CURRENT ONCOLOGY
A Canadian Cancer Research Journal

PRACTICE GUIDELINE

Complex surgery and perioperative systemic therapy for genitourinary cancer of the retroperitoneum

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ABSTRACT

Objective The purpose of the present guideline is to recommend surgical or systemic treatment for metastatic testicular cancer; T3b or T4, or node-positive, and metastatic renal cell cancer (RCC); and T3, T4, or node-positive upper tract urothelial (UTUC) cancer.

Methods Draft recommendations were formulated based on evidence obtained through a systematic review of randomized controlled trials, comparative retrospective studies, and guideline endorsement. The draft recommendations underwent an internal review by clinical and methodology experts, and an external review by clinical practitioners.

Results The primary literature search yielded eight guidelines, five systematic reviews, and twenty-seven primary studies that met the eligibility criteria.

Conclusions Cytoreductive nephrectomy should no longer be considered the standard of care in patients with T3b or T4, or node-positive, and metastatic RCC. Eligible patients should be treated with systemic therapy and have their primary tumour removed only after review at a multidisciplinary case conference (MCC). Adjuvant sunitinib after surgery is not recommended. Patients with venous tumour thrombus should be considered for surgical intervention. Patients with T3, T4, or node-positive UTUC should have their tumour removed without delay. Decisions concerning lymph node dissection should be done at a MCC and be based on stage, expertise, and imaging. Adjuvant systemic treatment is recommended for resected high-risk UTUC. Patients with metastasis-positive testicular cancer with residual tumour after systemic treatment should be treated at specialized centres. For all complex retroperitoneal surgeries, the evidence shows that higher-volume centres are associated with lower rates of procedure-related mortality, and patients should be referred to higher-volume centres for surgical resection.

Key Words Ontario Health (Cancer Care Ontario); surgery; systemic treatment; testicular cancer, metastatic; renal cell cancer, T3b or T4, or node-positive, and metastatic; urothelial cancer, upper tract, T3, T4, or node-positive; guideline recommendations

Curr Oncol. 2020 February;27(1):e34–e42 www.current-oncology.com

INTRODUCTION

Renal cell carcinoma (RCC) accounts for 5% of all cancers in men and 3% in women, and approximately 15% of those cancers are metastatic at diagnosis[1]. Upper tract urothelial cancers (UTUCs) comprise 5%–10% of all urothelial carcinomas; the rest are urothelial bladder carcinomas. New evidence has shown that UTUCs represent a disease distinct from urothelial bladder carcinomas, which might account for the more than 60% of UTUCs and only 15%–25% of urothelial bladder cancers that present with invasion at diagnosis[2]. Although testicular cancer has a high 5-year survival rate of 95.3%[3], 12% of patients are diagnosed with metastases[3].

Patients with these retroperitoneal genitourinary cancers do not constitute a substantial portion of cancer cases, but their treatment can be complicated. Those complications can lead to worse outcomes for patients—

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including mortality, return trips to the hospital, and adverse events. Currently, no standard of care has been established for these types of surgical patients, and care varies from hospital to hospital. For those reasons, the Genitourinary Disease Site Group at Ontario Health (Cancer Care Ontario) chose this topic for guideline creation. Because there are well-established protocols for managing metastatic testicular cancer with systemic treatment, that disease is not discussed as part of this guideline.

RESEARCH QUESTIONS

- What is the most appropriate role for surgical intervention in patients with T3b or T4, or node-positive, and metastatic RCC, metastatic UTUC, and metastatic testicular cancer?
- Does neoadjuvant or adjuvant chemotherapy improve outcomes for patients receiving surgery for the treatment of T3b or T4, or node-positive, metastatic renal cancer; metastatic UTUC; and metastatic testicular cancer?
- Do patients with T3b or T4, or node-positive, and metastatic RCC; metastatic UTUC; and metastatic testicular cancer have better oncologic outcomes or fewer complications (or both) at higher-volume or academic centres compared with lower-volume and community centres?
- Are there other considerations in relation to the implementation of surgery in patients with T3b or T4, or node-positive, and metastatic RCC; metastatic UTUC; and metastatic testicular cancer to ensure that the procedure is done safely?

TARGET POPULATION

This guideline applies to people with metastatic testicular cancer; T3b or T4, or node-positive, and metastatic RCC; and T3, T4, or node-positive UTUC[4].

