



## Guideline 3-20

A Quality Initiative of the  
Program in Evidence-Based Care (PEBC), Cancer Care Ontario  
(CCO)

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

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**Report Date: August 8, 2019**

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**PEBC Report Citation (Vancouver Style):** Finelli A, Coakley N, Chin J, Flood T, Loblaw A, Morash C, et al. Complex surgery and perioperative systemic therapy for genitourinary cancer of the retroperitoneum. Toronto (ON): Cancer Care Ontario; 2019 August 8. Program in Evidence-Based Care Guideline No.: 3-20.

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

## Section 1: Recommendations

*This section is a quick reference guide and provides the guideline recommendations only. For key evidence associated with each recommendation, see [Section 2](#).*

### GUIDELINE OBJECTIVES

To provide guidance on aspects of complex retroperitoneal surgical technique, including extent of resection and timing of surgery with respect to chemotherapy, and to investigate what other considerations are necessary to ensure safe surgery in this group of patients.

### TARGET POPULATION

This guideline applies to people with metastatic testicular cancer, T3b or T4 or node positive and metastatic renal cell cancer and T3, T4 or node positive upper tract urothelial cancer[1].

### 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.

### RECOMMENDATIONS

#### Renal cell cancer and surgery

##### Recommendation 1

- Cytoreductive nephrectomy (CN) has been the standard of care in patients with metastatic clear-cell renal cancer who present with the tumour in place. **Immediate CN should no longer be considered the standard of care in patients diagnosed with intermediate and poor risk when medical treatment is required.**
- Removal of the primary tumour should only be considered after review at multidisciplinary case conferences (MCC) and in certain situations such as high tumour load and symptoms from the primary tumour.

#### Renal cell cancer and venous tumour thrombus

##### Recommendation 2

All patients with metastatic renal cell carcinoma and venous tumour thrombus should be considered for surgical intervention, irrespective of the extent of tumour thrombus at presentation. This is endorsed from Ljungberg et al., 2015 [4].

#### Renal cell cancer 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., 2018 [5] and Escudier et al., 2016 [6].

#### Renal cell cancer and adjuvant systemic therapy

**Recommendation 4**

Adjuvant therapy following surgically resected high-risk clear cell carcinoma is not recommended. Endorsed from Bex et al., 2017 [7], Karakiewicz et al. [8] and Gallardo et al. [5].

**Upper tract urothelial cancer and surgery****Recommendation 5**

- Once a decision regarding radical nephroureterectomy (RNU) has been made the procedure should be carried out as soon as possible, preferably within 28 days [15].
- A delay between diagnosis of an invasive tumour and its removal may increase the risk of disease progression.
- Endorsed from Rouprêt et al., 2017 [16].

**Radical nephroureterectomy**

- Open RNU with bladder cuff excision is the standard treatment for high-risk upper tract urothelial cancer (UTUC). RNU must comply with oncological principles; that is, preventing tumour seeding by avoidance of entry into the urinary tract during resection.
- Resection of the distal ureter and its orifice is performed because there is a considerable risk of tumour recurrence in this area. After removal of the proximal ureter, it is difficult to image or approach it by endoscopy.
- 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 radical nephroureterectomy**

- Retroperitoneal metastatic dissemination and metastasis along the trocar pathway following manipulation of large tumours in a pneumoperitoneal environment have been reported in few cases. Several precautions may lower the risk of tumour spillage:
  - Avoid entering the urinary tract
  - Avoid direct contact between instruments and the tumour
  - Laparoscopic RNU must take place in a closed system.
  - Avoid morcellation of the tumour and use an endobag for tumour extraction
  - The kidney and ureter must be removed *en bloc* with the bladder cuff
  - Invasive or large (T3/T4 and/or N+/M+) tumours are contraindications for laparoscopic RNU until proven otherwise.
- Laparoscopic RNU is safe in experienced hands when adhering to strict oncologic principles. There is a tendency toward equivalent oncological outcomes after laparoscopic or open RNU.
- Endorsed from Rouprêt et al., 2017 [16].

**Upper tract urothelial cancer 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. These decisions should be made preferably in an MCC and based on stage, expertise, and imaging.
- Endorsed from Rouprêt et al., 2015 [17].

**Upper tract urothelial cancer and distant metastases****Recommendation 7**

- There is no oncologic benefit for RNU in patients with distant metastatic UTUC except for palliative considerations.
- Endorsed from Rouprêt et al., 2017 [16].

**Upper tract urothelial cancer 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 for neoadjuvant chemotherapy is recommended to be made in the setting of a multidisciplinary case conference.

**Testicular cancer and surgery****Recommendation 9****Residual tumour resection - Seminoma**

- A residual mass of seminoma should not be primarily resected, irrespective of the size, but investigated by imaging investigations and tumour markers.
- In patients with residuals of >3 cm, fluorodeoxyglucose-positron emission tomography (FDG-PET) should be performed in order to gain more information on the viability of these residuals. In patients with residuals of <3 cm, the use of FDG-PET is optional.
- In patients with post-chemotherapy masses >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 so follow-up imaging and/or a biopsy to confirm residual disease are prudent.
- Patients who progress post-systemic treatment have disease that is difficult to cure and must be managed by a multidisciplinary team.
- Patients with persistent and progressing human chorionic gonadotropin (hCG) elevation after first-line chemotherapy should immediately proceed with salvage chemotherapy. Progressing patients without hCG progression should undergo histological verification (e.g., by biopsy or mini invasive or open surgery) before salvage chemotherapy is given.
- When RPLND is indicated, this should be performed. Patients must be treated at highly specialized referral centres that perform RPLND surgery, hepato-pancreatic-biliary surgery, neurosurgery, and vascular surgery, as residuals from seminoma may be difficult to remove due to intense fibrosis. Preservation of ejaculatory function should be made in these cases whenever technically feasible.
- Endorsed from Albers et al., 2016 [22].

**Recommendation 10****Non-seminoma**

- Residual post-chemotherapy tumour resection is highly recommended in all patients with a residual mass >1 cm in the short axis at cross-sectional computed tomography imaging.
- Patients after salvage chemotherapy or high-dose chemotherapy in first or subsequent salvage situations harbour viable tumour at a much higher rate. Therefore, there is a consideration to perform surgery in salvage patients even with residual disease <1 cm.
- If residual surgery is indicated, all areas of primary metastatic sites must be

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

- In persistent larger-volume retroperitoneal disease, all areas of primary metastatic sites must be completely resected within six weeks of completion of chemotherapy. If technically feasible, a nerve-sparing procedure should be performed.
- Laparoscopic RPLND may yield similar outcomes to the open procedure in very selected cases of very low residual disease and in very experienced hands, but it is not recommended outside a specialized laparoscopic centre.
- Endorsed from Albers et al., 2016 [22]

### Testicular cancer and quality and intensity of surgery

#### Recommendation 11

- In patients with intermediate or poor risk and residual disease >5 cm the probability of vascular procedures is as high as 20%. This surgery must therefore be referred to specialized centres capable of interdisciplinary surgery (hepatic resections, vessel replacement, spinal neurosurgery, thoracic surgery).
- Endorsed from Albers et al., 2016 [22]

### Testicular cancer and salvage surgery

#### Recommendation 12

Surgery of resectable disease after salvage treatment remains a potentially curative option in all patients with any residual mass following salvage chemotherapy. Endorsed from Albers et al., 2016 [22].

### Testicular cancer and retroperitoneal lymph node dissection

#### Recommendation 13

- Nerve-sparing RPLND should be performed only by an experienced surgeon.
- It is preferable that this 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., 2016 [22]

### 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.

### Renal cell cancer with venous thrombectomy and surgical volumes

#### Recommendation 15

The Working Group members recommend that renal cell cancer with venous thrombectomy take place with additional perioperative services as outlined in Recommendation 16.

**Safe surgery**

**Recommendation 16**

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



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

## Section 2: Guideline - Recommendations and Key Evidence

### GUIDELINE OBJECTIVES

To provide guidance on aspects of complex retroperitoneal surgical technique, including extent of resection and timing of surgery with respect to chemotherapy, and to investigate what other considerations are necessary to ensure safe surgery in this group of patients.

### TARGET POPULATION

This guideline applies to people with metastatic testicular cancer, T3b or T4 or node positive and metastatic renal cell cancer and T3, T4 or node positive upper tract urothelial cancer [1].

### 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.

### RECOMMENDATIONS, KEY EVIDENCE, AND INTERPRETATION OF EVIDENCE

#### Renal cell cancer and surgery

<b>Recommendation 1</b>
<ul style="list-style-type: none"> <li>• Cytoreductive nephrectomy (CN) has been the standard of care in patients with metastatic clear-cell renal cancer who present with the tumour in place. <b>Immediate CN should no longer be considered the standard of care in patients diagnosed with intermediate and poor risk when medical treatment is required.</b></li> <li>• Removal of the primary tumour should only be considered after review at multidisciplinary case conferences (MCC) and in certain situations such as high tumour load and symptoms from the primary tumour.</li> </ul>
<b>Key Evidence for Recommendation 1</b>
<ul style="list-style-type: none"> <li>• Key evidence is derived from two randomized controlled trials (RCTs) by Mejean et al. [2] and Bex et al. [3].</li> <li>• The Mejean et al. RCT showed that the results for overall survival (OS) in the sunitinib-alone group were noninferior to those in the nephrectomy and 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, <math>\leq 1.20</math>). The median OS was 18.4 months in the sunitinib-alone group and 13.9 months in the nephrectomy-sunitinib group. There were no significant differences in response rate or progression-free survival (PFS) [2].</li> <li>• The Bex et al. RCT (without reaching statistical power calculation for sample size) reported that the HR for OS in the intention to treat (ITT) population for deferred versus immediate CN was HR, 0.57 (95% CI, 0.34 to 0.95; p=0.03). The median OS was 32.4 months in the deferred CN arm and 15.0 months in the immediate CN arm [3].</li> </ul>
<b>Interpretation of Evidence for Recommendation 1</b>

- Both trials had the advantage of a low risk of bias on three methodological features: randomization method, completeness of outcome data, and the survival outcome (as it is objective). However, with the other outcomes, the risk of bias was elevated to high, as the assessments of these outcomes were not blinded. Moreover, the Bex et al. trial also had additional biases due to the change in primary outcome from PFS to progression-free rate in the ITT population.

### Renal cell cancer and venous tumour thrombus

<b>Recommendation 2</b>
All patients with metastatic renal cell carcinoma (mRCC) and venous tumour thrombus (VTT) should be considered for surgical intervention, irrespective of the extent of tumour thrombus at presentation. This is endorsed from Ljungberg et al., 2015 [4].
<b>Qualifying Statements for Recommendation 2</b>
<ul style="list-style-type: none"> <li>Performance status (PS) can significantly improve after removal; therefore, deterioration of PS due to thrombus should not be an exclusion criterion for surgery.</li> <li>There is no distinct surgical method that seems superior for VTT excision, although the surgical method appears to depend on the VTT level and the grade of occlusion of the inferior vena cava (IVC).</li> <li>For adequate removal of the thrombus, caval vein control is key, which may require liver mobilisation and cardiac bypass. Preoperative embolization does not seem to have any therapeutic value, although it may, in certain situations, provide some technical advantage.</li> <li>The relative benefits and harms of other strategies and approaches regarding IVC access and the role of IVC filters and bypass procedures remain uncertain.</li> </ul>
<b>Key Evidence for Recommendation 2</b>
We endorse the recommendations from the clinical practice guideline conducted by Ljungberg et al. [4] on behalf of the European Association of Urology (EAU). This guideline scored well on the AGREE II scale. The scores can be seen in Table 2-1 at the end of the recommendations. The evidence underpinning the recommendations is primarily comprised of comparative studies.
<b>Interpretation of Evidence for Recommendation 2</b>
The Working Group members are confident in their endorsement of the recommendation. The source had adequate quality ratings, there is an excellent alignment with research questions of interest by the Working Group, methods and evidence and synthesis are convincing, and the treatments and patients included in the evidence base are generalizable to the Ontario context.

### Renal cell cancer and metastasis-directed therapy

<b>Recommendation 3</b>
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., 2018 [5] and Escudier et al., 2016 [6].
<b>Qualifying Statements for Recommendation 3</b>
<ul style="list-style-type: none"> <li>The only evidence comes from retrospective and nonrandomized studies of patients with mRCC, which have demonstrated a prolonged median survival in those with metachronous lung metastases and an interval of at least two years. Metastasectomy may provide a possible survival benefit for a selected group of patients with lung metastases only, a long metachronous disease-free interval, and a response to immunotherapy targeted therapy before resection. No systemic treatment is</li> </ul>

recommended after metastasectomy [6].
<b>Key Evidence for Recommendation 3</b>
We endorse the recommendations from the clinical practice guidelines conducted by Gallardo et al. on behalf of the Spanish Oncology Genitourinary Group [5] and Escudier et al. [6] on behalf of the European Society of Medical Oncology. The guideline by Gallardo et al. scored well on the AGREE II scale and the recommendations were upheld by the guideline by Escudier et al. The scores can be seen in Table 2-1 at the end of the recommendations. The evidence underpinning the recommendations is primarily comprised of retrospective and cohort studies.
<b>Interpretation of Evidence for Recommendation 3</b>
The Working Group members are confident in their endorsement of the recommendation. The source had adequate quality ratings, there is an excellent alignment with research questions of interest by the Working Group, methods and evidence and synthesis are convincing, and the treatments and patients included in the evidence base are generalizable to the Ontario context.

### Renal cell cancer and adjuvant systemic therapy

<b>Recommendation 4</b>
Adjuvant therapy following surgically resected high-risk clear cell carcinoma is not recommended. Endorsed from Bex et al., 2017 [7], Karakiewicz et al. [8] and Gallardo et al. [5].
<b>Qualifying Statements for Recommendation 4</b>
<ul style="list-style-type: none"> <li>Given the rapidly changing therapeutic landscape for renal cell carcinoma, patients should be encouraged to participating in ongoing and future clinical trials of adjuvant therapy after surgical resection for clear cell carcinoma.</li> </ul>
<b>Key Evidence for Recommendation 4</b>
<ul style="list-style-type: none"> <li>Key evidence derived from three clinical practice guidelines conducted by Bex al. [7] on behalf of the European Association for Urology and Karakiewicz et al. [8] on behalf of the Kidney Cancer Research Network of Canada and Gallardo et al. on behalf of the Spanish Oncology Genitourinary Group [5]. The AGREE scores for the guidelines can be seen in Table 2-1 below the recommendations.</li> <li>The Bex et al. EAU guideline [7] is an update to the current EAU guideline following the publication of two phase 3 randomized trials (ASSURE and S-TRAC) [9,10]. A meta-analysis was performed with the two trials and it showed that adjuvant sunitinib following surgically resected high-risk clear cell carcinoma is not recommended.</li> <li>Further evidence underpinning the recommendations is comprised from one systematic review [11] based on 12 randomized trials and three additional randomized trials not included in the systematic reviews [12-14].</li> </ul>
<b>Interpretation of Evidence for Recommendation 4</b>
The Working Group members are confident in their endorsement of the recommendation. The source had adequate quality ratings, there is an excellent alignment with research questions of interest by the Working Group, methods and evidence and synthesis are convincing, and the treatments and patients included in the evidence base are generalizable to the Ontario context.

### Upper tract urothelial cancer and surgery

<b>Recommendation 5</b>
<ul style="list-style-type: none"> <li>Once a decision regarding radical nephroureterectomy (RNU) has been made the procedure should be carried out as soon as possible, preferably within 28 days [15].</li> </ul>

- A delay between diagnosis of an invasive tumour and its removal may increase the risk of disease progression.
- Endorsed from Rouprêt et al., 2017 [16].

