiographic signs of local invasion (ureteral thickness, inflammatory stranding).
2. *Intracavitary therapy* The EAU recommends percutaneous antegrade BCG instillation using a three-valve system open at 20 cm H_2O pressure owing to the concern of failure of agents to reach the renal pelvis through a refluxing ureteral stent.
3. *Follow-up*
   - Urine cytology and CTU at 3 and 6 months following treatment, then yearly.
   - Cystoscopy, and ureteroscopy at 3 and 6 months, then every 6 months till 2 years from initial treatment then yearly.

Bladder-sparing procedures in urothelial bladder cancer

Introduction

Bladder cancer (BC) is the second most common genitourinary malignancy and is one of the most common causes of cancer-associated mortality. Radical cystectomy (RC) with pelvic lymph node dissection is the gold-standard treatment of muscle invasive bladder cancer (MIBC). However, even in contemporary era, the 5-year overall survival following RC is 50% [18]. In addition, morbidity associated with RC and urinary diversion-related complications make extirpative surgery questionable for comorbid patients in addition to the urinary, sexual and psychological implications of RC and urine diversion on quality of life.

Patient selection for bladder-sparing procedures

This can be classified into patient and tumor factors. Patient factors include: medically unfit and the unwilling patient to have RC. Patient compliance to long-term follow-up is a prerequisite for bladder preservation procedures. Regarding tumor factors, ideally tumors should not exhibit high-risk features defined as the presence of CIS, cT4 (non-organ confined BC), node positive or metastatic disease, multifocal

tumor, incomplete transurethral resection of bladder tumor (TURBT), tumor-causing hydronephrosis or variant/aggressive histology [19].

Techniques of bladder preservation in urothelial BC

(A) Radical TURBT

Radical TURBT involves complete transmural resection of all visible tumors, including resection into the perivesical fat if necessary. It may carry the risk of extravesical seeding of tumor cells, although this is exceedingly rare, anecdotal and not reported in contemporary literature especially with the increased use of chemotherapy following TURBT [20]. The ideal candidate with MIBC should have no hydronephrosis, with negative resection bed biopsies at initial or restaging TURBT and no UTUC. However, only a small proportion of patients (11–35%) with MIBC might be eligible for radical TURBT alone as treatment for their disease [21]. Oncological outcomes: in the properly selected patients, Herr et al. reported 10-year disease-specific survival up to 80% and with bladder preservation in 57% of patients [22].

(B) Radiotherapy as a monotherapy for bladder preservation

Though rarely utilized, radiotherapy (RT) as a monotherapy may be used after failure of other treatment modalities or in the unfit patients with MIBC for RC or chemotherapy. The extent of the radiation field is either to the whole pelvis with higher dose targeting the bladder and gross tumor (cone down/boost volume). The rationale is to control micrometastasis in the pelvic lymph nodes. A more limited radiation field involving the bladder with an additional margin is utilized, though more popular in Europe [19, 23].

Dose and schedule

(a) Split RT approach: popular in North America; the split course (60–65 Gy total) is administered as 40 Gy induction course followed by cystoscopic examination of the urinary bladder. Incomplete responders should be offered immediate RC. Patients with no evidence of tumor will complete an additional 20–25 Gy.
(b) Continuous RT approach: popular in Europe; EBRT is administered as 65 Gy, continuous course without a cystoscopic assessment break.

Overall, there are no head to head trials that compare the split versus continuous RT approach or the extent of the radiation field.