INTENDED USERS

This guideline is intended for genitourinary surgeons involved in retroperitoneal surgery, clinicians involved in the care of cancer patients who have received retroperitoneal surgery, and doctors referring patients for retroperitoneal surgery.

DEVELOPMENT OF RECOMMENDATIONS

The Program in Evidence-Based Care produces evidence-based and evidence-informed guidance documents using the methods of the practice guidelines development cycle[5,6]. That process includes a systematic review, interpretation of the evidence and drafting of recommendations by the Working Group, internal review by content and methodology experts, patient and caregiver review, and external review by Ontario clinicians and other stakeholders.

The project was led by a small Working Group of the Genitourinary Disease Site Group members, which was responsible for reviewing the evidence base, drafting the guideline recommendations, and responding to comments received during the document review process. The Working Group had expertise in surgical oncology, radiation oncology, medical oncology, pathology, and health research methodology.

LITERATURE SEARCH RESULTS

Search for Existing Guidelines, Systematic Reviews, and Primary Literature

As a first step in developing the guideline, a search for existing guidelines and systematic reviews was undertaken to determine if an existing guideline or systematic review could be adapted or endorsed. To that end, searches of practice guideline databases, guideline developer Web sites, and the databases MEDLINE, Cochrane Database of Systematic Reviews, and EMBASE (2015–2018) were conducted. Identified guidelines were evaluated using the AGREE II tool[7]. Any identified systematic reviews that addressed the research questions were assessed using AMSTAR 2[8]. The results of the AMSTAR 2 assessment were used to determine whether any existing review could be incorporated as part of the evidentiary base.

The search for guidelines and systematic reviews uncovered 591 documents, of which 113 underwent full-text review. Eight guidelines and five systematic reviews were subsequently retained. The guidelines were found to be suitable and were endorsed for parts of questions 1 and 2. No systematic review fully answered the research questions, and a search for primary literature was undertaken for parts of questions 1 and 2 and all of questions 3 and 4.

The Working Group members reviewed the guidelines in detail and reviewed each recommendation of the guidelines to determine whether recommendations could be endorsed, endorsed with changes, or rejected. The determination was based on agreement of the Working Group members with the interpretation of the available evidence presented in the guideline, whether the recommendation was applicable to and acceptable for the Ontario context, and whether new evidence since the guideline had been developed might change any of the recommendations. When new evidence was available, recommendations were based on the new data.

Study Selection Criteria and Process

Included studies were published in English; examined adult patients with metastatic testicular cancer, UTUC, and T3b or T4, or node-positive, and metastatic RCC; and compared surgical or systemic treatments that included at least 1 outcome of interest [morbidity, disease-free survival (DFS), or overall survival (OS)]. The minimum study size was 20, and participants had to have received no prior systemic treatment. Publications were excluded if they were case studies, single-arm studies, commentaries, or editorials.

A search for primary literature conducted in MEDLINE and EMBASE (2007 to 16 January 2019) produced 5174 hits. Of those hits, 474 were retained for full-text review, with 27 being retained in the guideline.

Data from the included guidelines, systematic reviews, and primary studies were extracted by 1 member of the Working Group (NC). The remaining authors reviewed the articles considered for inclusion and agreed on the full-text

articles to be included. All extracted data and information were audited by an independent auditor (Katie Beaulne).

For each study that was not a randomized controlled trial (RTC), important quality features such as industry funding, control details, blinding, and power calculations were extracted. All RTCs were evaluated using the Cochrane Risk of Bias tool[9].

RECOMMENDATIONS, KEY EVIDENCE, AND INTERPRETATION OF EVIDENCE

RCC and Surgery

Recommendation 1

Cytoreductive nephrectomy has been the standard of care in patients with metastatic clear cell renal cancer who present with the tumour in place. Immediate cytoreductive nephrectomy should no longer be considered to be the standard of care in patients diagnosed with intermediate- and poor-risk disease when medical treatment is required.

Removal of the primary tumour should be considered only after review at a multidisciplinary case conference (MCC) and in certain situations such as high tumour load and symptoms from the primary tumour.

Key Evidence for Recommendation 1

Key evidence is derived from two RTCs by Mejean *et al.*[1] and Bex *et al.*[10].