#### **Radical nephroureterectomy**

- Open RNU with bladder cuff excision is the standard treatment for high-risk upper tract urothelial cancer (UTUC). RNU must comply with oncological principles; that is, preventing tumour seeding by avoidance of entry into the urinary tract during resection.
- Resection of the distal ureter and its orifice is performed because there is a considerable risk of tumour recurrence in this area. After removal of the proximal ureter, it is difficult to image or approach it by endoscopy.
- 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 radical nephroureterectomy**

- Retroperitoneal metastatic dissemination and metastasis along the trocar pathway following manipulation of large tumours in a pneumoperitoneal environment have been reported in few cases. Several precautions may lower the risk of tumour spillage:
  - Avoid entering the urinary tract
  - Avoid direct contact between instruments and the tumour
  - Laparoscopic RNU must take place in a closed system.
  - Avoid morcellation of the tumour and use an endobag for tumour extraction
  - The kidney and ureter must be removed *en bloc* with the bladder cuff
  - Invasive or large (T3/T4 and/or N+/M+) tumours are contraindications for laparoscopic RNU until proven otherwise.
- Laparoscopic RNU is safe in experienced hands when adhering to strict oncologic principles. There is a tendency towards equivalent oncological outcomes after laparoscopic or open RNU.
- Endorsed from Rouprêt et al., 2017 [16].

#### **Qualifying Statements for Recommendation 5**

- Only one prospective randomized study has shown that laparoscopic RNU is not inferior to open RNU for non-invasive UTUC. In contrast, oncological outcomes were in favour of the open approach in pT3 and/or high-grade tumours. Oncological outcomes after RNU have not changed significantly over the past three decades despite staging and refinements in staging and surgical technique.

#### **Key Evidence for Recommendation 5**

- The Working Group members endorse the recommendations from the clinical practice guideline conducted by Rouprêt et al. [16] on behalf of the EAU. The guideline by Rouprêt et al. scored well on the AGREE II scale and the scores can be seen in Table 2-1 at the end of the recommendations. The evidence underpinning the recommendations is primarily comprised of one prospective randomized trial and retrospective and cohort studies.
- The Working Group members modified the wait time of the recommendation to align with practice in Ontario [15].

#### **Interpretation of Evidence for Recommendation 5**

The Working Group members are confident in their endorsement of the recommendation. The source had adequate quality ratings, there is an excellent alignment with research questions of interest by the Working Group, methods and evidence and synthesis are convincing, and the treatments and patients included in the evidence base are generalizable to the Ontario context.

### Upper tract urothelial cancer 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. These decisions should be made preferably in an MCC and based on stage, expertise, and imaging.
- Endorsed from Rouprêt et al., 2015 [17].

#### *Qualifying Statements for Recommendation 6*

- Lymph node dissection (LND) appears to be uninformative in cases of TaT1 UTUC because lymph node retrieval is reported in only 2.2% of T1 versus 16% of pT2-4 tumours.
- An increase in the probability of lymph node-positive disease is related to pT classification. However, it is likely that the true rate of node-positive disease has been under-reported because these data are retrospective.
- LND can be achieved following lymphatic drainage as follows: LND on the side of the affected ureter, RPLND for higher ureteral tumour and/or tumour of the renal pelvis (i.e., right side: border vena cava or right side of the aorta; and left side: border aorta).

#### *Key Evidence for Recommendation 6*

The Working Group members endorse the recommendations from the clinical practice guideline conducted by Rouprêt et al. [17] on behalf of the EAU. The guideline by Rouprêt et al. scored well on the AGREE II scale and the scores can be seen in Table 2-1 at the end of the recommendations. The evidence underpinning the recommendations is primarily comprised of one systematic review and two retrospective studies.

#### *Interpretation of Evidence for Recommendation 6*

The Working Group members are confident in their endorsement of the recommendation. The source had adequate quality ratings, there is an excellent alignment with research questions of interest by the Working Group, methods and evidence and synthesis are convincing, and the treatments and patients included in the evidence base are generalizable to the Ontario context.

### Upper tract urothelial cancer and distant metastases

#### Recommendation 7

- There is no oncologic benefit for RNU in patients with distant metastatic UTUC except for palliative considerations.
- Endorsed from Rouprêt et al., 2017 [16].

#### *Qualifying Statements for Recommendation 7*

- In cases where there is locoregional involvement or distant metastases with excellent response following systemic chemotherapy, consideration could be given to RNU or surgical consolidation after an MCC.

#### *Key Evidence for Recommendation 7*

The Working Group members endorse the recommendations from the clinical practice guideline conducted by Rouprêt et al. [16] on behalf of the EAU. The guideline by Rouprêt et al. scored well on the AGREE II scale and the scores can be seen in Table 2-1 at the end of the

recommendations. The evidence underpinning the recommendations is primarily comprised of one prospective randomized trial and retrospective and cohort studies.

#### ***Interpretation of Evidence for Recommendation 7***

The Working Group members are confident in their endorsement of the recommendation. The source had adequate quality ratings, there is an excellent alignment with research questions of interest by the Working Group, methods and evidence and synthesis are convincing, and the treatments and patients included in the evidence base are generalizable to the Ontario context.

### **Upper tract urothelial cancer 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 for neoadjuvant chemotherapy is recommended to be made in the setting of a multidisciplinary case conference.

#### ***Key Evidence for Recommendation 8***

- Key evidence was derived from three systematic reviews and meta-analyses [18-20] and one randomized trial (conference abstract) [21]. (This study will be fully published later this year [*study authors, personal communication*])
- The systematic review and meta-analysis by Gregg et al. investigated systemic treatment in UTUC. Perioperative chemotherapy was associated with an improved OS (HR, 0.75; 95% CI, 0.57 to 0.99; p=0.05; I<sup>2</sup>=57). It was also associated with an improved disease-free survival (DFS) (HR, 0.54; 95% CI, 0.32 to 0.92; p=0.02; I<sup>2</sup>=0) [19].
- A network meta-analysis was performed by Yang et al. This analysis 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 (RFS) by 51% (HR, 0.49; 95% CI, 0.23 to 0.85). A longer OS with neoadjuvant treatment was observed but was not significant [20].
- The systematic review and meta-analysis by Leow et al. demonstrated a pooled HR of 0.43 (95% CI, 0.21 to 0.89; p=0.023; I<sup>2</sup>=46%). This represents a 57% benefit in OS for those treated with adjuvant treatment compared to surgery alone [18]. The pooled HR was 0.49 (95% CI 0.24 to 0.99; p=0.08; I<sup>2</sup>=0%), which represents a 51% benefit in DFS in patients receiving adjuvant treatment compared to surgery alone [18].
- In the POUT study, the two-year DFS rate was 51% for surveillance and 70% for chemotherapy. Metastasis-free survival showed a HR of 0.49 (95% CI, 0.30 to 0.79; p=0.003), which favoured chemotherapy [21].

#### ***Interpretation of Evidence for Recommendation 8***

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

### **Testicular cancer and surgery**

#### **Recommendation 9**

##### **Residual tumour resection - Seminoma**

- A residual mass of seminoma should not be primarily resected, irrespective of the size, but investigated by imaging investigations and tumour markers.
- In patients with residuals of >3 cm, fluorodeoxyglucose-positron emission tomography (FDG-PET) should be performed in order to gain more information on the viability of these residuals. In patients with residuals of <3 cm, the use of FDG-PET is optional.
- In patients with post-chemotherapy masses >3 cm, PET can be considered. In the

<p>absence of tumour growth or PET avidity, surveillance is recommended. Many patients with PET-avid residual lesions will not progress so follow-up imaging and/or a biopsy to confirm residual disease are prudent.</p> <ul style="list-style-type: none"> <li>• Patients who progress post-systemic treatment have disease that is difficult to cure and must be managed by a multi-disciplinary team.</li> <li>• Patients with persistent and progressing human chorionic gonadotropin (hCG) elevation after first-line chemotherapy should immediately proceed with salvage chemotherapy. Progressing patients without hCG progression should undergo histological verification (e.g., by biopsy or mini invasive or open surgery) before salvage chemotherapy is given.</li> <li>• When RPLND is indicated, this should be performed. Patients must be treated at highly specialized referral centres that perform RPLND surgery, hepato-pancreatic-biliary surgery, neurosurgery, and vascular surgery, as residuals from seminoma may be difficult to remove due to intense fibrosis. Preservation of ejaculatory function should be made in these cases whenever technically feasible.</li> <li>• Endorsed from Albers et al., 2016 [22].</li> </ul>
<p><b>Qualifying Statements for Recommendation 9</b></p> <ul style="list-style-type: none"> <li>• FDG-PET scans should be scheduled &gt;2 months after chemotherapy to avoid false positive results after chemotherapy.</li> </ul>
<p><b>Key Evidence for Recommendation 9</b></p> <p>The Working Group members endorse the recommendations from the clinical practice guideline conducted by Albers et al. [22] on behalf of the EAU. The guideline by Albers et al. scored well on the AGREE II scale and the scores can be seen in Table 2-1 at the end of the recommendations. The evidence underpinning the recommendations is primarily comprised of eight retrospective studies.</p>
<p><b>Interpretation of Evidence for Recommendation 9</b></p> <p>The Working Group members are confident in their endorsement of the recommendation. The source had adequate quality ratings, there is an excellent alignment with research questions of interest by the Working Group, methods and evidence and synthesis are convincing, and the treatments and patients included in the evidence base are generalizable to the Ontario context.</p>

<p><b>Recommendation 10</b></p> <p><b>Non-seminoma</b></p> <ul style="list-style-type: none"> <li>• Residual post-chemotherapy tumour resection is highly recommended in all patients with a residual mass &gt;1 cm in the short axis at cross-sectional computed tomography (CT) imaging.</li> <li>• Patients after salvage chemotherapy or high-dose chemotherapy in first or subsequent salvage situations harbour viable tumour at a much higher rate. Therefore, there is a consideration to perform surgery in salvage patients even with residual disease &lt;1 cm.</li> <li>• If residual surgery is indicated, all areas of primary metastatic sites must be completely resected within two to six weeks of completion of chemotherapy. If technically feasible, a bilateral nerve-sparing procedure should be performed. There is growing evidence that template resections with unilateral preservation of nerves yield equivalent long-term results compared to bilateral systematic resections in all patients. The mere resection of the residual tumour (so-called lumpectomy) should not be performed.</li> <li>• In persistent larger-volume retroperitoneal disease, all areas of primary metastatic sites must be completely resected within six weeks of completion of chemotherapy. If</li> </ul>
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<p>technically feasible, a nerve-sparing procedure should be performed.</p> <ul style="list-style-type: none"> <li>Laparoscopic RPLND may yield similar outcomes to the open procedure in very selected cases of very low residual disease and in very experienced hands, but it is not recommended outside a specialized laparoscopic centre.</li> <li>Endorsed from Albers et al., 2016 [22]</li> </ul>
<b>Key Evidence for Recommendation 10</b>
The Working Group members endorse the recommendations from the clinical practice guideline conducted by Albers et al. [22] on behalf of the EAU. The guideline by Albers et al. scored well on the AGREE II scale and the scores can be seen in Table 2-1 at the end of the recommendations. The evidence underpinning the recommendations is primarily comprised of six retrospective studies.
<b>Interpretation of Evidence for Recommendation 10</b>
The Working Group members are confident in their endorsement of the recommendation. The source had adequate quality ratings, there is an excellent alignment with research questions of interest by the Working Group, methods and evidence and synthesis are convincing, and the treatments and patients included in the evidence base are generalizable to the Ontario context.

### Testicular cancer and quality and intensity of surgery

<b>Recommendation 11</b>
<ul style="list-style-type: none"> <li>In patients with intermediate or poor risk and residual disease &gt;5 cm the probability of vascular procedures is as high as 20%. This surgery must therefore be referred to specialized centres capable of interdisciplinary surgery (hepatic resections, vessel replacement, spinal neurosurgery, thoracic surgery).</li> <li>Endorsed from Albers et al., 2016 [22]</li> </ul>
<b>Qualifying Statements for Recommendation 11</b>
<ul style="list-style-type: none"> <li>Patients treated within such centres benefit from a significant reduction in perioperative mortality from 6% to 0.8%. In addition, specialized urologic surgeons are capable of reducing the local recurrence rate from 16% to 3% with a higher rate of complete resections.</li> </ul>
<b>Key Evidence for Recommendation 11</b>
The Working Group members endorse the recommendations from the clinical practice guideline conducted by Albers et al. [22] on behalf of the EAU. The guideline by Albers et al. scored well on the AGREE II scale and the scores can be seen in Table 2-1 at the end of the recommendations. The evidence underpinning the recommendations is primarily comprised of three retrospective studies.
<b>Interpretation of Evidence for Recommendation 11</b>
The Working Group members are confident in their endorsement of the recommendation. The source had adequate quality ratings, there is an excellent alignment with research questions of interest by the Working Group, methods and evidence and synthesis are convincing, and the treatments and patients included in the evidence base are generalizable to the Ontario context.

### Testicular cancer and salvage surgery

<b>Recommendation 12</b>
Surgery of resectable disease after salvage treatment remains a potentially curative option in all patients with any residual mass following salvage chemotherapy. Endorsed from Albers et al., 2016 [22].
<b>Qualifying Statements for Recommendation 12</b>



- Survival after surgery and first salvage chemotherapy was improved, 70% at 10 years, following 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 endorse the recommendations from the clinical practice guideline conducted by Albers et al. [22] on behalf of the EAU. The guideline by Albers et al. scored well on the AGREE II scale and the scores can be seen in Table 2-1 at the end of the recommendations. The evidence underpinning the recommendations is primarily comprised of three retrospective studies.

#### ***Interpretation of Evidence for Recommendation 12***

The Working Group members are confident in their endorsement of the recommendation. The source had adequate quality ratings, there is an excellent alignment with research questions of interest by the Working Group, methods and evidence and synthesis are convincing, and the treatments and patients included in the evidence base are generalizable to the Ontario context.

### **Testicular cancer and retroperitoneal lymph node dissection**

#### **Recommendation 13**

- Nerve-sparing RPLND should be performed only by an experienced surgeon.
- It is preferable that this 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., 2016 [22]

#### ***Key Evidence for Recommendation 13***

We endorse the recommendations from the clinical practice guideline conducted by Albers et al. [22] on behalf of the EAU. The guideline by Albers et al. scored well on the AGREE II scale and the scores can be seen in Table 2-1 at the end of the recommendations. The evidence underpinning the recommendations is primarily comprised of one randomized controlled study and one retrospective study.

#### ***Interpretation of Evidence for Recommendation 13***

The Working Group members are confident in their endorsement of the recommendation. The source had adequate quality ratings, there is an excellent alignment with research questions of interest by the Working Group, methods and evidence and synthesis are convincing, and the treatments and patients included in the evidence base are generalizable to the Ontario context.