(C) Systemic chemotherapy as a monotherapy for bladder preservation

The interest in systemic chemotherapy alone in treating MIBC has gained attention since the introduction of neoadjuvant chemotherapy (NAC) in North American and European guidelines of MIBC. The use of neoadjuvant methotrexate, vinblastine, doxorubicin and cisplatin (MVAC), dose-dense MVAC or gemcitabine with cisplatin chemotherapy regimens in patients with MIBC treated by cystectomy and/or RT were investigated. The results showed long-term statistically significant reduction in risk of death and estimated 5% increase in a 10-year survival after NAC therapy in comparison with RT or RC alone [24]. In a meta-analysis comprised of 886 patients who received NAC and RC for MIBC, pathological complete response rate (pT0N0M0) was achieved in 28.6%. Also, this proportion of patients demonstrated better overall and recurrence-free survival than patients without pathological complete response [25]. However, currently neither guidelines to recommend systemic chemotherapy as a monotherapy after TURBT for MIBC nor selection criteria for systemic chemotherapy monotherapy in MIBC exist.

(D) Trimodal therapy (TMT)

TMT involved radical TURBT followed by chemo-radiation therapy (CRT). Concurrent systemic chemotherapy and RT aims to prevent distant failure by providing systemic chemotherapy and local failure by radiation therapy. Chemotherapy has the additional benefit of radio-sensitizing the tumor. Currently, the TMT is considered the most promising among bladder preservation techniques (BPT). However, recent research showed that it is associated with higher costs (average 136 K) over RC, 1 year after diagnosis, mostly related to outpatient care costs, radiation and medication costs [26].

Components of TMT

A. *Radical TURBT* Radical (or maximal) TURBT up to resection into the perivesical fat is recommended.
B. *Systemic chemotherapy* Chemotherapy regimens included:

1. Cisplatin-based chemotherapy is the most common used regimen (35–40 mg/m^2 weekly or 100 mg/m^2 every 3 weeks); however, it is deemed unsuitable in TMT candidates with renal impairment.
2. For patients with renal impairment, fluorouracil (5-FU) with MMC combination is an alternative option.

3. Intravenous Gemcitabine was tested as a radiosensitizer agent after TURBT in patients with MIBC in a phase II trial [27].

C. *Radiation therapy* Dose and radiation field are similar to previously described EBRT.

We have summarized the outcomes of pertinent prospective studies regarding TMT in Table 1.

Quality of life after TMT

Assessment of bladder function was performed in 71 patients in TMT approach with median follow-up 6.3 years. Results showed that 75% had normally functioning bladders based on urodynamic studies and 85% reported no urgency. The majority of men retained sexual function and 11% of all women used pads for urine incontinence [33].

Future directions in TMT

Immunotherapy agents in the form of immune checkpoint inhibitors are evaluated in the treatment of metastatic or surgically unrespectable urothelial BC. The programmed death-1 (PD-1) blocker, pembrolizumab (Keytruda®), has been recently approved as a first-line therapy for metastatic BC in patients who are ineligible for cisplatin chemotherapy. Nivolumab (Opdivo®) is utilized as second-line therapy for those who have received platinum-based chemotherapy after proven clinical benefit [34, 35]. There are single-arm small trials where immunotherapy will be used as neoadjuvant/adjuvant therapy with radiation or combined with TMT. Also, the use of NAC of gemcitabine and cisplatin for 2–4 cycles followed by CRT using cisplatin regimen is tried with a 2-year overall and disease-specific survival of 74% and 2-year bladder intact disease-free survival of 64% [36].

(E) Partial cystectomy

Partial cystectomy (PC) with bilateral pelvic lymph node dissection is a less morbid procedure and with better functional (voiding and sexual) outcomes, compared to RC. Optimal candidates for PC are those who have solitary lesions in areas amenable for TURBT (anterior wall and dome), no CIS and no hydronephrosis. Only 7–10% of all cystectomies performed nationally are PCs [37]. Regarding the oncological outcomes, in a matched case control study, PC was compared to RC. The recorded intravesical recurrence rate after PC was 38%, which was non-muscle invasive in 52% and muscle invasive in 48% and with no difference in the 10-year metastasis, cancer or overall survivals [38]. In addition, PC may be combined with NAC/RT. In Memorial Sloan Kettering Cancer Center (MSKCC)