The Mejean *et al.* RTC showed that the OS results in the sunitinib-only group were noninferior to those in the nephrectomy–sunitinib group [stratified hazard ratio (HR) for death: 0.89; 95% confidence interval (CI): 0.71 to 1.10; upper boundary of the 95% CI for noninferiority: ≤1.20]. Median OS duration was 18.4 months in the sunitinib-only group and 13.9 months in the nephrectomy–sunitinib group. No significant differences in response rate or progression-free survival were evident[1].

The Bex *et al.* RTC (without reaching the statistical power calculation for sample size) reported that the HR for OS in the intention-to-treat population for deferred compared with immediate cytoreductive nephrectomy was 0.57 (95% CI: 0.34 to 0.95; $p = 0.03$). The median OS duration was 32.4 months in the deferred arm and 15.0 months in the immediate arm[10].

Interpretation of Evidence for Recommendation 1

Both RCTs had the advantage of a low risk of bias on 3 methodologic features: randomization method, completeness of outcomes data, and survival outcome (in being objective). However, the risks of bias for the other outcomes were elevated to high, because the assessments of those outcomes were not blinded. Moreover, the Bex *et al.* RCT also had additional biases attributable to a change in the primary outcome from progression-free survival to progression-free rate in the intention-to-treat population.

RCC and Venous Tumour Thrombus

Recommendation 2

All patients with metastatic RCC and venous tumour thrombus should be considered for surgical intervention, regardless of the extent of tumour thrombus at presentation (endorsed from Ljungberg *et al.*[11]).

Qualifying Statements for Recommendation 2

Performance status can significantly improve after removal; deterioration of performance status because of thrombus should therefore not be an exclusion criterion for surgery.

There is no distinct surgical method that seems superior for venous tumour thrombus excision, although the surgical method appears to depend on the level and the grade of thrombus occlusion of the inferior vena cava.

For adequate removal of the thrombus, caval vein control is key, which could require liver mobilization and cardiac bypass. Preoperative embolization does not seem to have any therapeutic value, although it might, in certain situations, provide some technical advantage.

The relative benefits and harms of other strategies and approaches for inferior vena cava access and the role of inferior vena cava filters and bypass procedures remain uncertain.

Key Evidence for Recommendation 2

We endorse the recommendations in the clinical practice guideline by Ljungberg *et al.*[11] on behalf of the European Association of Urology (EAU). The evidence underpinning the recommendations primarily comprises comparative studies.

RCC and Metastasis-Directed Therapy

Recommendation 3

Metastasis-directed therapy can be considered in selected patients with a limited number of metastases and a long disease-free interval (endorsed from Gallardo *et al.*[12] and Escudier *et al.*[13]).

Qualifying Statements for Recommendation 3

The only evidence comes from retrospective and nonrandomized studies of patients with metastatic RCC, which demonstrated prolonged median survival in individuals with metachronous lung metastases and an interval of at least 2 years. Metastasectomy might possibly provide a survival benefit for a selected group of patients with lung metastases only, a long metachronous disease-free interval, and a response to targeted immunotherapy before resection. No systemic treatment is recommended after metastasectomy[13].

Key Evidence for Recommendation 3

We endorse the recommendations from the clinical practice guideline by Gallardo *et al.*[12] on behalf of the Spanish Oncology Genitourinary Group and Escudier *et al.*[13] on behalf of the European Society for Medical Oncology. The guideline by Gallardo *et al.* was upheld in the guideline by Escudier *et al.* The evidence underpinning the recommendations primarily comprises retrospective and cohort studies.

RCC and Adjuvant Systemic Therapy

Recommendation 4

Adjuvant therapy after surgically resected high-risk clear cell carcinoma is not recommended (endorsed from Bex *et al.*[14], Karakiewicz *et al.*[15], and Gallardo *et al.*[12]).

Qualifying Statements for Recommendation 4

Given the rapidly changing therapeutic landscape for RCC, patients should be encouraged to participate in ongoing and future clinical trials of adjuvant therapy after surgical resection for clear cell carcinoma.

Key Evidence for Recommendation 4

Key evidence is derived from three clinical practice guidelines: Bex *et al.*[14] on behalf of the EAU, Karakiewicz *et al.*[15] on behalf of the Kidney Cancer Research Network of Canada, and Gallardo *et al.*[12] on behalf of the Spanish Oncology Genitourinary Group.