### **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. There is no common definition of a high-volume centre compared with medium or low volume within the studies; however, it should be noted that five or fewer annual cases are considered low, or very low volume in all studies for renal and testicular cancer. However, based on the evidence and the rarity of the upper tract urothelial cancer in

<p>Ontario, centres should consider performing these surgeries if they perform three a year.</p> <ul style="list-style-type: none"> <li>Specifically trained urologists in specific surgical centres as detailed in Recommendation 16 should perform these surgeries, as they are uncommon, requiring multidisciplinary personnel and support services.</li> </ul>
<b>Key Evidence for Recommendation 14</b>
<ul style="list-style-type: none"> <li>Key evidence derived from one meta-analysis, 12 studies, and two abstracts.</li> <li>The meta-analysis by Hsu et al. showed that patients who underwent a radical nephrectomy in a high-volume hospital had a 26% reduction in postoperative mortality (odds ratio [OR], 0.74; 95% CI, 0.61 to 0.90, <math>p &lt; 0.01</math>) [23].</li> </ul>
<b>Interpretation of Evidence for Recommendation 14</b>
<ul style="list-style-type: none"> <li>In most studies, higher-volume centres are associated with improved outcomes. There is no common definition of a high-volume centre compared with medium or low volume within the studies; however, it should be noted that five or fewer annual cases are considered low, or very low volume in all studies.</li> <li>Hospitals performing complex genitourinary surgery should know their mortality rates, and recognize that lower volumes create larger CIs for mortality estimates.</li> </ul>

### Renal cell cancer with venous thrombectomy and surgical volumes

<b>Recommendation 15</b>
The Working Group members recommend that renal cell cancer with venous thrombectomy take place with additional perioperative services as outlined in Recommendation 16.
<b>Qualifying Statements for Recommendation 15</b>
<ul style="list-style-type: none"> <li>Radical nephrectomies with venous thrombosis are less common, but are more complex surgical scenarios.</li> </ul>
<b>Key Evidence for Recommendation 15</b>
<p>Key evidence is from two studies by Toren et al. [24,25] and a study by Hsu et al. [23]. The in-hospital mortality rate was 7%, with 75% of the deaths occurring in the first two cases of the surgeon's experience. Multivariate logistic regression analysis shows a trend to lower in-hospital mortality with surgeons who performed the surgery more frequently, which was significant at the highest quartile (OR for highest vs. lowest quartile 0.42; 95% CI, 0.18 to 0.98; <math>p &lt; 0.05</math>). This relationship was not seen with hospital volume (<math>p = 0.34</math>). Surgeon volume, and not hospital volume is associated with lower in-hospital mortality, and age and co-morbidities remain strong predictors of in-hospital mortality [24,25].</p>

### Safe surgery

<b>Recommendation 16</b>
Complex retroperitoneal surgery often requires surgery on great vessels. These procedures should be performed in centres with sufficient support to prevent or manage complications such as appropriate vascular and cardiac services, interventional radiology, and level 3 intensive care units.
<b>Key Evidence for Recommendation 16</b>
<i>Key evidence from one report [26] and group consensus</i>

Table 2-1: Agree Scores

Guideline	Scope and purpose	Stakeholder involvement	Rigour	Clarity presentation	Applicability	Editorial independence
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Guideline 3-20

Canadian Kidney Cancer Forum (CKCF) Karakiewicz 2018 [8]	27%	55%	21%	69%	20%	54%
EAU Renal Ljungberg [4] 2015	61%	50%	59%	72%	18%	91%
ESMO Escudier [6] 2016	39%	19%	32%	77%	8%	58%
SOME-E [5] 2018	63%	33%	54%	94%	4%	58%
EAU Bex [7], 2017	86%	55%	71%	80%	14%	100%
EAU Rouprêt [16,17], 2017 (both Guidelines used the same methods)	56%	39%	66%	61%	21%	71%
EAU Albers 2016 [22]	61%	38%	55%	88%	30%	63%

Abbreviations: EAU, European Association of Urology; ESMO, European Society for Medical Oncology

The endorsed guidelines [4,5,7,8,16,17,22,27], were assessed by two independent reviewers using the AGREE II tool [28]. The guidelines scored well on several domains. Generally the PEBC considers guidelines for endorsing that have scored over 50% on the Rigour portion of the AGREE II tool.

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

## Section 3: Guideline Methods Overview

*This section summarizes the methods used to create the guideline. For the systematic review, see [Section 4](#).*

### THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-Based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO). The PEBC mandate is to improve the lives of Ontarians affected by cancer through the development, dissemination, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer control.

The PEBC supports the work of Guideline Development Groups (GDGs) in the development of various PEBC products. The GDGs are composed of clinicians, other healthcare providers and decision makers, methodologists, and community representatives from across the province.

### JUSTIFICATION FOR GUIDELINE

A quality problem was identified with respect to surgical approaches and patient safety to genitourinary cancer of the retroperitoneum. The Genitourinary Disease Site Group (GU DSG) believed this was an important topic and prioritized it.

### GUIDELINE DEVELOPERS

This guideline was developed by the Complex Surgery for Genitourinary Cancer of the Retroperitoneum GDG (Appendix 1), which was convened at the requests of the Genitourinary Cancer and Surgical Oncology GDGs.

The project was led by a small Working Group of the Complex surgery for genitourinary cancer of the retroperitoneum GDG, 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, medical oncology, pathology, and health research methodology. Other members of the GU GDG served as the Expert Panel and were responsible for the review and approval of the draft document produced by the Working Group. Conflict of interest declarations for all GDG members are summarized in Appendix 1, and were managed in accordance with the [PEBC Conflict of Interest Policy](#).

### GUIDELINE DEVELOPMENT METHODS

The PEBC produces evidence-based and evidence-informed guidance documents using the methods of the Practice Guidelines Development Cycle. [29,30] This process includes a systematic review, interpretation of the evidence by the Working Group and draft recommendations, internal review by content and methodology experts, and external review by Ontario clinicians and other stakeholders.

The PEBC uses the AGREE II framework [28] as a methodological strategy for guideline development. AGREE II is a 23-item validated tool that is designed to assess the methodological rigour and transparency of guideline development and to improve the completeness and transparency of reporting in practice guidelines.

The currency of each document is ensured through periodic review and evaluation of the scientific literature and, where appropriate, the addition of newer literature to the original evidence-base. This is described in the [PEBC Document Assessment and Review Protocol](#). PEBC guideline recommendations are based on clinical evidence, and not on feasibility of implementation; however, a list of implementation considerations such as costs, human resources, and unique requirements for special or disadvantaged populations is provided along with the recommendations for information purposes. PEBC guideline development methods are described in more detail in the [PEBC Handbook](#) and the [PEBC Methods Handbook](#).

### Search for Existing Guidelines

As a first step in developing this guideline, a search for existing guidelines was undertaken to determine if an existing guideline could be adapted or endorsed. To this end, the following sources were searched for existing guidelines that addressed the research questions:

- Practice guideline databases: [Agency for Healthcare Research and Quality \(AHRQ\) National Guideline Clearinghouse](#), and the [Canadian Medical Association Infobase](#).
- Guideline developer websites: [National Institute for Health and Care Excellence \(NICE\)](#), [Scottish Intercollegiate Guidelines Network \(SIGN\)](#), [American Society of Clinical Oncology \(ASCO\)](#), and [National Health and Medical Research Council - Australia](#).

A guideline search from the above websites was conducted along with a search of the primary literature.

## GUIDELINE REVIEW AND APPROVAL

### Internal Review

For the guideline document to be approved, 75% of the content experts who comprise the GDG Expert Panel must cast a vote indicating whether or not they approve the document, or abstain from voting for a specified reason, and of those that vote, 75% must approve the document. In addition, the PEBC Report Approval Panel (RAP), a three-person panel with methodology expertise, must unanimously approve the document. The Expert Panel and RAP members may specify that approval is conditional, and that changes to the document are required. If substantial changes are subsequently made to the recommendations during external review, then the revised draft must be resubmitted for approval by RAP and the GDG Expert Panel.

### External Review

Feedback on the approved draft guideline is obtained from content experts and the target users through two processes. Through the Targeted Peer Review, several individuals with content expertise are identified by the GDG and asked to review and provide feedback on the guideline document. Through Professional Consultation, relevant care providers and other potential users of the guideline are contacted and asked to provide feedback on the guideline recommendations through a brief online survey. This consultation is intended to facilitate the dissemination of the final guidance report to Ontario practitioners.

### PATIENT- AND CAREGIVER-SPECIFIC CONSULTATION GROUP

Four patients participated as Consultation Group members for the Complex surgery for genitourinary cancer of the retroperitoneum Working Group. They reviewed copies of the recommendations and provided feedback on their comprehensibility, appropriateness, and

feasibility to the Working Group's health research methodologist. The health research methodologist relayed the feedback to the Working Group for consideration.

#### **ACKNOWLEDGEMENTS**

The Complex Surgery for Genitourinary Cancer of the Retroperitoneum GDG would like to thank 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 copy editing.
- The Canadian Kidney Cancer Forum and Canadian Urological Association, the European Association of Urology, the European Society of Medical Oncology, and the Spanish Oncology Genitourinary group for allowing endorsement of their guidelines.

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

## Section 4: Systematic Review

### INTRODUCTION

Renal cell carcinoma accounts for 5% of all cancers in men and 3% in women, and approximately 15% of these are metastatic at diagnosis [2]. UTUCs comprise of 5-10% of all urothelial carcinomas, and the rest are urothelial bladder carcinomas. New evidence has shown that UTUCs are a distinct disease from urothelial bladder carcinomas and this may account for why greater than 60% of UTUCs and only 15-25% of urothelial bladder cancer present with invasion at diagnosis [31]. Although testicular cancer has a high five-year survival rate of 95.3% [32], 12% of patients are diagnosed with metastases [32].

While these patients with retroperitoneal genitourinary cancers do not comprise a substantial portion of cancer cases, their treatment can be complicated. These complications can lead to worse outcomes for patients such as mortality, return trips to the hospital, and adverse events. Currently, there is no standard of care for these types of surgical patients and care varies from hospital to hospital. For these reasons, the GU DSG chose this as a guideline topic. Since there are well-established protocols for managing metastatic testicular cancer with systemic treatment it is discussed as part of this guideline.

The Working Group members of the Complex Surgery for Genitourinary Cancer of the Retroperitoneum GDG developed this evidentiary base to inform recommendations as part of a clinical practice guideline. Based on the objectives of this guideline (Section 2), the Working Group derived the research questions outlined below.

### RESEARCH QUESTIONS

1. What is the most appropriate role for surgical intervention in patients with T3b, T4 or node-positive mRCC, metastatic UTUC, and metastatic testicular cancer?
2. Does neoadjuvant or adjuvant chemotherapy improve outcomes for patients receiving surgery for the treatment of T3b, T4 or node-positive metastatic renal cancer, metastatic UTUC, and metastatic testicular cancer?
3. Do patients with T3b, T4 or node-positive mRCC, metastatic UTUC, and metastatic testicular cancer have better oncologic outcomes and/or lower complications at higher volume or academic centres (compared to lower volume and community centres)?
4. Are there other considerations around implementation of surgery in patients with T3b, T4 or node-positive mRCC, metastatic UTUC and metastatic testicular cancer to ensure it is done safely?

### METHODS

This evidence review was conducted in two planned stages, including a search for systematic reviews followed by a search for primary literature. These stages are described in subsequent sections.

#### Search for Existing guidelines and Systematic Reviews

A search was conducted for existing guidelines and systematic reviews. Methods for locating and evaluation of existing guidelines and systematic reviews are described here:

- Databases searched (MEDLINE, EMBASE, Cochrane Database of Systematic Reviews)
- Years covered 2007-September 2018

- Search terms - see Appendix 2
- Selection criteria
  - English language and all included studies in English
  - Directly related to one or more guideline questions
  - At least one original study that meets the inclusion criteria for primary literature

Identified guidelines were evaluated using the AGREE II tool [28]. Identified systematic reviews were evaluated based on their clinical content and relevance. Any identified systematic reviews that addressed the research questions were assessed using A Measurement Tool to Assess Systematic Reviews (AMSTAR 2) [33]. The results of the AMSTAR 2 assessment were used to determine whether or not any existing review could be incorporated as part of the evidentiary base.

### **Search for Primary Literature**

A search for primary studies was undertaken. Medline and EMBASE databases were searched from 2007 to January 16 2019.

### ***Literature Search Strategy***

Please see Appendix 2 for the primary literature search strategy for each question.

### ***Study Selection Criteria and Process***

#### ***Inclusion Criteria***

- English language
- Adult cancer patients with metastatic testicular cancer, UTUC, and T3b, T4 or node-positive mRCC
- Comparative surgical or systemic treatment studies on that include at least one outcome of interest (morbidity, DFS, OS)
- Comparative studies in which N=20 minimally
- No prior systemic treatments

#### ***Exclusion Criteria***

- Case studies, commentaries, editorials
- Single-arm studies

A review of the titles and abstracts that resulted from the search was independently conducted by one reviewer (NC). For those items that warranted full-text review, one reviewer reviewed each item (NC) independently.

### **Data Extraction and Assessment of Study Quality and Potential for Bias**

Data from the included guidelines, systematic reviews, and primary studies were extracted by one member of the Working Group (NC). All extracted data and information were audited by an independent auditor (KB).

Important quality features, such as industry funding, control details, blinding, and power calculations, for each non-RCT study were extracted. RCTs were evaluated using the Cochrane Risk of Bias tool (chapter 8.5) (<http://handbook.cochrane.org/>). Systematic reviews were evaluated using the AMSTAR tool [33] and guidelines were evaluated using AGREE II [28].

Ratios, including HRs, were expressed with a ratio <1.0 indicating that the treatment group experienced the better outcome. An HR <1.0 indicates that patients had a lower



probability of experiencing an event. All extracted data and information were audited by an independent auditor.

### Synthesizing the Evidence

Meta-analysis was not planned as many of the studies included in this systematic review were quite varied and retrospective.

## RESULTS

### Search for Existing Guidelines and Systematic Reviews

A literature search for guidelines and systematic reviews and uncovered 591 documents. Of these, 113 underwent full-text review and eight guidelines and five systematic reviews were retained (Table 4-1). The seven guidelines were evaluated using the AGREE II tool [28] and the systematic reviews were evaluated with the AMSTAR 2 tool [33].

### Literature Search Results

A search for primary literature was conducted. For the three sites there were 5174 hits. Of these, 474 were retained for full-text review. Of these, 27 were retained in the guideline. For a summary of the full literature search results (including guidelines and systematic reviews), please refer to Appendix 3, which is a flow diagram depicting the inclusion and exclusion of all studies for this guidance document. A summary of all included studies can be found in Table 4-1 below.