Table 1 Summary of pertinent prospective TMT studies for MIBC

Study	Phase	Stage	*N*	Chemo-radiotherapy		Adjuvant chemotherapy	CR (%)	Bladder preservation (%) (mean F/U years)	OSS (%) (mean F/U years)	Year
				Chemotherapy	Radiotherapy (Gy)					
RTOG 97-06 [28]	I/II	T2–T4a	46	CP	40.8 + 24	MCV × 3	74	47 (3)	61 (3)	2003
RTOG 99-06 [29]	I/II	T2–T4a	80	CP + paclitaxel	40.3 + 24	Gem CP × 4	81	47 (5)	56 (5)	2009
RTOG 85-12 [30]	II	T2–T4	42	CP	40 + 24	N/A	66	N/A	52 (5)	2011
BC 2001 [31]	III	T2–T4a	360	5-FU + mitomycin[a]	55 of 64	N/A	N/A	N/A	48 (5)	2012
RTOG 02-33 [32]	II	T2–T4a	46	CP + paclitaxel	40.3 + 24	Gem + (CP or paclitaxel)	72	67 (5)	71 (5)	2013
			47	CP + 5-FU	40.3 + 24	Gem + (CP or paclitaxel)	62	71 (5)	75 (5)	

CP cisplatin, *CR* complete response, *5-FU* fluorouracil, *GC* gemcitabine and cisplatin, *MCV* methotrexate, cisplatin and vinblastine, *N* number, *NAC* neoadjuvant chemotherapy, *OSS* overall survival, *RTOG* radiation therapy oncology group

[a]Some patients received additional platinum-based chemotherapy

report on the outcome of PC after NAC, results showed 74% of patients were down-staged with 58% having a complete clinical response. Two- and five-year overall survival rates were 71% and 63%, respectively [39].

Predictive factors of tumor recurrence and poor survival after PC include the presence of lymphovascular invasion, ureteral reimplantation and prior history of urothelial carcinoma [40]. Bruins and colleagues studied outcomes of 72 patients who received salvage RC for recurrence following PC. The recurrent disease was organ confined in 61.2%, extravesical in 19.4% and with positive lymph nodes in 19.4%. The recorded 5-year recurrence-free survival and overall survivals were 56% and 41%, respectively [41].

Summary of recommendations of urological guidelines on BPT in urothelial MIBC

(A) The American Urological Association (AUA)/American Society of Clinical Oncology (ASCO)/American Society for Radiation Oncology (ASTRO) and Society of Urologic Oncology (SUO) joint Guidelines [42]

1. *Patient selection* Patients who desire to retain their bladder or unfit to RC.
2. *Maximal TURBT and PC* Not recommended in the medically fit patient for RC.
3. *Primary RT* Not recommended.
4. *TMT* (1) Asses for CIS and multifocal disease during maximal TURBT. (2) Concurrent chemo-radiation therapy is recommended. (3) Chemotherapy regimens should include radio-sensitizing agents as cisplatin, MMC and 5-FU.
5. Following BPTs, regular surveillance cystoscopy, urine cytology and CT scan should be performed.
6. *Management of recurrence after BPTs* In the setting of MIBC, RC and bilateral pelvic lymph node dissection. In non-MIBC, conservative measures with TURBT and intravesical BCG/chemotherapy versus RC and bilateral pelvic lymph node dissection may be offered.

(B) National Comprehensive Cancer Network (NCCN) guidelines [43]

1. *TMT* Concurrent CRT is recommended with radio-sensitizing chemotherapeutic agent. Treatment failure is similar to the AUA/ASCO/ASTRO and SUO guidelines.
2. *Neoadjuvant cisplatin chemotherapy followed by PC* May be recommended in highly selected patients (solitary lesion in a suitable location for PC and no CIS).
3. *In the unfit patient for RC* Maximal TURBT ± intravesical BCG, CRT, or RT can be offered.
4. *Follow-up* First surveillance cystoscopy is usually at 2–3 months after BPTs.