The Bex *et al.*[14] guideline for the EAU is an update to the then-current EAU guideline. The update followed the publication of two phase III randomized trials (ASSURE and S-TRAC)[16,17]. A meta-analyses based on those two trials showed that adjuvant sunitinib after surgical resection of high-risk clear cell carcinoma is not recommended.

Further evidence underpinning the recommendations consists of one systematic review[18] of twelve randomized trials and three additional randomized trials not included in the systematic review[19–21].

UTUC and Surgery

Recommendation 5

Once a decision for radical nephroureterectomy (RNU) has been made, the procedure should be carried out as soon as possible, preferably within 28 days[22]. A delay between diagnosis of an invasive tumour and its removal might increase the risk of disease progression (endorsed from Rouprêt *et al.*[23]).

Open RNU: Open RNU with bladder cuff excision is the standard treatment for high-risk UTUC. The procedure must comply with oncologic principles: that is, prevention of tumour seeding by avoiding entry into the urinary tract during resection.

Resection of the distal ureter and its orifice is performed because the risk of tumour recurrence in that area is considerable. After removal of the proximal ureter, imaging it or approaching it by endoscopy is difficult.

Several techniques have been considered to simplify distal ureter resection, including pluck technique, transurethral resection of the intramural ureter, and intussusception. Ureteral stripping is not recommended.

Laparoscopic RNU: Retroperitoneal metastatic dissemination and metastasis along the trocar pathway after manipulation of large tumours in an environment of pneumoperitoneum has been reported in few cases. Several precautions might lower the risk of tumour spillage:

- Avoiding entry into the urinary tract
- Avoiding direct contact between instruments and the tumour
- Performing the laparoscopic RNU in a closed system
- Avoiding morcellation of the tumour and using a specimen retrieval bag for tumour extraction
- Removing the kidney and ureter *en bloc* with the bladder cuff

Invasive or large tumours (T3–4, or N+ or M+, or both) are contraindications to laparoscopic RNU until proven otherwise.

Laparoscopic RNU is safe in experienced hands when strict oncologic principles are adhered to. There is a tendency toward equivalent oncologic outcomes after laparoscopic or open RNU (endorsed from Rouprêt *et al.*[23]).

Qualifying Statements for Recommendation 5

Only one prospective randomized study showed that laparoscopic RNU is not inferior to open RNU for noninvasive UTUC. In contrast, oncologic outcomes have favoured the open approach in pT3 or high-grade tumours. Despite refinements in staging and surgical technique, oncologic outcomes after RNU have not changed significantly since the early 1990s.

Key Evidence for Recommendation 5

The Working Group members endorsed the recommendations from the clinical practice guideline by Rouprêt *et al.*[23] on behalf of the EAU. The evidence underpinning the recommendations primarily consists of one prospective randomized trial and retrospective and cohort studies.

The Working Group members modified the wait time in the recommendation to align with practice in Ontario[22].

UTUC and Lymph Node Dissection

Recommendation 6

The role of retroperitoneal lymph node dissection (RPLND) in UTUC is undetermined, and specifically, the template is not standardized. Such decisions should preferably be made in a MCC and be based on stage, expertise, and imaging (endorsed from Rouprêt *et al.*[24]).

Qualifying Statements for Recommendation 6

Lymph node dissection appears to be uninformative in cases of Ta–1 UTUC because lymph node retrieval is reported in only 2.2% of T1 tumours compared with 16% of pT2–4 tumours.

An increase in the probability of lymph node–positive disease is related to pT classification. However, the true rate of node-positive disease has likely been underreported because the available data are retrospective.

Lymph node dissection can be achieved after lymphatic drainage as follows: lymph node dissection on the side of the affected ureter, and RPLND for higher ureteral tumour or tumour of the renal pelvis, or both (that is, right side: border vena cava or right side of the aorta; left side: border aorta).

Key Evidence for Recommendation 6

The Working Group members endorsed the recommendations from the clinical practice guideline by Rouprêt *et al.*[24] on behalf of the EAU. The evidence underpinning the recommendations primarily consists of one systematic review and two retrospective studies.

UTUC and Distant Metastases

Recommendation 7

There is no oncologic benefit of RNU in patients with distant metastatic UTUC, except for palliative considerations (endorsed from Rouprêt *et al.*[23]).

Qualifying Statements for Recommendation 7

In cases of locoregional involvement or distant metastases with excellent response after systemic chemotherapy, consideration could be given to RNU or surgical consolidation after a MCC.