**Table 4-1. Studies selected for inclusion.**

Reference	Study Type
<b>Renal cancer</b>	
Gallardo [5] Spanish Oncology Genitourinary Group 2014 and 2017	Guideline
Karakiewicz [8] Canadian Kidney Cancer Forum (CKCF) 2018	Guideline
Bex [7] European Association of Urology 2017	Guideline
Escudier [6] ESMO Clinical Practice Guidelines for Renal Cell Carcinoma 2016	Guideline
Ljungberg [4] European Association of Urology 2015	Guideline
Bai [11] 2017	Meta-analysis
Hsu [23] 2017	Meta-analysis
Bex [3] SURTIME 2019	Randomized controlled trial
Mejean [2] CARMENA	Randomized controlled trial

2018[2]	
Motzer [12] PROTECT 2017	Randomized controlled trial
Rini [14] INTORACT 2014	Randomized controlled trial
Motzer [13] 2013	Randomized controlled trial
Chen [34] 2018	Retrospective 2006-2015 United States
Hsu [35] 2018 ABSTRACT	Retrospective 2000-2010 UK
Joshi [36] 2018	Retrospective 2004-2013 United States
Xia [37] 2018	Retrospective 2006-2013 United States
Lawson [38] 2017	Retrospective 2004-2014 Canada
Lawson [39] 2017	Prospective cohort 1988-2011 Canada
Borza [40] 2014 ABSTRACT	Retrospective 2003-2010 US
Kardos SV [41] 2014 ABSTRACT	Retrospective 2006-2008 US
Toren [24] [25] 2013	Retrospective 1998-2007 Canada
Abouassaly [42] 2012	Retrospective 1998-2008 Canada
<b>Testicular Cancer</b>	
Albers 2016 [22] European Association of Urology 2016	Guideline
Woldu [43] 2018	Retrospective 2004-2014 Testicular germ cell tumours
Flum [44] 2014	Retrospective 2003-2013

Yu [45] 2012	Retrospective 2001-2008
<b>Upper Tract Urothelial Cancer</b>	
Rouprêt 2015 and 2017 [16,17] European Association of Urology	Guideline
Gregg [19] 2018	Meta-analysis
Yang [20] 2017	Meta-analysis
Leow [18] 2014	Meta-analysis
Birtle [21] POUT 2018 ABSTRACT (Full publication expected in 2019)	Randomized controlled trial
Macleod [46] 2017 ABSTRACT	Retrospective 2004-2012
Leow [47] 2014 ABSTRACT	Retrospective 2003-2010 US
Lee [48] 2014	Retrospective 2001-2010
<b>Studies on volumes in retroperitoneal surgery</b>	
Nayak [49] 2015 ABSTRACT	Retrospective 2009-2013 US
Nayak [50] 2015 ABSTRACT	Retrospective 2009-2013 US
<b>Safe Surgery requirements</b>	
World Health Organization [26] 2003	Report
Lee [48] 2014	Retrospective 2001-2010 Korea

### Study Design and Quality

Various study designs are included in this guidance document. The guidelines being endorsed for Questions 1 and 2 [4,5,7,8,16,17,22,27] were assessed using the AGREE II tool [28]. A summary of the findings can be seen in Table 4-2. There were six RCTs, which were assessed for risk of bias (Appendix 4). The systematic reviews were assessed using the AMSTAR 2 tool [33] and can be seen in Appendix 5. The remaining studies included in Question 3 and 4 were retrospective and were not assessed for quality.

### Guidelines

The endorsed guidelines [4,5,7,8,16,17,22,27] were assessed by two independent reviewers using the AGREE II tool [28]. The scores are reported in Table 4-2. The guidelines scored well on several domains. Generally, the PEBC considers guidelines for endorsing that

have scored over 50% on the Rigour portion of the AGREE II tool. The AGREE score of the Rigour portion of the European Society for Medical Oncology (ESMO) guideline by Escudier et al. [6] is 32% because it provided very few details about a systematic review for evidence. According to the ESMO guideline development methods, the experts review the literature and predetermined levels of evidence and grades of recommendations are assigned by the expert reviewers [51]. The guideline by Karakiewicz et al. did poorly on the Rigor section as well (AGREE score=21%) [28]. This is because the guideline is consensus based. While the PEBC generally does not endorse consensus guidelines, the Working Group members believed that in this instance the recommendations from Karakiewicz et al. are important because they are from a Canadian group and they uphold the recommendations from other groups.

**Table 4-2: Agree Scores**

Guideline	Scope and purpose	Stakeholder involvement	Rigour	Clarity presentation	Applicability	Editorial independence
Canadian Kidney Cancer Forum (CKCF) Karakiewicz 2018 [8]	27%	55%	21%	69%	20%	54%
EAU Renal Ljungberg [4] 2015	61%	50%	59%	72%	18%	91%
ESMO Escudier [6] 2016	39%	19%	32%	77%	8%	58%
SOME-E [5] 2018	63%	33%	54%	94%	4%	58%
EAU Bex [7], 2017	86%	55%	71%	80%	14%	100%
EAU [16,17], 2017 (both Guidelines used the same methods)	56%	39%	66%	61%	21%	71%
EAU Albers 2016 [22]	61%	38%	55%	88%	30%	63%

Abbreviations: EAU, European Association of Urology; ESMO, European Society for Medical Oncology

## ENDORSEMENT PROCESS

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

## Outcomes

1. **What is the most appropriate role for surgical intervention in patients with T3b, T4 or node-positive mRCC, metastatic UTUC, and metastatic testicular cancer?**

### **Renal Cancer (T3b, T4 or node positive metastatic)**

Two guidelines produced by the EAU [4] and the EMSO [6] were retained from the guideline search as they sufficiently addressed the issue of the most appropriate surgical intervention in patients with T3b, T4 or node-positive mRCC and were therefore endorsed by the Complex Surgery for Genitourinary Cancer of the Retroperitoneum Working Group. Only certain sections of the guidelines are being endorsed. In the Ljungberg et al. EAU guideline, sections pertaining to surgery for mRCC and management of venous thrombus are being endorsed (see page 919 of the Ljungberg et al. guideline [4]). “All patients with non-metastatic RCC and VTT should be considered for surgical intervention, irrespective of the extent of tumour thrombus at presentation.”

In the Escudier et al. guideline the section pertaining to metastasectomy is being endorsed (see page v63 of the Escudier et al. guideline [6]). The authors of this guideline conclude that: “Metastasectomy can be considered and performed after multidisciplinary review for selected patients with solitary or easily accessible pulmonary metastases, solitary resectable intraabdominal metastases, a long disease-free interval after nephrectomy, or a partial response in metastases to immunotherapy or targeted therapy.” The section on metastectomy in the Gallardo et al. guideline is also being endorsed (see page 52). It states that “metastasectomy can be considered in selected patients with limited number of metastases with a long metachronous disease-free interval [5].”

In the recent CARMENA trial by Mejean et al. [2], 450 patients were randomized to either undergo nephrectomy and then receive sunitinib (standard therapy) or to receive sunitinib alone. The dose of sunitinib was 50 mg daily in cycles of 28 days on and 14 days off every six weeks. The median follow-up was 50.9 months, with 326 deaths observed. The results for OS in the sunitinib-alone group were noninferior to those in the nephrectomy and sunitinib group (stratified HR for death, 0.89; 95% CI, 0.71 to 1.10; upper boundary of the 95% CI for noninferiority,  $\leq 1.20$ ). The median OS was 18.4 months in the sunitinib-alone group and 13.9 months in the nephrectomy-sunitinib group. There were no significant differences in response rate or PFS [2]. Sixty-one patients (32.8%) in the nephrectomy-sunitinib group and 91 (42.7%) in the sunitinib-alone group reported adverse events of grade 3 or 4 ( $p=0.04$ ). The most common grade 3 or 4 adverse events seen in the 152 patients treated with sunitinib were asthenia (37 patients), hand-foot syndrome (20 patients), anemia (16 patients), and neutropenia (15 patients) [2]. Quality of life was not reported. This trial was evaluated with the Cochrane risk-of-bias tool (see Appendix 4). The trial scored high on many factors such as blinding allocation and selective reporting; however, due to the nature of the trial being surgical blinding was clearly difficult to achieve.

In the SURTIME randomized trial by Bex et al. [3], patients with mRCC had either an immediate CN followed by sunitinib or three cycles of sunitinib followed by CN. PFS was the primary end point; however, the sample size was not achieved due to poor accrual. Therefore, the independent data monitoring committee endorsed reporting the ITT 28-week progression-free rate (PFR) instead. OS, adverse events, and postoperative progression were secondary end points. The study closed with 99 patients. The 28-week PFR was 42% in the immediate CN arm and 43% in the deferred CN arm ( $p=0.61$ ). The HR for OS in the ITT population for deferred versus immediate CN was 0.57 (95% CI, 0.34 to 0.95;  $p=0.03$ ). The median OS was 32.4 months in the deferred CN arm and 15.0 months in the immediate CN arm [3].

### **Metastatic Upper Tract Urothelial Cancer**

One guideline produced by the EAU [16] was retained from the guideline search as it sufficiently addressed the issue of the most appropriate surgical intervention in patients with metastatic UTUC and was therefore endorsed by the Complex Surgery for Genitourinary

Cancer of the Retroperitoneum Working Group. Only certain sections of the guideline are being endorsed. In this guideline, the sections pertaining to surgery and lymph node dissection for UTUC are being endorsed (see pages 11, 14, 15 and 17 of the 2017 Rouprêt et al. guideline). The authors of this guideline conclude that: “A delay between diagnosis of an invasive tumour and its removal may increase the risk of disease progression. Once a decision regarding RNU has been made the procedure should be carried-out within twelve weeks. Open RNU with bladder cuff excision is the standard treatment for high-risk UTUC, regardless of tumour location. Radical nephroureterectomy must comply with oncological principles, that is preventing tumour seeding by avoidance of entry into the urinary tract during resection. Resection of the distal ureter and its orifice is performed because there is a considerable risk of tumour recurrence in this area. After removal of the proximal ureter, it is difficult to image or approach it by endoscopy. Several techniques have been considered to simplify distal ureter resection, including pluck technique, stripping, transurethral resection of the intramural ureter, and intussusception. Except for ureteral stripping, none of these techniques is inferior to bladder cuff excision. Retroperitoneal metastatic dissemination and metastasis along the trocar pathway following manipulation of large tumours in a pneumoperitoneal environment have been reported in few cases. Several precautions may lower the risk of tumour spillage: avoid entering the urinary tract; avoid direct contact between instruments and the tumour; laparoscopic RNU must take place in a closed system. Avoid morcellation of the tumour and use an endobag for tumour extraction; the kidney and ureter must be removed *en-bloc* with the bladder cuff; invasive or large (T3/T4 and/or N+/M+) tumours are contraindications for laparoscopic RNU until proven otherwise. Laparoscopic RNU is safe in experienced hands when adhering to strict oncologic principles. There is a tendency towards equivalent oncological outcomes after laparoscopic or open RNU. A robot-assisted laparoscopic approach can be considered, but solid data are still lacking [16].” The Working Group members modified the recommendation for the timing of RNU surgery once a decision to have surgery has been made to be in line with practice in Ontario. The time was changed from 12 weeks to as soon as possible within 28 days from the date of decision to have surgery [15].

The anatomic sites of lymph node drainage have not been clearly defined yet. The use of an LND template is likely to have a greater impact on patient survival than the number of removed lymph nodes. LND appears to be unnecessary in cases of TaT1 UTUC because lymph node retrieval is reported in only 2.2% of T1 versus 16% of pT2-4 tumours. An increase in the probability of lymph node-positive disease is related to pT classification. However, it is likely that the true rate of node-positive disease has been under-reported because these data are retrospective

Despite available studies evaluating templates to date, it is not possible to standardize indication or extent of LND. LND can be achieved following lymphatic drainage as follows: LND on the side of the affected ureter, retroperitoneal LND for higher ureteral tumour and/or tumour of the renal pelvis (i.e., right side: border vena cava or right side of the aorta; and left side: border aorta). There is no oncologic benefit for RNU in patients with metastatic UTUC except for palliative considerations.

### **Testicular Cancer**

One guideline produced by the EAU [22] was retained from the guideline search as it sufficiently addressed the issue of the most appropriate surgical intervention in patients with metastatic testicular cancer and was therefore endorsed by the Complex Surgery for Genitourinary Cancer of the Retroperitoneum Working Group. Only certain sections of the guideline are being endorsed. In this guideline the sections pertaining to surgery and RPLND of metastatic testicular cancer are being endorsed (see page 18, 19, 24 and 25 of the Albers

et al. guideline). The authors of this guideline conclude that: “A residual mass of seminoma should not be primarily resected, irrespective of the size, but controlled by imaging investigations and tumour markers. FDG-PET has a high negative predictive value in patients with residual masses after treatment of seminoma. False positive results are less frequent when scans are scheduled > 2 months after chemotherapy. In patients with residuals of > 3 cm, FDG-PET should be performed in order to gain more information on the viability of these residuals. In patients with residuals of < 3 cm, the use of FDG-PET is optional. In the case of a post-chemotherapy mass that is still positive at reclassification FDG-PET with no volume increase, a second FDG-PET should be performed 6 weeks later. Alternatively, a biopsy should be taken to ascertain persistent disease. In these cases as well as in those with progressive disease (i.e. a growing mass which up-takes contrast medium at CT scans or radionuclide tracer at FDG-PET), salvage therapy is indicated (usually chemotherapy or radiotherapy). Patients with persistent and progressing hCG elevation after first line chemotherapy should immediately proceed with salvage chemotherapy. Progressing patients without hCG progression should undergo histological verification (e. g. by biopsy or mini-invasive or open surgery) before salvage chemotherapy is given. When RPLND is indicated, this should be performed in referral centres, as residuals from seminoma may be difficult to remove due to intense fibrosis. Ejaculation may be preserved in these cases. In patients with Non-seminoma, residual tumour resection is mandatory in all patients with a residual mass > 1 cm in the short axis at cross-sectional CT imaging. Patients after salvage chemotherapy or high-dose chemotherapy in first or subsequent salvage situations harbour vital tumour at a much higher rate. Therefore, there is an indication to perform surgery in salvage patients even with residual disease < 1 cm. If residual surgery is indicated, all areas of primary metastatic sites must be completely resected within 2-6 weeks of completion of chemotherapy. If technically feasible, a bilateral nerve-sparing procedure should be performed. There is growing evidence that template resections with unilateral preservation of nerves in selected patients yield equivalent long-term results compared to bilateral systematic resections in all patients. The mere resection of the residual tumour (so called lumpectomy) should not be performed. In persistent larger volume retroperitoneal disease, all areas of primary metastatic sites must be completely resected within 2-6 weeks of completion of chemotherapy. If technically feasible, a nerve-sparing procedure should be performed. Laparoscopic RPLND may yield similar outcomes to the open procedure in very selected cases of very low residual disease and in very experienced hands, but it is not recommended outside a specialized laparoscopic centre. In patients with intermediate or poor risk and residual disease > 5 cm the probability of vascular procedures is as high as 20%. This surgery must therefore be referred to specialized centres capable of interdisciplinary surgery (hepatic resections, vessel replacement, spinal neurosurgery, thoracic surgery). Surgery of resectable disease after salvage treatment remains a potentially curative option in all patients with any residual mass following salvage chemotherapy. When RPLND is performed in a multicentre setting, higher rates of in-field recurrences and complications were reported. Therefore, nerve-sparing RPLND - if indicated - should be performed by an experienced surgeon in specialized centres” [22].

“If there is an indication to perform a staging RPLND, a laparoscopic or robot-assisted RPLND is feasible in expert hands. This minimal-invasive approach cannot be recommended as the standard approach outside of a specialized laparoscopic centre” [22].

2. **Does neoadjuvant or adjuvant chemotherapy improve outcomes for patients receiving surgery for the treatment of UTUC and T3b, T4 or node-positive mRCC?**

## Renal Cancer

Three guidelines produced by the EAU [7], the Kidney Cancer Research Network of Canada [8], and the Spanish Oncology Genitourinary Group [5] were retained from the guideline search. These guidelines sufficiently addressed the issue whether neoadjuvant or adjuvant chemotherapy improves outcomes for patients with T3b, T4 or node-positive mRCC receiving surgery and were therefore endorsed by the Complex Surgery for Genitourinary Cancer of the Retroperitoneum Working Group. Only certain sections of the guidelines are being endorsed. In the Kidney Cancer Research Network of Canada consensus statement [8], the role of adjuvant therapy after nephrectomy is being endorsed (see page 176 of the Karakiewicz et al. guideline). The authors of this guideline conclude that enrolling patients in clinical trials should always be considered the first option for patients with advanced or mRCC. When prescribing systemic therapy for advanced or mRCC, several key factors must be taken into account: patients are best served if the prescribing physician is an oncology specialist knowledgeable of acute and long-term toxicities, drug interactions, and monitoring of treatment and response. Patients should be managed in a multidisciplinary environment with adequate resources, including nursing care, dietary care, and pharmacy support. Patients must be evaluated frequently to ensure toxicities are recognized and managed appropriately. Patients and caregivers should be provided with information concerning potential side effects, as well as their prevention and management.