(C) EAU guidelines

The EAU guidelines follow its North American counterpart. Additional recommendations include:

1. *Maximal TURBT* As the AUA/ASCO/ASTRO and SUO guidelines, it is not recommended as a monotherapy except in the unfit/unwilling patient for RC. However, if indicated, restaging TURBT must be performed to ensure no residual tumor.
2. If maximal TURBT and systemic chemotherapy will be offered to the unfit/unwilling patient to undergo RC, then MVAC regimen is preferred over gemcitabine/cisplatin regimen as the incidence of downstaging to pT0 is higher with the former regimen.

Urethra-sparing procedures in urothelial carcinoma

Introduction

Primary urethral carcinomas are rare tumors and account for $<1\%$ of all genitourinary cancers and with a peak incidence ≥ 75 years. The predominant histologic types are urothelial carcinoma (55%), followed by squamous cell carcinoma (SCC; 21.5%) and adenocarcinoma (AC; 16.4%) [44].

Techniques of urethral preservation in urethral carcinoma

(A) Male urethral cancer

Organ preservation for localized distal urethral carcinoma in male patients

These tumors tend to be of low stage and grade. Organ preservation techniques include transurethral fulguration, local excision with defect coverage, or partial urethrectomy. Smith et al. described various techniques for urethral preservation in male distal urethral carcinoma. (a) For lesions visible at the urethral meatus, hypospadias formation (slitting of the ventral surface) with excisional biopsy of the lesion and application of topical 5-FU (5%) can be performed. To ensure local control, the glandular urethra remained hypospadiac for at least 6 months with possible repeat biopsy as indicated. (b) For proven superficial T1 lesions, two-stage procedure, first, distal urethrectomy via bivalving till beyond the tumor and excision with 5-mm margin, the defect is covered by buccal mucosal graft. A second-stage urethral closure over a urethral catheter is performed at least 3 months later. (c) For tumors extending into the glans, glansectomy is performed with 5 mm safety margin on the urethra with

split thickness skin graft to cover the defect. (d) For tumors invading the distal corpora, distal corporectomy with graft and penile lengthening can be performed. Using these techniques, the authors reported no local recurrences and 78% of their patients were alive over a mean follow-up of 26 months [45].

Organ preservation for urothelial carcinoma of the prostate

In this setting, urethra-sparing approach with TUR and subsequent 6 weeks of intravesical BCG instillation can be attempted in Ta, T1 and CIS lesions of the prostatic urethra. In one study, this approach was proven to be effective, with 64.3% exhibiting a complete response in the bladder and prostate at 6-month follow-up [46]. Follow-up prostatic urethral biopsies are crucial to detect early tumor recurrence which is usually an indication for cystectomy. Invasion of the prostatic stroma or ductal involvement is an indication for more aggressive treatment with radical cystoprostatectomy rather than organ preservation since the reported survival outcomes were dismal.

(B) Female urethral cancer

Partial urethrectomy, TUR and laser ablation for small distal urethral tumors have been tried. However, excision of the distal urethra with adequate margin carries the risk of sphincteric injury. RT (median 65 Gy) might be an alternative for conserving surgery in female urethral cancer. However, it carries the risk of urethral stenosis, fistula, cystitis and/or hemorrhage [47].

Summary of recommendations of urological guidelines on urethral preservation in urethral cancer

(A) EAU Guidelines [48]

1. *In male distal urethral cancer* Partial urethrectomy rather than penile amputation is offered as long as a negative margin can be achieved.
2. *In female anterior urethral cancer* Partial (distal urethrectomy) is offered as long as a negative margin with an intraoperative frozen section is achieved. Radiotherapy can be offered; however, local toxicity should be discussed with the patient.

Conclusions

We have described various surgical and non-surgical, alone or combined approaches for organ preservation in urothelial cancers of the upper tract, bladder and urethra. We stress on the appropriate patient selection, adherence to indications for organ preservation and most important adequate patient compliance with follow-up protocols. This leads to comparable oncological outcomes to extirpative surgery and in the meantime improved quality of life

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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