Key Evidence for Recommendation 7

The Working Group members endorsed the recommendations from the clinical practice guideline by Rouprêt *et al.*[23] on behalf of the EAU. The evidence underpinning the recommendations primarily consists of one prospective randomized trial and retrospective and cohort studies.

UTUC and Systemic Treatment

Recommendation 8

Adjuvant systemic treatment is recommended for resected high-risk UTUC. Given the challenges of renal compromise in the postoperative setting, consideration of neoadjuvant chemotherapy is recommended in the setting of a MCC.

Key Evidence for Recommendation 8

Key evidence was derived from three systematic reviews and meta-analyses[25–27] and one randomized trial (conference abstract)[28,a].

The systematic review and meta-analysis by Gregg *et al.*[26] investigated systemic treatment in UTUC. Perioperative chemotherapy was associated with improved OS (HR: 0.75; 95% CI: 0.57 to 0.99; $p = 0.05$; $I^2 = 57$). It was also associated with improved DFS (HR: 0.54; 95% CI: 0.32 to 0.92; $p = 0.02$; $I^2 = 0$).

A network meta-analysis by Yang *et al.*[27] showed that adjuvant systemic treatment could improve OS by 32% (HR: 0.68; 95% CI: 0.51 to 0.89), DFS by 29% (HR: 0.71; 95% CI: 0.54 to 0.89), and recurrence-free survival by 51% (HR: 0.49; 95% CI: 0.23 to 0.85). A longer OS with neoadjuvant treatment was observed, but was nonsignificant.

The systematic review and meta-analysis by Leow *et al.*[25] demonstrated a pooled HR of 0.43 (95% CI: 0.21 to 0.89; $p = 0.023$; $I^2 = 46\%$), representing a 57% benefit in OS for those receiving adjuvant treatment rather than just surgery alone. The pooled HR was 0.49 (95% CI: 0.24 to 0.99; $p = 0.08$; $I^2 = 0\%$), which represents a 51% benefit in DFS in patients receiving adjuvant treatment.

In the POUT study[28], the 2-year DFS was 51% for surveillance and 70% for chemotherapy. Metastasis-free survival was associated with a HR of 0.49 (95% CI: 0.30 to 0.79; $p = 0.003$) that favoured chemotherapy.

[a] Study is expected to be fully published soon (Birtle A. Personal communication).

Interpretation of Evidence for Recommendation 8

The only randomized trial investigating UTUC and systemic treatment is the POUT study. That study upholds the findings in the meta-analyses.

Testicular Cancer and Surgery

Recommendation 9 (Residual Tumour Resection—Seminoma)

Regardless of size, a residual mass of seminoma should not be primarily resected, but be investigated by imaging and tumour marker tests.

In patients with a residual greater than 3 cm, fluorodeoxyglucose positron-emission tomography (PET) should be performed to gain more information about the viability of the residual. In patients with a residual less than 3 cm, the use of fluorodeoxyglucose PET is optional.

In patients with post-chemotherapy masses greater than 3 cm, PET can be considered. In the absence of tumour growth or PET avidity, surveillance is recommended. Many patients with PET-avid residual lesions will not progress, and so follow-up imaging or a biopsy (or both) to confirm residual disease is prudent.

Patients who progress after systemic treatment have disease that is difficult to cure and must be managed by a multidisciplinary team.

Patients with persistent and progressing elevation in human chorionic gonadotropin after first-line chemotherapy should immediately proceed with salvage chemotherapy. Progressing patients without progressing elevation in human chorionic gonadotropin should undergo histology verification (for example, by biopsy, or mini-invasive or open surgery) before salvage chemotherapy is given.

When RPLND is indicated, it should be performed. Patients must be treated at highly specialized referral centres that perform RPLND surgery, hepatopancreatobiliary surgery, neurosurgery, and vascular surgery, because residuals from seminoma might be difficult to remove because of intense fibrosis. Ejaculatory function should be preserved in these cases whenever technically feasible (endorsed from Albers *et al.*[29]).

Qualifying Statements for Recommendation 9

To avoid false-positive results, fluorodeoxyglucose PET imaging should be scheduled more than 2 months after chemotherapy.

Key Evidence for Recommendation 9

The Working Group members endorsed the recommendations from the clinical practice guideline by Albers *et al.*[29] on behalf of the EAU. The evidence underpinning the recommendations primarily consists of eight retrospective studies.