In the Gallardo et al. [5] guideline only the section on adjuvant and neoadjuvant systemic treatment for the above-mentioned condition is being endorsed (see page 50 of the Gallardo et al. guideline). The authors of this guideline conclude that adjuvant therapy with sunitinib over one year after nephrectomy could be an option to consider individually in patients with high-risk features. However, there is still insufficient evidence to recommend this therapy routinely in clinical practice.

The Bex et al. EAU guideline [7] is an update to the guideline following the publication of two phase 3 randomized trials (ASSURE and S-TRAC) [9,10]. A meta-analysis was performed with the two trials for this guideline update and the authors conclude that adjuvant sunitinib following surgically resected high-risk clear cell carcinoma is not recommended (see page 721 of the Bex et al. guideline).

One systematic review and meta-analysis by Bai et al. was found [11]. This review examined adjuvant therapy for locally advanced renal cell cancer. Twelve randomized studies were found. The results of this meta-analysis demonstrated that adjuvant therapy did not prolong OS (HR, 1.04; 95% CI, 0.95 to 1.15;  $p=0.395$ ;  $I^2=0\%$ ) [11].

An additional three randomized trials were found that addressed adjuvant therapy that were not included in the above systematic review. These are reported in Table 4-3. The PROTECT study by Motzer et al. investigated pazopanib versus placebo. This study did not meet its primary endpoint of DFS in the ITT analysis (HR, 0.86; 95% CI, 0.70 to 1.06;  $p=0.16$ ). After an additional year of follow-up the updated DFS showed an HR of 0.94 (95% CI, 0.77 to 1.14;  $p=0.51$ ) [12]. The Functional Assessment of Cancer Therapy-Kidney Symptom Index (FKSI)-19 showed that both groups had similarly high scores. Increased alanine aminotransferase and aspartate aminotransferase were common adverse events that led to the discontinuation of treatment in the pazopanib group [12].

The INTORACT trial by Rini et al. addresses the use of temsirolimus and bevacizumab versus interferon alfa and bevacizumab. The differences in DFS, OS, and objective response rate (ORR) were not significant. However, patients reported significantly higher overall mean scores in the FKSI-15 and FKSI-disease-related symptoms subscale when receiving temsirolimus and bevacizumab. The adverse events of grade 3 or greater that were more common with temsirolimus and bevacizumab include mucosal inflammation, stomatitis,



hypophosphatemia, hyperglycemia, and hypercholesterolemia. Neutropenia was more common with interferon alfa and bevacizumab [14].

The final randomized trial that was found investigated tivozanib versus sorafenib. This trial combined patients that were treatment naïve and those that had prior treatment. However, the results for PFS were reported separately. PFS was significantly longer in the tivozanib arm and 12.7 versus 9.1 months (HR, 0.756; 95% CI, 0.580 to 0.985;  $p=0.037$ ) for the treatment-naïve group. Quality of life questionnaires were also balanced between groups. Adverse events that were more commonly seen in the tivozanib arm include hypertension and dysphonia. In the sorafenib arm, hand-foot skin reaction and diarrhea were more common [13].

**Table 4-3: RCTs of adjuvant therapy in renal cell cancer**

Reference	Type	Intervention	ORR	DFS/PFS	OS
Motzer [12] PROTECT 2017	Phase 3 RCT	Pazopanib 800 mg N=198 then lowered to 600 mg N=571  Placebo N= 769	NR	The study did not meet the primary DFS end point HR 0.86 (95% CI 0.70-1.06) $p=0.16$	NR
Rini [14] 2014 INTORACT	Phase 3, Randomized, open label	IV Temsirolimus 25 mg + bevacizumab 10mg/kg N=400 or IFN 9 million U subcutaneously + bevacizumab 10 mg/kg N=391	27.0%  27.4%	Median PFS 9.1 months  9.3 months HR 1.1 (95% CI 0.9-1.3) $p=0.8$	25.8 months  25.5 months
Motzer [13] 2013	Phase 3 RCT open label	Tivozanib N=260  Sorafenib N=257	NR	PFS 12.7 months  9.1 months HR 0.756 (95% CI 0.580-0.985); $p=0.037$	NR

**Abbreviations:** CI, confidence interval; DFS, disease-free survival; IFN, interferon alfa; HR, hazard ratio; NR, not reported; OS, overall survival; ORR, objective response rate; PFS, progression-free survival; RCT, randomized controlled trial

### Upper Tract Urothelial Cancer

Three systematic reviews and an abstract from an RCT were found that pertain to systemic treatment and UTUC. This abstract is the only randomized trial of adjuvant chemotherapy and UTUC. The systematic reviews do not contain randomized trials since they were conducted before the POUT trial was completed. The systematic review and meta-analysis by Gregg et al. investigated systemic treatment in UTUC. There were no randomized trials and all the data came from 11 retrospective studies: seven single institution studies and four multi-institutional studies. Perioperative chemotherapy was associated with an improved OS (HR, 0.75; 95% CI, 0.57 to 0.99;  $p=0.05$ ;  $I^2=57$ ). Sequential exclusion of studies did not identify the source of heterogeneity. It was also associated with an improved DFS (HR, 0.54; 95% CI, 0.32 to 0.92;  $p=0.02$ ;  $I^2=0$ ) [19].

A network meta-analysis was performed by Yang et al. Data from 31 studies with respect to adjuvant radiation, adjuvant systemic treatment, neoadjuvant systemic treatment, concurrent chemoradiotherapy, and intravesical systemic treatment were examined. Studies were chosen if they compared treatment to placebo or another treatment involved. This analysis 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 RFS by 51% (HR, 0.49; 95% CI, 0.23 to 0.85). A longer OS was observed with neoadjuvant treatment but was not significant [20]. There are several limitations with this network meta-analysis. The analysis used data from trials rather than individual patient data, which is considered the gold standard. This could be problematic as it may affect the final outcome [52]. Using individual patient data also offers the chance to examine differences in effects among subgroups [52]. There was only one study in the analysis for neoadjuvant treatment versus adjuvant treatment. This result could change if there were more studies. Another limitation is that different surgeons, surgical techniques, and timing of surgery could influence survival in the studies. The same can be applied to different systemic treatment drugs, cycles, and dosages. This can create heterogeneity among the results [20].

The final systematic review and meta-analysis for UTUC by Leow et al. examined the role of adjuvant and neoadjuvant systemic treatment [18]. No randomized studies were found. The OS for adjuvant treatment combined data from five studies. Three of the five studies evaluated cisplatin-based treatments and the other two non-cisplatin-based treatments. The results for the cisplatin-based studies demonstrated a pooled HR of 0.43 (95% CI, 0.21 to 0.89;  $p=0.023$ ;  $I^2=46\%$ ). This represents a 57% benefit in OS for those treated with adjuvant treatment compared to surgery alone [18]. There were only two studies that evaluated DFS and both were cisplatin based. The pooled HR was 0.49 (95% CI, 0.24 to 0.99;  $p=0.48$ ;  $I^2=0\%$ ), which represents a 51% benefit in OS in patients receiving adjuvant treatment compared to surgery alone [18]. There were two retrospective studies that investigated neoadjuvant chemotherapy. There was a benefit in disease-specific survival (HR, 0.41; 95% CI, 0.22 to 0.76;  $p=0.005$ ;  $I^2=16\%$ ). No other analyses were reported on for neoadjuvant chemotherapy in this analysis.

One phase 3 randomized study was found in abstract form. This study will be fully published later in 2019. In the POUT study, patients were randomized to either gemcitabine and cisplatin or surveillance. Two hundred forty-eight patients entered the study before the independent trial oversight committee recommended the trial to close as it met the early stopping rule for efficacy. The two-year DFS rate was 51% for surveillance and 70% for chemotherapy. Metastasis-free survival showed a HR of 0.49 (95% CI, 0.30 to 0.79;  $p=0.003$ ), which favoured chemotherapy. Sixty percent of patients reported grade 3 or higher adverse events in the chemotherapy arm compared to 24% in the surveillance arm. The most common adverse events were neutropenia grade 3 (29%), grade 4 (5%) versus 0% and thrombocytopenia grade 3 (7%), grade 4 (6%) versus 0% in the chemotherapy and surveillance arms, respectively [21].

3. **Do patients with metastatic testicular cancer, UTUC, and T3b, T4 or node-positive mRCC have better oncologic outcomes and/or lower complications at higher volume or academic centres (compared to lower volume and community centres)?**

Two studies were retrospective abstracts that included several retroperitoneal sites. They will be discussed separately from the other sites. Both studies were done by Nayak et al. and used retrospective data from the United States from 2009-2013 [49,50]. The two studies are very similar. In the first study, 4542 patients were identified who underwent major

urological cancer surgery. Fifty-six percent of the patients had a radical nephrectomy, 26% had a partial nephrectomy, 15% had a radical cystectomy, and 2% had a RPLND. There were 795 (18%) patients who experienced an adverse event after surgery that required hospital admission. Over one-half of the patients (64%) returned to their primary hospital. However, this was contingent on the surgery performed (60% radical nephrectomy, 65% partial nephrectomy, 67% radical cystectomy, and 83% RPLND). When the results were stratified by hospital volume it was discovered that patients were more likely to return to their primary hospital ( $p=0.0005$ ), and more patients returned to their primary hospital if it was a low versus high volume centre (72% vs. 55%). These results were not affected by either comorbidities or length of stay. The overall mortality rate was 5%. However, on multivariate analysis, patients who had surgery at a high-volume primary hospital and went to a secondary hospital for adverse event management had higher rates of mortality ( $p=0.03$ ) [49].

The second study by Nayak et al. had a total of 11,536 patients. Sixty-one percent had a radical prostatectomy, 22% had a radical nephrectomy, 10% had a partial nephrectomy, 6% had a radical cystectomy, and 1% had RPLND. This study compared failure to rescue rates and compared those readmitted to their index surgery hospital (primary hospital) with those to a secondary hospital. On the whole, 10% (range, 6-37%) were readmitted within 90 days of surgery and of these 61% were readmitted to their primary hospital. However, this varied according to procedure type (57% were readmitted to primary hospital after radical prostatectomy as opposed to 60% after radical nephrectomy, 65% after partial nephrectomy, 67% after radical cystectomy, and 83% after RPLND). It was found that the chance of readmission to the primary hospital decreased with increasing hospital volume ( $p<0.0001$ ) [50].

### Renal Cancer

There is one systematic review [23] and nine studies that are not included in the systematic review that address volumes and renal cancer [24,34-42]. Of the other nine studies, all are retrospective; three are abstracts and six are fully published. The systematic review used in this guidance document was assessed using the AMSTAR 2 tool [33]. Overall, the included systematic review scored well on those items that were applicable. It provided an a priori design, conducted duplicate study selection and data extraction, performed a comprehensive literature search, assessed the risk of bias for each study, and its impact on the results. The review did not provide information on the funding of each study or provide a reference list of excluded studies. This information can be seen in Appendix 5.

The systematic review by Hsu et al. included data from 226,372 patients in 16 publications. The meta-analysis showed that patients who underwent a radical nephrectomy in a high-volume hospital had a 26% reduction in postoperative mortality (OR, 0.74; 95% CI, 0.61 to 0.90;  $p<0.01$ ) [23]. Although there was significant heterogeneity ( $I^2=75%$ ) in this analysis, a meta-regression was done to determine the cause. The threshold values for high-volume hospitals was shown to be a significant contributor. The analysis was also done with excluding the most heavily weighted study and this led to a similar result (OR, 0.70; 95% CI, 0.55 to 0.88;  $p<0.01$ ) [23]. Patients who underwent a nephrectomy with a venous thrombectomy in high-volume hospitals also showed a 52% reduction in short-term mortality (OR, 0.48; 95% CI, 0.29 to 0.81;  $p<0.01$ ). There was an 18% reduction in complications for radical nephrectomies performed in high-volume centres (OR, 0.82; 95% CI, 0.73 to 0.92;  $p<0.01$ ). Once again the  $I^2$  was high (76.25%) and no factors in the meta-regression significantly contributed to this effect. In addition, this meta-analysis by Hsu et al. performed secondary analyses using different methods for dichotomizing high and low volumes. Since there is no definition or consensus to what is considered high or low volume this may introduce a bias to the results. The results of the secondary analyses show that there are

significant lower risks for mortality for both radical nephrectomy and venous thrombectomy in high-volume hospitals. The risks of complications for radical nephrectomy were significantly decreased in high-volume hospitals when the dichotomy was increased, but when the dichotomy threshold for high-volume hospitals was lowered significance was lost [23].

The studies by Joshi et al. and Chen et al. both showed that treatment at higher-volume centres was associated with improved outcomes. In the study by Joshi et al., the adjusted one-year survival rate was 0.36 at two patients per year, 0.39 at five patients per year, 0.42 at 10 patients per year, and 0.46 at 20 patients per year [36]. High-volume treatment facilities were defined a priori as those in the top 20<sup>th</sup> percentile of mean number of mRCC patients treated per year, which was determined to be  $\geq 4.8$  patients per year. The unadjusted median OS of all mRCC patients (cohort A) treated at high- versus low-volume treatment facilities was 9.5 versus 6.5 months ( $p < 0.001$ ) [36]. The study by Chen et al. demonstrated that when facility case volume was coded as a continuous variable, each increment of 10 mRCC cases a year was linked with reduced all-cause mortality (adjusted HR, 0.93; 95% CI, 0.90 to 0.96;  $p < 0.0001$ ) [34].

Hospital volume and short-term outcomes after CN were evaluated by Xia et al. [37]. This study showed that high-volume centres were associated with lower odds of 30-day mortality (OR, 0.69;  $p = 0.013$ ), 90-day mortality (OR, 0.65;  $p < 0.001$ ), prolonged length of stay (OR, 0.82;  $p = 0.002$ ), and 30-day readmission (OR, 0.78;  $p = 0.028$ ). Sensitivity analyses showed that increasing hospital volume (per case) was associated with lower odds of 30-day mortality (OR, 0.965;  $p = 0.008$ ), 90-day mortality (OR, 0.966;  $p < 0.001$ ), prolonged length of stay (OR, 0.982;  $p = 0.001$ ), and 30-day readmission (OR, 0.975;  $p = 0.012$ ). In this study, high volume was determined to be greater than eight cases per year and seven and lower was defined as low volume. The median interquartile range of hospital volume was two to six cases per year [37].

Two studies by Lawson et al. examined quality indicators for renal cancer surgery [38,39]. The first study used information from the Canadian Kidney Cancer information system and measured six quality indicators: laproscopic approach; partial nephrectomy; partial nephrectomy in patients with chronic kidney disease; positive margin rate; partial nephrectomy complication rate, and warm ischemia time. National averages of 74%, 73%, and 70% were seen for the laproscopic approach, partial nephrectomy, and partial nephrectomy in patients with chronic kidney disease quality indicators and used to benchmark individual hospital performance. Three (23%), two (15%), and two (15%) performed lower than expected for laproscopic approach, partial nephrectomy, and partial nephrectomy in patients with chronic kidney disease, respectively. Hospital identity was an independent predictor of quality of care for laparoscopic and partial nephrectomy in patients with chronic kidney disease ( $p < 0.001$ ) [39]. This study demonstrates that there is significant variability among hospitals for three of the surgical quality indicators.