Recommendation 10 (Residual Tumour Resection—Non-seminoma)

Residual post-chemotherapy tumour resection is highly recommended in all patients with a residual mass greater than 1 cm in the short axis at cross-sectional computed tomography imaging.

After salvage chemotherapy or high-dose chemotherapy in a first or subsequent salvage situation, patients harbour viable tumour at a much higher rate. There is therefore a consideration to perform salvage surgery in those patients even with residual disease smaller than 1 cm.

If residual surgery is indicated, all primary metastatic sites must be completely resected within 2–6 weeks of chemotherapy completion. If technically feasible, a bilateral nerve-sparing procedure should be performed. There is growing evidence that, in all patients, template resections with unilateral preservation of nerves yield long-term results equivalent to those with bilateral systematic resections. The mere resection of the residual tumour (so-called lumpectomy) should not be performed.

In persistent larger-volume retroperitoneal disease, all primary metastatic sites must be completely resected within 6 weeks of chemotherapy completion. If technically feasible, a nerve-sparing procedure should be performed.

In very selected cases of very low residual disease managed in highly experienced hands, laparoscopic RPLND might yield outcomes similar to those with an open procedure; however, a laparoscopic procedure is not recommended outside a specialized laparoscopic centre (endorsed from Albers *et al.*[29]).

Key Evidence for Recommendation 10

The Working Group members endorsed the recommendations from the clinical practice guideline by Albers *et al.*[29] on behalf of the EAU. The evidence underpinning the recommendations primarily consists of six retrospective studies.

Testicular Cancer and Quality and Intensity of Surgery

Recommendation 11

In patients at intermediate or poor risk and with residual disease greater than 5 cm, the probability of vascular procedures is as high as 20%. Such a surgery must therefore be referred to a specialized centre capable of interdisciplinary surgery—hepatic resection, vessel replacement, spinal neurosurgery, thoracic surgery (endorsed from Albers *et al.*[29]).

Qualifying Statements for Recommendation 11

Patients treated within specialized centres benefit from a significant reduction in perioperative mortality to 0.8% from 6%. In addition, specialized urologic surgeons are capable of lowering the local recurrence rate to 3% from 16%, with a higher rate of complete resections.

Key Evidence for Recommendation 11

The Working Group members endorsed the recommendations from the clinical practice guideline by Albers *et al.*[29] on behalf of the EAU. The evidence underpinning the recommendations primarily consists of three retrospective studies.

Testicular Cancer and Salvage Surgery

Recommendation 12

Surgery for resectable disease after salvage treatment remains a potentially curative option in all patients with any residual mass after salvage chemotherapy (endorsed from Albers *et al.*[29]).

Qualifying Statements for Recommendation 12

Survival after surgery and first salvage chemotherapy was improved (70% at 10 years) with taxane-containing regimens. Also, in the case of extensive salvage chemotherapy, surgery remains a fundamental tool to achieve durable complete remissions in up to 20% of patients.

Key Evidence for Recommendation 12

The Working Group members endorsed the recommendations from the clinical practice guideline by Albers *et al.*[29] on behalf of the EAU. The evidence underpinning the recommendations primarily consists of three retrospective studies.

Testicular Cancer and RPLND

Recommendation 13

Nerve-sparing RPLND should be performed only by an experienced surgeon. It is preferable that such surgery take place in a specialized centre with laparoscopic and robot-assisted expertise.

Patients with residual testicular cancer (not necrosis or teratoma) in resected retroperitoneal nodes should be assessed for systemic treatment by a medical oncologist (endorsed from Albers *et al.*[29]).

Key Evidence for Recommendation 13

The Working Group members endorsed the recommendations from the clinical practice guideline by Albers *et al.*[29] on behalf of the EAU. The evidence underpinning the recommendations primarily consists of one randomized controlled study and one retrospective study.

Complex Genitourinary Surgeries of the Retroperitoneum and Surgical Volumes

Recommendation 14

Given evidence that higher-volume centres are associated with lower rates of procedure-related mortality, patients should be referred to higher-volume centres for surgical resection.

Qualifying Statements for Recommendation 14

In most studies, higher-volume centres are associated with improved outcomes. Those studies have no common definition of a high-volume centre compared with a medium- or low-volume centre; however, it should be noted that 5 or fewer cases annually is considered low-volume or very-low-volume in all studies in renal and testicular cancer. However, based on the evidence and the rarity of UTUC in Ontario, centres should consider performing those surgeries if they perform 3 annually.