The second study by Lawson et al. [38] used RCC data from an American database during the years 2004-2014. This study specifically assessed variations in surgical quality for RCC surgery. In this study, more than 1100 hospitals were evaluated for quality and 10-31% were shown to provide poor care. These lower-quality hospitals had lower referral volumes and were less academic compared with the high-quality hospitals ( $p < 0.001$ ). This result was confirmed when it was independently analyzed. High-quality hospitals were associated with lower 30- and 90-day mortality Adjusted OR (CI 0.92 [95% CI, 0.90 to 0.95]; OR, 0.94 [95% CI, 0.91 to 0.96]; HR, 0.97 [95% CI, 0.96 to 0.98]) [38].

The study by Toren et al. [24] compared surgeon or hospital volume on in-hospital mortality and complications for RCC with vena cava involvement. This study used data from 1998-2007 and was based on 816 procedures. The in-hospital mortality rate was 7% with 75% of the deaths occurring in the first two cases of the surgeon's experience. Multivariate logistic regression analysis showed a trend to lower in-hospital mortality with surgeons who

performed the surgery more frequently, which was significant at the highest quartile (OR for highest vs. lowest quartile 0.42; 95% CI, 0.18 to 0.98;  $p < 0.05$ ) [25]. This relationship was not seen with hospital volume ( $p = 0.34$ ). This study showed that surgeon volume, and not hospital volume is associated with lower in-hospital mortality and that age and co-morbidities remain strong predictors of in-hospital mortality [24]. Quartiles for in-hospital death and surgical complications are reported in Table 4-4.

**Table 4-4: Quartiles for in hospital death and surgical complications [24]**

		Univariate Model		Multivariate model	
		OR (95% CI)	P value	OR (95% CI)	P value
<b>Logistic regression analysis for in-hospital death</b>					
Surgeon quartile volume	1	Referent		Referent	
	2	0.56 (0.30-1.12)	0.10	0.52 (0.26-1.04)	0.07
	3	0.48 (0.23-1.00)	0.05	0.42 (0.19-0.95)	0.04
	4	0.38 (0.16-0.92)	0.03	0.43 (0.16-1.20)	0.11
Hospital quartile volume	1	Referent		Referent	
	2	0.91 (0.45-1.84)	0.80	0.98 (0.46-2.08)	0.95
	3	0.61 (0.29-1.29)	0.19	0.68 (0.30-1.54)	0.35
	4	0.66 (0.32-1.39)	0.27	0.67 (0.25-1.75)	0.41
<b>Logistic regression analysis for in-hospital complications</b>					
Surgeon quartile volume	1	Referent		Referent	
	2	0.93 (0.64-1.35)	0.71	1.75 (1.04-2.94)	0.03
	3	0.67 (0.45-1.01)	0.05	1.38 (0.85-2.26)	0.19
	4	0.98 (0.64-1.49)	0.93	0.96 (0.58-1.57)	0.86
Hospital quartile volume	1	Referent		Referent	
	2	1.60 (1.06-2.42)	0.03	2.01 (1.34-3.92)	0.001
	3	1.94 (1.31-2.87)	0.001	2.11 (1.34-3.33)	0.001
	4	1.59 (1.07-2.37)	0.02	1.75 (1.06-2.88)	0.03

Abbreviations: CI, confidence interval; OR, odds ratio

Three studies were abstracts. The first is a study by Borza et al. [40]. This study looked at postoperative complication of radical nephrectomy with atrial thrombectomy. The study took place between 2003 and 2010 and analyzed 1417 patients. The results demonstrated the predictors of a major complication were age  $< 50$  years (vs.  $> 70$  years; OR, 3.1;  $p = 0.01$ ), Charlson Comorbidity Score  $\geq 3$  (vs. CCS0, OR, 5.7;  $p < 0.0001$ ), and surgery in an urban hospital (vs. rural; OR, 8.5;  $p = 0.047$ ). Increased complication rate was not associated with sex, race, metastatic disease, teaching institution, or hospital size. The second abstract was a study by Kardos et al. [41]. This study examined whether the presence of robotic surgery increased the likelihood of patients receiving partial nephrectomy. The study identified 21,999 patients from 2006 to 2008. On multivariable analysis, patients undergoing surgery were more likely to receive partial nephrectomy at academic (OR, 2.77;  $p < 0.001$ ), urban (OR, 3.66;  $p < 0.001$ ), and American College of Surgeons-designated cancer centres (OR, 1.10;  $p < 0.05$ ) compared with non-academic, rural, and non-designated hospitals,

respectively. After adjusting for patient and hospital characteristics, patients undergoing surgery at hospitals with presence of robotic surgery were also associated with higher adjusted ORs for receipt of partial nephrectomy compared with those treated at hospitals without the presence of this advanced treatment technology (OR, 1.28;  $p < 0.001$ ) [41]. Another abstract by Hsu et al. [35] demonstrated that patients whose treatment occurred in the highest volume category hospitals had higher one-year survival compared with those treated in the lowest volume category (HR, 0.72; 95% CI, 0.58 to 0.90;  $p < 0.01$ ). Beyond the first year there was no significant association between hospital volume and survival [35].

### Upper Tract Urothelial Cancer

Two abstracts were found that discussed UTUC and volumes. The study by Macleod et al. [46] examined trends in the utilization of LND during radical nephrectomy for high-grade UTUC. This study examined 11,258 patients between 2004 and 2012. Eighteen percent of the patients ( $n=2028$ ) had minimally invasive disease, and of those, 1009 (9%) underwent LND. The LND rate for open radical nephrectomy was 11.6% versus 6.3% for minimally invasive radical nephrectomy (OR, 0.50; 95% CI, 0.39 to 0.67). By 2012, the open LND rate rose to 15.8%; minimally invasive LND remained stable at 6.4% ( $p < 0.001$ ). There were 79 unique centres in this study and of those, 18 centres were low volume ( $< 2$  cases/year), 40 were intermediate volume (2 to 4 cases/year), and 21 were high volume ( $\geq 5$  cases/year). It was apparent that centre volume was associated with LND (16.9% in top quartile volume centres, compared with 5.5% in lowest quartile volume centres (OR, 3.9; 95% CI, 3.3 to 4.6) [46].

The second study by Leow et al. [47] measured the impact of surgeon volume on the morbidity and cost of nephrectomy. This was a weighted cohort analysis of 49,009 patients. The overall 90-day major complication and readmission rates were 8.8% and 20.0%, respectively. Compared to surgeons performing one nephrectomy a year, surgeons performing  $\geq 3$  each year had a 27% decreased odds of major complications (OR, 0.63; 95% CI, 0.4 to 0.98;  $p = 0.04$ ). Compared with low-volume hospitals ( $\geq 3$ /year), high-volume hospitals ( $\geq 7$ /year) were associated with reduced costs by \$1,140 ( $p = 0.001$ ). Compared with patients who did not have any complications, those who suffered a major complication had significantly higher 90-day median direct hospital costs (\$31,697 vs. \$14,690,  $p < 0.0001$ ) [47].

### Testicular Cancer

Three fully published studies were found that discussed testicular cancer and volumes. The study by Wolde et al. [43] was conducted on data from 33,417 patients with seminoma or nonseminomatous germ cell tumours of any stage between 2004-2014. Hospitals were classified by case volume as high (99th percentile,  $\geq 26.1$  cases annually), high-intermediate (95-99th percentile, 14.6-26.0 cases annually), intermediate (75-95th percentile, 6.1-14.5 cases annually), low-intermediate (25-75th percentile, 1.8-6.0 cases annually), and low (25th percentile,  $< 1.8$  cases annually). The median (interquartile range) number of testicular germ cell tumour cases per institution per year was 3.4 (1.8-6.1). There were 1239 hospitals that met the inclusion criteria. Although the patients treated at high-volume hospitals had worse disease characteristics, hospital volume was positively associated with survival outcomes in more advanced cases of testicular germ cell tumour. In the whole group, the HRs for overall mortality were 1.28, 1.45, 1.48, and 1.83, respectively ( $p < 0.05$ ), for patients treated at high-intermediate, intermediate, low-intermediate, and low-volume hospitals compared with high-volume hospitals. Analysis of patients with stage II or III nonseminoma germ cell tumour showed that increasing hospital volume was associated with a higher rate of performance of post-chemotherapy RPLND ( $p < 0.001$ ) [43].

The study by Flum et al. [44] reviewed six-month case log data from urologists certifying between 2003 and 2013. This was obtained from the American Board of Urology.

There were 8545 certifying urologists, of which 290 (3.4% of all) urologists logged 553 RPLNDs with 21 (3.6%) performed laparoscopically. The median number of RPLNDs logged annually was 1 (range, 1-59; interquartile range, 1-1) with three urologists performing 23% of all RPLNDs. On univariate regression analysis, oncology specialization (OR, 5.1; 95% CI, 2.2 to 11.6;  $p=0.0001$ ) and non-private practice type (OR, 2.8; 95% CI, 1.1 to 7.1;  $p=0.03$ ) were predictive of top 10% ( $\geq 3$  cases) of surgeon RPLND volume. While this study did not provide patient outcome, it was informative to have a picture of the volume of surgeries that were performed by a surgeon and in what type of centres [44].

The study by Yu et al. [45] used a propensity score method to assess utilization, costs and inpatient outcomes based on hospital surgical volume. Data were obtained from 993 patients undergoing RPLNDs from 2001-2008. Just over one-half (51.6%) of RPLNDs were done at hospitals that were performing two or fewer cases per year. Hospitals with higher volumes were associated with fewer complications and more routine home discharges (all  $p \leq 0.047$ ). However, these higher-volume hospitals had more transfusions ( $p=0.004$ ) and incurred \$1,435 more in median costs ( $p < 0.001$ ). Some of the limitations of this study were the inability to adjust for tumour characteristics and the absence of outpatient outcomes [45].

#### 4. Are there other considerations around implementation of surgery in patients with metastatic testicular cancer, UTUC and T3b, T4 or node-positive mRCC to ensure it is done safely?

Only one document was found that listed hospital requirements. The “Surgical Care at the District Hospital” produced by the World Health Organization [26] in 2003 has listing of key equipment and services for three levels of hospitals. The first is a small hospital or health centre. This would be a rural hospital or health centre with a small number of beds equipped for minor procedures. The second level would be a larger district hospital with 100-300 beds and adequately equipped with major and minor operating theatres. This hospital should be able to treat 95-99% of the major life-threatening conditions. It should also be able to do the following procedures:

- Caesarean section
- Laparotomy (usually not for bowel obstruction)
- Amputation
- Hernia repair
- Tubal ligation
- Closed fracture treatment and application of Plaster of Paris
- Eye operations, including cataract extraction
- Removal of foreign bodies; for example, in the airway
- Emergency ventilation and airway management for referred patients such as those with chest and head injuries

A level 3 hospital should be a referral centre with of 300-1000 or more beds with basic intensive care unit (ICU) facilities. The treatment aims are the same as for Level 2, with the addition of:

- Ventilation in operating room and ICU
- Prolonged endotracheal intubation
- Thoracic trauma care
- Hemodynamic and inotropic treatment

- Basic ICU patient management and monitoring for up to 1 week: all types of cases, but with limited or no provision for:
  - Multi-organ system failure
  - Hemodialysis
  - Complex neurological and cardiac surgery
  - Prolonged respiratory failure
  - Metabolic care or monitoring procedures

The following types of surgeries would be able to be performed at this type of centre:

- Facial and intracranial surgery
- Bowel surgery
- Pediatric and neonatal surgery
- Thoracic surgery
- Major eye surgery
- Major gynecological surgery

The following equipment would be necessary in this type of centre:

- Pulse oximeter, spare probes, adult and paediatric
- Electrocardiogram monitor
- Anesthesia ventilator, electric power source with manual override
- Infusion pumps (2 per bed)
- Pressure bag for Intravenous injection
- Electric sucker
- Defibrillator (one per operating room/ICU)
- Automatic blood pressure machine
- Capnograph
- Oxygen analyzer
- Thermometer (temperature probe)
- Electric warming blanket
- Electric overhead heater
- Infant incubator
- Laryngeal mask airways sizes 2, 3, 4 (3 sets per operating room)
- Intubating bougies, adult and child (1 set per operating room)

Another study by Lee et al. [48] was found that addressed wait times on outcomes in upper urinary tract cancer. This study used data from 156 consecutive UTUC patients from 2001 and 2010. The patients were divided into two groups. One hundred thirty-eight (early group) received surgery within one month and 63 had to wait longer than one month to receive surgery (late group). Cancer-specific survival and RFS rates were not significantly different between the two groups. However, a subgroup analysis of the 80 patients with ureteral urothelial carcinoma showed that cancer-specific survival and RFS rates were significantly higher in the early subgroup, and multivariate analysis showed that a surgical wait time of >1 month was an independent prognostic factor of cancer-specific survival and RFS rates in ureteral urothelial carcinoma ( $p=0.04$  and  $p<0.001$ ) [48].

Studies that are relevant, but that are ongoing, unpublished, incomplete, or have not yet started are listed in Table 4-5.



**Table 4-5: Ongoing, Unpublished, or Incomplete Studies Randomized Phase 3 Studies**

ClinicalTrials.gov Identifier	Title	Brief summary
NCT02231749	Nivolumab Combined With Ipilimumab Versus Sunitinib in Previously Untreated Advanced or Metastatic Renal Cell Carcinoma (CheckMate 214)	The purpose of this study is to compare the objective response rate, progression free survival and the overall survival of nivolumab combined with ipilimumab to sunitinib monotherapy in patients with previously untreated renal cell cancer.
NCT03592472	A Study of Pazopanib With or Without Abexinostat in Patients With Locally Advanced or Metastatic Renal Cell Carcinoma (RENAVIV)	This is a randomized, phase 3, double-blind, placebo-controlled study of pazopanib plus abexinostat versus pazopanib plus placebo in patients with locally advanced unresectable or metastatic RCC.
NCT03141177	A Phase 3, Randomized, Open-Label Study of Nivolumab Combined With Cabozantinib Versus Sunitinib in Participants With Previously Untreated Advanced or Metastatic Renal Cell Carcinoma	The purpose of this study is to determine whether nivolumab combined with cabozantinib is safe and effective compared to Sunitinib in previously untreated advanced or metastatic RCC.
NCT00720941	Pazopanib Versus Sunitinib in the Treatment of Locally Advanced and/or Metastatic Renal Cell Carcinoma (COMPARZ)	This study is being conducted to provide a direct comparison of the efficacy, safety and tolerability for pazopanib and sunitinib (SUTENT)
NCT02853331	Study to Evaluate the Efficacy and Safety of Pembrolizumab (MK-3475) in Combination With Axitinib Versus Sunitinib Monotherapy in Participants With Renal Cell Carcinoma (MK-3475-426/KEYNOTE-426)	The purpose of this study is to evaluate the efficacy and safety of pembrolizumab (MK-3475) in combination with axitinib versus sunitinib monotherapy as a first-line treatment for participants with advanced/metastatic RCC
NCT03260894	Pembrolizumab (MK-3475) Plus Epacadostat vs Standard of Care in mRCC	The purpose of this study is to evaluate the efficacy and safety of pembrolizumab plus epacadostat compared to sunitinib or pazopanib in participants with locally advanced/mRCC with clear cell component who have not received prior systemic therapy for their mRCC.
NCT01865747	A Study of Cabozantinib (XL184) vs Everolimus in Subjects With Metastatic Renal Cell Carcinoma (METEOR)	The purpose of this study is to evaluate the effect of cabozantinib (XL184) compared with everolimus (Afinitor) on PFS and OS in subjects with advanced RCC that has progressed after prior VEGFR tyrosine kinase inhibitor therapy.
NCT02420821	A Study of Atezolizumab in Combination With Bevacizumab Versus Sunitinib in Participants With Untreated Advanced Renal Cell Carcinoma (RCC) (IMmotion151)	This multi-centre, randomized, open-label study will evaluate the efficacy and safety of atezolizumab plus bevacizumab versus sunitinib in participants with inoperable, locally advanced, or mRCC who have not received prior systemic active or experimental therapy, either in the adjuvant or metastatic setting.

NCT03095040	The Efficacy and Safety of CM082 Combined With Everolimus in Chinese Patients With Metastatic Renal Cell Carcinoma: a Randomized, Double-blind, Double Dummy, Multicenter Study	This randomized, double-blind, phase 2/3 study is aimed to evaluate the efficacy and safety of CM082 in combination with everolimus in Chinese patients with advanced RCC. The primary endpoint is PFS.
NCT03091192	A Phase III, Open Label, Randomised, Controlled, Multi-Centre Study To Assess the Efficacy and Safety of Savolitinib Versus Sunitinib in Patients With MET-Driven, Unresectable and Locally Advanced, Or Metastatic Papillary Renal Cell Carcinoma (PRCC)	This study is designed for patients diagnosed with MET-driven, unresectable and locally advanced or metastatic papillary renal cell carcinoma. The purpose of this study is to see if an investigational new anti-cancer medication, savolitinib, is effective in treating patients with MET-driven papillary renal cell carcinoma, how it compares with another medication frequently used to treat this disease called sunitinib, and what side effects it might cause.
NCT00920816	Ag-013736 (Axitinib) For The Treatment Of Metastatic Renal Cell Cancer	The study is designed to demonstrate that axitinib (AG-013736) is superior to sorafenib in delaying tumor progression in patients with mRCC.

## DISCUSSION

Retroperitoneal cancers of the genito-urinary system are relatively rare within Ontario, but can be associated with significant morbidity and mortality. These include advanced and invasive cancers of germ cell origin (non-seminoma and seminoma testicular cancers), UTUC, and renal parenchyma (RCC). These tumours often require multidisciplinary care, and surgery is considered complex. This guideline addresses the role of surgery in T3b, T4, or node-positive mRCC, metastatic UTUC, and metastatic testicular cancer.

Recent evidence from two RCTs[2,3] have shown that CN should no longer be considered standard of care in patients with intermediate- or poor-risk mRCC. CN in mRCC should be decided through MCCs. Metastasis-driven therapy including surgery or other ablative interventions may be considered after multidisciplinary review. The SABR-COMET randomized study was presented as a plenary at ASTRO18. It showed that stereotactic ablative radiotherapy applied to metastases of various tumours showed a PFS advantage and OS trend [53]. In the setting of an associated venal cava thrombus, whether metastatic or not, surgery should be considered regardless of the extent of tumour thrombus at presentation. The results of two RCTs have failed to show any benefit for adjuvant systemic therapy after resection of high-risk RCC [9,10].

Invasive UTUC is rarer than RCC. Radical nephroureterectomy with cuff of bladder is the standard of care for high-risk UTUC. In experienced hands, laparoscopic radical nephroureterectomy yields similar outcomes to open radical nephroureterectomy. The role of LND remains controversial with no strong evidence to support a therapeutic benefit. Based on the current literature it is not possible to standardize the template and indications for LND in UTUC. There is no role for radical nephroureterectomy in distant asymptomatic metastatic UTUC, with the primary treatment being systemic therapy. Systemic therapy is also been shown to be of value in the adjuvant setting after radical nephroureterectomy and, thus, patients should be referred to medical oncology for an opinion, ideally preoperatively and if not postoperatively.

Metastatic testicular cancer, most often non-seminoma and seminoma germ cell tumours, should be managed in through multidisciplinary meetings and consultation. These tumours are highly chemosensitive, but there are clear indications for surgery. RPLND is a complex procedure that requires skill and experience and should be performed in referral centres only. Patients treated at specialized cancer centres have fewer complications, less perioperative mortality, and are more likely to have complete resections.

In the studies that examined the relationship between volume and patient outcomes, each study had slightly different definitions for morbidity and mortality, and various end-points for volume considerations. Since the studies were retrospective and patient and hospital characteristics varied, the interpretation of the volume-outcome relationship is difficult. However, a clear improvement in operative mortality is found in higher-volume centres. Therefore, patients should be referred to higher-volume centres with the ability to manage postoperative complications.

## **CONCLUSIONS**

Treatment of retroperitoneal cancers should follow the recommendations outlined in Section 1. The CARMENA trial demonstrated that CN should no longer be considered the standard of care in patients with T3b or T4 or node-positive and mRCC. Eligible patients should be treated with systemic therapy and patients should have their primary tumour removed only after review at an MCC. Adjuvant sunitinib following surgery is not recommended as demonstrated by two trials. However, patients with VTT should be considered for surgical intervention. Patients with T3, T4 or node-positive UTUC should have their tumour removed without delay. Decisions concerning LND should be done at MCC and based on stage, expertise, and imaging. The POUT study demonstrated that adjuvant systemic treatment is recommended for resected high-risk UTUC. Patients with metastatic-positive testicular cancer who have 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. These patients should be referred to higher-volume centres for surgical resection.

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

## Section 5: Internal and External Review

### INTERNAL REVIEW

The guideline was evaluated by the GDG Expert Panel and the PEBC Report Approval Panel (RAP) (Appendix 1). The results of these evaluations and the Working Group's responses are described below.

#### Expert Panel Review and Approval

Of the 15 members of the GDG Expert Panel, 13 members cast votes and none abstained, for a total of 86% response in May 2019. Of those that cast votes, all approved the document (100%). The main comments from the Expert Panel and the Working Group's responses are summarized in Table 5-1.

**Table 5-1. Summary of the Working Group's responses to comments from the Expert Panel.**

Comments	Responses
1. Various typographical errors and formatting	We have modified the document.
2. Qualifying statement about clinical trials to be added to Recommendation 4	We have modified the document.
3. Re-wording of Recommendation 9 point 3	We have modified the document.
4. Define referral centre in Recommendation 11	We have modified the document.
5. Recommendation 5 has a wait time that is not within the Ontario context	We have modified the document.
6. Systemic treatment should be mentioned in the title of the document.	We have modified the document.
7. The first research question should be clarified since it pertains mostly to locally advanced and node-positive UTUC	We have not made any changes; we looked for studies with metastatic cancer, but did not find many and this is reflected in the results.
8. It should be mentioned that patients with residual testicular cancer in resected retroperitoneal nodes should be assessed for systemic treatment.	We have modified the document.

#### RAP Review and Approval

Three RAP members, including the PEBC Director, reviewed this document in April 2019. The RAP approved the document on June 10, 2019. The main comments from the RAP and the Working Group's responses are summarized in Table 5-2.

**Table 5-2. Summary of the Working Group's responses to comments from RAP.**

Comments	Responses
1. Recommendation 1 should be bolded since it is practice changing	We have moved bolded the significant parts of the recommendation.
2. Rewording of interpretation of evidence for all recommendations	We have modified the wording to make it less awkward.
3. Rewording of interpretation of evidence for Recommendation 2	We have modified the wording.

4. Recommendation 9 use of PET scan after chemotherapy was not clear	We have modified the wording.
5. AGREE scores after each recommendation was too cluttered	We have modified the document and moved the AGREE scores to the end of the recommendations.
6. Various instances of word-smithing in recommendations	We have modified the document.
7. Evidence base is slim in endorsed guidelines	The key evidence section for the guidelines being endorsed was expanded to show the evidence that was used to formulate the recommendations
8. Too much key evidence for recommendation 14	The evidence was removed and only the evidence from the meta analysis was retained.
9. T3 and T4 should be clearly defined and the year of TMN referenced	We have modified the document.
10. Any evidence of LND in RCC?	There is no template and node dissection is not discussed. There are sparse high-level data concerning LND in RCC.

**Table 5-3. Summary of the Working Group's responses to comments from the Patient Consultation Group.**

Comments	Responses
1. Recommendation 12 is hard to understand.	We have looked at the recommendation and have not made any changes. Salvage treatment is a common medical term.
2. How do you define high- and low-volume centres?	We do not want to be prescriptive in the recommendations and are unable define it for Ontario.
3. What about treatments other than surgery such as radiation therapy?	This guideline pertains to surgery only and options that can affect surgical outcomes.
4. Interpretation of evidence all the same	When guidelines were endorsed we used the same statement since it was applicable.
5. Recommendation 5 follows a different format	Its format is a little different since it is outlining safe surgical practices.

## EXTERNAL REVIEW

### External Review by Ontario Clinicians and Other Experts

#### *Targeted Peer Review*

Four targeted peer reviewers from Ontario who are considered to be clinical and/or methodological experts on the topic were identified by the Working. Three agreed to be the reviewers (Appendix 1) and three responses were received. Results of the feedback survey are summarized in Table 5-3. The comments from targeted peer reviewers and the Working Group's responses are summarized in Table 5-4.

**Table 5-3. Responses to nine items on the targeted peer reviewer questionnaire.**

Question	Reviewer Ratings (N=3)				
	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the guideline development methods.				2	1

2. Rate the guideline presentation.		1			2
3. Rate the guideline recommendations.				1	2
4. Rate the completeness of reporting.				1	2
5. Does this document provide sufficient information to inform your decisions? If not, what areas are missing?			1	1	1
6. Rate the overall quality of the guideline report.			1	1	1
	Strongly Disagree (1)	(2)	Neutral (3)	(4)	Strongly Agree (5)
7. I would make use of this guideline in my professional decisions.			1		2
8. I would recommend this guideline for use in practice.			1		2
9. What are the barriers or enablers to the implementation of this guideline report?	<ul style="list-style-type: none"> <li>• Access to centres where such complex surgery is best performed and their capacity to absorb such referrals in a timely fashion.</li> <li>• Reluctance of community surgeons to refer complex cases to centres with greater experience.</li> </ul>				

Table 5-4. Responses to comments from targeted peer reviewers.

Comments	Responses
1. Recommendation 13 that seems to imply that RPLNDs should only be done laparoscopically or robotically.	We have moved modified the document to make this clear.
2. For RPLND in non-seminomatous germ cell tumors (Recommendation 10), template resections are partially endorsed for unilateral nerve sparing “in selected patients” but no mention to who these patients might be is clarified	We have moved modified the document.

### Professional Consultation

Feedback was obtained through a brief online survey of healthcare professionals and other stakeholders who are the intended users of the guideline. Surgical and Medical Oncologists who treat genitourinary cancer in the PEBC database were contacted by email to inform them of the survey. Seventy-nine were contacted and 17 (21%) responses were received. Seven stated that they did not have interest in this area or were unavailable to review this guideline at the time. The results of the feedback survey from 10 people are summarized in Table 5-5. The main comments from the consultation and the Working Group’s responses are summarized in Table 5-6.

Table 5-5. Responses to four items on the professional consultation survey.

General Questions: Overall Guideline Assessment	Number 10 (12%)				
	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the overall quality of the guideline report.				6	4

Guideline 3-20

	Strongly Disagree (1)	(2)	(3)	(4)	Strongly Agree (5)
2. I would make use of this guideline in my professional decisions.			1	2	7
3. I would recommend this guideline for use in practice.				6	4
4. What are the barriers or enablers to the implementation of this guideline report?	<ul style="list-style-type: none"> <li>• Potential long wait times to highly specialized centres.</li> <li>• Age of patients with metastatic retroperitoneal disease and co-morbid factors may limit the need for intervention.</li> <li>• Enablers include collaborative multidisciplinary practice in the care of this group of patients aided by clear information sharing among health care practitioners.</li> <li>• Smaller centres that perform some of these complex surgeries in low volumes that still want to continue performing them. May require in-house presentations/seminars to convince them to refer these cases to larger centres.</li> <li>• Absence of randomized data in many clinical scenarios. Surgeon/provider factors.</li> <li>• PET scans are not available at all centres and this may result in some delay in treatment when a PET scan is required.</li> <li>• Those in very remote communities would have some difficulties but then the patients from these areas should be moved to areas of superior expertise</li> </ul>				

**Table 5-6. Modifications/Actions taken/Responses regarding main written comments from professional consultants.**

Comments	Responses
1. From a pathology perspective, renal veins/renal vein thrombi/portions of IVC can on occasion be challenging to interpret with respect to margin assessment. Ideally, the surgeon should comment (either in the operative report or on the pathology specimen requisition) as to the adequacy of margin excision.	We have not modified the document as this outside the scope of this guideline.
2. The phrase "Consideration of removing the primary tumour should only be considered..." has too much consideration going on. It is a very weak statement. A slightly stronger alternative would be: Removal of the primary tumour should only be	We have modified the document.

considered...."	
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**CONCLUSION**

The final guideline recommendations contained in Section 2 and summarized in Section 1 reflect the integration of feedback obtained through the external review processes with the document as drafted by the GDG Working Group and approved by the GDG Expert Panel and the PEBC RAP.



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## Appendix 1: Affiliations and Conflict of Interest Declarations

### Members of the Complex surgery for genitourinary cancer of the retroperitoneum Working Group

Name	Affiliation	Declarations of interest
<b>Working Group members</b>		
Antonio Finelli Working Group Chair Urologic oncologist and surgeon investigator	Head, Division of Urology GU Site Lead, Princess Margaret Cancer Centre  GU Cancer Lead, Cancer Care Ontario  Associate Professor, University of Toronto  Toronto, Ontario	None declared
Joseph Chin Surgeon	Professor of Surgery, Division of Urology and Professor of Oncology, Department of Oncology London Health Sciences  London, Ontario	<ul style="list-style-type: none"> <li>• Member of an Advisory Board or equivalent with the following commercial organizations: Profound Med Inc, US HIFU, Amgen, Janssen, Astellas, Ferring, Bayer, Sanofi-Aventis and AbbVie</li> <li>• Participating in or have participated in a clinical trial within the past two years funded by the following agencies: OICR, CIHR, Profound Medical Inc, US HIFU, Astellas, AbbVie, Novartis, DiagnoCure, Amgen, Sanofi-Aventis, AstraZeneca, and Ferring.</li> </ul>
Trevor Flood Pathologist	Pathology and Laboratory Medicine Faculty of Medicine University of Ottawa  Ottawa, Ontario	None declared
Sebastian Hotte Medical Oncologist	Head of the Phase I Research Program  Chair of the Head and Neck Disease Site Group.  Co-chair of the Genitourinary disease site group of the PEBC	None declared

Name	Affiliation	Declarations of interest
	Fellowship Program Director, Medical Oncology  Department of Oncology McMaster University  Hamilton, Ontario	
Andrew Loblaw Radiation Oncologist, Clinician Scientist	Co-Chair of the American Society of Clinical Oncology's Genitourinary Advisory Group  Co-Chair of the GU group for Cancer Care Ontario's PEBC  Toronto, Ontario	<ul style="list-style-type: none"> <li>• Earned more than \$5,000 in a year to act in a consulting capacity for Amgen, AstraZeneca, Elekta, GE, Janssen, Paladin, Sanofi, Astellas, and Atlas.</li> <li>• Had other financial or material support of \$5000 or more in a single year from Janssen, Astellas.</li> <li>• Received grants or other research support either as principle or co-investigator in any amount from a relevant business entity, Sanofi and Paladin.</li> <li>• Been a PI on a number of radiation trails and provided multiple news agencies about prostate cancer treatment and side effects</li> </ul>
Chris Morash Surgical Oncologist	Head of Urol Oncol in the Surgical Oncology Program Medical Director of the Ottawa Prostate Cancer Assessment Center. Head of the Prostate Robotics Program at the Ottawa Hospital.  Site Chief of Urology, The General Campus of The Ottawa Hospital Ottawa, Ontario	None declared
Bobby Shayegan Urologic oncologist	Associate Professor and Head, Division of Urology at McMaster University.  Holds the David Braley and Nancy Gordon Endowed Chair  Director of the McMaster Institute of Urology	None declared