Because the surgeries are uncommon, requiring multidisciplinary personnel and support services, they should be performed by specifically trained urologists in specific surgical centres as detailed in recommendation 16.

Key Evidence for Recommendation 14

Key evidence was derived from one meta-analysis[30] (sixteen studies[31–46]). That meta-analysis, by Hsu *et al.*, showed that patients who underwent a radical nephrectomy in a high-volume hospital experienced a 26% reduction in postoperative mortality (odds ratio: 0.74; 95% CI: 0.61 to 0.90; $p < 0.01$).

Interpretation of Evidence for Recommendation 14

In most studies, higher-volume centres are associated with improved outcomes. Those studies have no common definition of a high-volume centre compared with a medium- or low-volume centre; however, it should be noted that 5 or fewer cases annually is considered low-volume or very-low-volume in all studies.

Hospitals performing complex genitourinary surgery should know their mortality rates and recognize that lower volumes create larger CIs for mortality estimates.

RCC with Venous Thrombectomy and Surgical Volumes

Recommendation 15

The Working Group members recommend that RCC with venous thrombectomy take place with additional perioperative services as outlined in recommendation 16.

Qualifying Statements for Recommendation 15

Radical nephrectomy with venous thrombosis is a less common, but more complex, surgical scenario.

Key Evidence for Recommendation 15

Key evidence comes from two studies by Toren *et al.*[47,48] and a study by Hsu *et al.*[30].

The in-hospital mortality rate was 7%, with 75% of the deaths occurring in the first 2 cases of the surgeon's experience. Multivariate logistic regression analysis shows a trend to lower in-hospital mortality with surgeons who perform the surgery more frequently, which was significant at the highest quartile (odds ratio for highest vs. lowest quartile: 0.42; 95% CI: 0.18 to 0.98; $p < 0.05$). That relationship was not seen with hospital volume ($p = 0.34$). Surgeon volume, and not hospital volume, is associated with lower in-hospital mortality, with age and comorbidities remaining strong predictors of in-hospital mortality[47,48].

Safe Surgery

Recommendation 16

Complex retroperitoneal surgery often requires operating on great vessels. Such procedures should be performed in centres with sufficient support (appropriate vascular and cardiac services, interventional radiology, and level 3 intensive care units) to prevent or manage complications.

Key Evidence for Recommendation 16

Key evidence comes from one report[49] and group consensus.

REVIEW AND UPDATE

Guidelines developed by the Program in Evidence-Based Care are reviewed and updated regularly. Please visit the Ontario Health (Cancer Care Ontario) Web site (https://www.cancercareontario.ca/) for the full evidence-based series report and subsequent updates.

ACKNOWLEDGMENTS

The Complex Surgery for Genitourinary Cancer of the Retroperitoneum Guideline Development Group thanks the following individuals for their assistance in developing this report: Melissa Brouwers, Donna Maziak, Sheila McNair, Xiaomei Yao, Jonathan Sussman, Roxanne Cosby, Chika Agbassi, Christopher Booth, Armen Aprikian, and Nick Power for providing feedback on draft versions; Katie Beaulne for conducting a data audit; Sara Miller for copyediting; The Canadian Kidney Cancer Forum and Canadian Urological Association, the European Association of Urology, the European Society for Medical Oncology, and the Spanish Oncology Genitourinary Group for allowing endorsement of their guidelines.

The full recommendation report can be found on the Ontario Health (Cancer Care Ontario) Web site at the Genitourinary Cancer Projects page (https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/genitourinary).

The Program in Evidence-Based Care is funded by, but editorially independent from, Ontario Health (Cancer Care Ontario) and the Ontario Ministry of Health.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare the following interests: AL has received consulting fees from Amgen, AstraZeneca, Elekta, GE Healthcare, Janssen, Paladin, Sanofi, Astellas Pharma, and Atlas Pharmaceuticals; has received funding from Janssen and Astellas Pharma; and has received funding as an investigator from Sanofi and Paladin. RS has received funding as an investigator from Sanofi Canada, Janssen, Astellas Pharma, Titan Medical, Embark Healthcare, Terrain Pharmaceuticals, and BN ImmunoTherapeutics (for Prostvac). The remaining authors have no conflicts of interest to disclose.

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