Guideline 3-20

Name	Affiliation	Declarations of interest
	Hamilton, Ontario	
Rob Siemens Clinician Scientist	Head, Department of Urology, Queen's University, Kingston General Hospital and Hotel Dieu Hospital Kingston, Ontario	<ul style="list-style-type: none"> <li>Received any grants or other research support, either as principal or co-investigator, in any amount, from a relevant business entity; Sanofi-Canada Janssen Astellas</li> <li>Been a principal investigator for a clinical trial involving any of the objects of study, regardless of the source of funding; Titan Embark Terrain BNIT-Prostvac</li> </ul>
Nadia Coakley Health Research Methodologist	Program in Evidence-Based Care McMaster University Hamilton, Ontario	None declared
RAP panel		
Melissa Brouwers	Director School of Epidemiology and Public Health Faculty of Medicine University of Ottawa	None declared
Donna Maziak Surgical Oncologist	Department of Surgery, University of Ottawa Program Director and Director of Research in Thoracic Surgery Department of Thoracic Surgery, Ottawa Hospital - General Campus	None declared
Jonathan Sussman Radiation Oncologist	Professor and Chair Department of Oncology, Division of Radiation Oncology Director, Supportive Cancer Care Research Unit  Juravinski Cancer Centre Hamilton, ON	None declared
Expert Panel		
Jack Barkin Surgical Oncologist	Humber River Hospital, University Health Network, Toronto, ON	None declared
Glenn Bauman Radiation Oncologist	London Regional Cancer Program, London, ON	None declared
Rodney Breau Surgical Oncologist	Department of Surgery, University of Ottawa	None declared
Charles Catton	Princess Margaret Cancer	<ul style="list-style-type: none"> <li>Earned more than \$500 in a</li> </ul>

Name	Affiliation	Declarations of interest
Radiation Oncologist	Centre, Toronto, ON	year to act in a consulting capacity for Abbvie, Sanofi, Astellas and Janssen.
Urban Emmenegger Medical Oncologist	Odette Cancer Centre Sunnybrook Health Sciences Centre, Toronto, ON	<ul style="list-style-type: none"> <li>• Earned more than \$500 in a year to act in a consulting capacity for Amgen, Astellas, Bayer, Ferring, Janssen and Sanofi.</li> <li>• Received any grants or other research support, either as principal or co-investigator, in any amount, from a relevant business entity; Astellas, Bayer, Janssen</li> </ul>
Andrew Feifer Surgical Oncologist	Trillium Health Partners, Mississauga, ON University Health Network - Toronto General Hospital, Toronto, ON	<ul style="list-style-type: none"> <li>• Earned more than \$500 in a year to act in a consulting capacity for Astellas, Janssen and Sanofi.</li> </ul>
Michael Lock Radiation Oncologist	London Regional Cancer Program, London, ON	<ul style="list-style-type: none"> <li>• Earned more than \$500 in a year to act in a consulting capacity for AbbVie, 3M, Accuray consultancy and Ferring consultancy.</li> <li>• Received any grants or other research support, either as principal or co-investigator, in any amount, from a relevant business entity; 3M</li> </ul>
Aamer Mahmud Radiation Oncologist	Kingston Health Sciences Centre Cancer Centre of Southeastern Ontario at Kingston General Hospital, Kingston, ON	None declared
Scott Morgan Radiation Oncologist	Ottawa Hospital Research Institute University of Ottawa, Ottawa ON	<ul style="list-style-type: none"> <li>• Earned more than \$500 in a year to act in a consulting capacity for Astellas, Bayer and Janssen.</li> </ul>
Tom Short Surgical Oncologist	Trillium Health Partners, Mississauga, ON	None declared
John Srigley Pathologist	Trillium Health Partners, Mississauga, ON	None declared
Padraig Warde Radiation Oncologist	Provincial Head, Radiation Treatment Program Cancer Care Ontario Princess Margaret Hospital/University Health Network, Toronto, ON	None declared



Guideline 3-20

Name	Affiliation	Declarations of interest
Eric Winqvist Medical Oncologist	London Regional Cancer Program, London, ON	•Earned more than \$500 in a year to act in a consulting capacity for Amgen, AstraZeneca, Bayer, Aisai, Merck, Roche.
<b>Targeted Peer Reviewers</b>		
Armen Aprikian	McGill University Health Centre Montreal, QC	None declared
Christopher Michael Booth	Kingston Health Sciences Centre Kingston, ON	Non declared
Nick Power	London Health Science Centre, London, ON	None declared

The COI declared above did not disqualify any individuals from performing their designated role in the development of this guideline, in accordance with the PEBC COI Policy. To obtain a copy of the policy, please contact the PEBC office by email at [ccopgi@mcmaster.ca](mailto:ccopgi@mcmaster.ca)

## Appendix 2: Literature Search Strategy

### Renal Cell Cancer -Medline

1. Renal cancer.mp. or Kidney Neoplasms/
2. Kidney cancer.mp.
3. rcc.mp.
4. carcinoma renal cell.mp. or Carcinoma, Renal Cell/
5. renal cell neoplasm.mp.
6. or/1-5
7. advanced.mp.
8. metasta\$.mp.
9. node positive.mp.
10. t3b.mp.
11. t4.mp.
12. or/7-11
13. 6 and 12

### Renal Cell Cancer - EMBASE

1. kidney carcinoma/
2. carcinoma, renal cell.mp.
3. renal cell carcinoma.mp.
4. rcc.mp.
5. renal cancer.mp.
6. kidney carcinoma/ or kidney tumo?r/ or renal neoplasm.mp.
7. kidney neoplasm.mp.
8. or/1-7
9. advanced cancer/ or advanced.mp.
10. metasta\$.mp. or metastasis/
11. t3b.mp.
12. t4.mp.
13. or/9-12
14. 8 and 13
15. limit 14 to yr="2007 -Current"
16. limit 15 to english language
17. animal/ not (exp human/ or humans/)
18. 16 not 17

### Upper Tract Urothelial Cancer - Medline

1. Kidney Neoplasms/ or Carcinoma, Transitional Cell/ or Urologic Neoplasms/ or Urinary Bladder Neoplasms/ or Ureteral Neoplasms/
2. upper urinary tract carcinoma.mp.
3. ((ureter and neoplasm) or (ureter and tumo?r)).mp.

4. (ureter and cancer).mp. [mp=ti, ot, ab, nm, hw, tx, kw, ct, kf, px, rx, ui, sy]
5. upper urinary tract cancer.mp.
6. upper.mp.
7. or/1-5
8. 6 and 7

#### **Upper Tract Urothelial Cancer - EMBASE**

1. urinary tract cancer/ or transitional cell carcinoma/ or urogenital tract cancer/ or urogenital tract tumo?r/
2. (Upper tract urothelial cancer or Upper tract urothelial carcinoma or Upper tract urothelial neoplasm or Upper tract urothelial tumo?r).mp.
3. (urinary tract cancer or urinary tract tumo?r or urinary tract carcinoma or urinary tract neoplasm).mp.
4. (urogenital tract carcinoma or urogenital tract tumo?r or urogenital tract cancer or urogenital tract neoplasm).mp.
5. (transitional cell carcinoma or transitional cell cancer or transitional cell tumo?r or transitional cell neoplasm).mp.
6. (urogenital tract cancer or urothelial cancer).mp.
7. (urothelial carcinoma or urothelial tumo?r or urothelial cancer or urothelial neoplasm).mp.
8. urogenital tract cancer/ or urothelial cancer.mp.
9. animal/ not (exp human/ or humans/)

#### **Testicular Cancer - Medline**

1. testicular Neoplasms/
2. testicular cancer.mp.
3. testis cancer.mp.
4. germ cell cancer.mp. or "Neoplasms, Germ Cell and Embryonal"/
5. Seminoma/ or Seminoma testicular.mp.
6. Nonseminoma testicular.mp. or Germinoma/
7. NSGCT.mp.
8. or/1-7
9. advanced.mp.
10. metasta\$.mp.
11. 9 or 10
12. 8 and 11
13. limit 12 to yr="2007 -Current"
14. limit 13 to english
15. animal/ not (exp human/ or humans/)
16. 14 not 15

#### **Testicular Cancer - EMBASE**

1. Testicular cancer.mp. or testis cancer/

2. non seminomatous germinoma/ or testis cancer/ or NSGCT.mp. or germ cell tumor/
3. Germinoma.mp.
4. seminoma/ or testis cancer/ or non seminomatous germinoma/ or Nonseminoma testicular.mp. or testis nonseminoma cancer/
5. testis neoplasm.mp. or testis tumor/
6. testicular neoplasm.mp.
7. or/1-6
8. advanced cancer/ or advanced.mp.
9. metastasis.mp. or metastasis/
10. 8 or 9
11. 7 and 10
12. limit 11 to english language
13. limit 12 to yr="2007 -Current"
14. animal/ not (exp human/ or humans/)
15. 13 not 14

#### **Surgery - Medline**

1. surgery.mp. or General Surgery/
2. operation.mp. or Laparoscopy/
3. resection.mp.
4. operative.mp. or Surgical Procedures, Operative/
5. Postoperative Complications/di, dg, ec, mo, pc, rt, su, th [Diagnosis, Diagnostic Imaging, Economics, Mortality, Prevention & Control, Radiotherapy, Surgery, Therapy]
6. surgical intervention.mp.
7. Urologic Surgical Procedures, Male/
8. or/1-7
9. limit 8 to english language
10. animal/ not (exp human/ or humans/)
11. 9 not 10
12. limit 11 to yr="2007 - 2017"

#### **Surgery - EMBASE**

1. cancer surgery/
2. male genital system surgery/ or robot assisted surgery/ or urologic surgery/ or surgery/ or laparoscopic surgery/ or general surgery/ or open surgery/
3. operation.mp.
4. resection.mp.
5. operative surgical procedure.mp.
6. surgical procedures, operative.mp.
7. surgical intervention.mp.
8. surgical operation.mp.

9. operative intervention.mp.
10. or/1-9

#### **Systemic Treatment - Medline**

1. chemotherapy, Adjuvant/
2. adjuvant chemotherapy.mp.
3. neoadjuvant Therapy/ or neoadjuvant chemotherapy.mp.
4. 1 or 2 or 3
5. Antineoplastic Agents/
6. chemotherapy.mp.
7. 5 or 6
8. adjuvant.mp.
9. neoadjuvant.mp.
10. 8 or 9
11. 7 and 10
12. 4 or 11

#### **Systemic Treatment - EMBASE**

1. adjuvant chemotherapy/
2. neoadjuvant chemotherapy.mp.
3. cancer chemotherapy/ or chemotherapy/ or cancer combination chemotherapy/
4. antineoplastic agent/
5. or/1-4
6. adjuvant.mp.
7. adjuvant.mp.
8. 6 or 7
9. 8 and 5

#### **Volumes and requirements for safe surgery - Medline**

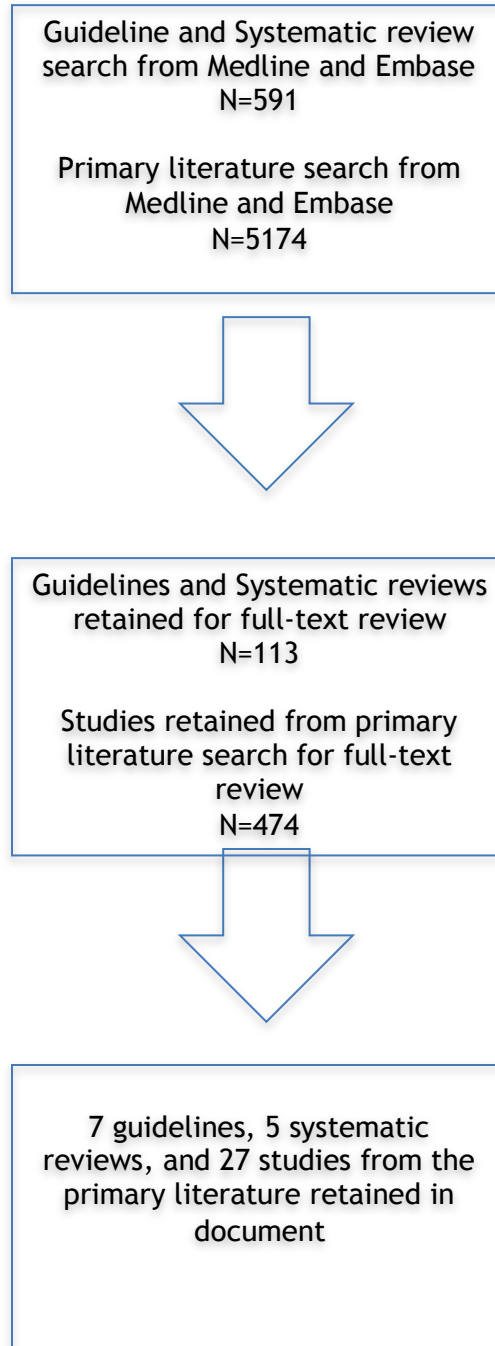
1. (resources or health care planning).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
2. ("ancillary service\$" or "support service\$" or "hospital adj2 (laborator\$ or radiology or pharmac\$)").mp.
3. interventional radiology/
4. coronary care unit/ or intensive care unit/
5. exp intensive care/
6. recovery room/
7. interventional radiology.mp.
8. (respiratory care unit\$ or ICU or pediatric intensive care unit).mp.

9. preoperative care/ or perioperative period/ or peroperative care/ or postoperative care/
10. or/1-9
11. (hospital volume or surgeon volume or volume outcome or facility volume or institution volume or center volume or centre volume).mp.

**Volumes and requirements for safe surgery - EMBASE**

1. (resources or health care planning).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]
2. ("ancillary service\$" or "support service\$" or "hospital adj2 (laborator\$ or radiology or pharmac\$)").mp.
3. interventional radiology/ or coronary care unit/ or intensive care unit/
4. exp intensive care/
5. recovery room/
6. interventional radiology.mp.
7. preoperative care/ or perioperative period/ or peroperative care/ or postoperative care/
8. or/1-7
9. (hospital volume or surgeon volume or volume outcome or facility volume or institution volume or center volume or centre volume).mp.

Appendix 3: Prisma flow diagram



## Appendix 4. Risk of Bias Table

Study	Comparison	Randomization method	Blinding	Incomplete outcome data	Selective reporting	Other sources of bias
<b>Renal Cancer</b>						
Bex [3] 2019 SURTIME	Sunitinib + delayed nephrectomy versus immediate nephrectomy + sunitinib	Low risk Stratified by risk group, number of metastatic sites and centre	Low risk for overall survival <b>High risk</b> for other outcomes - Patients & physicians not blinded	Low risk	<b>Moderate risk</b> Primary outcome changed from PFS to progression-free rate in ITT population	Low risk
Mejaen [2] 2018 CARMENA	Sunitinib versus sunitinib + nephrectomy	Low risk Stratified by risk group, and centre	Low risk for overall survival <b>High risk</b> for other outcomes - Open label	Low risk	Low risk Primary outcome - overall survival	Low risk
Motzer [12] 2017 PROTECT	Pazopanib versus placebo	Low risk Stratified by partial versus radical nephrectomy, TMN staging and	Low risk for overall survival <b>High risk</b> for other outcomes - Patients & physicians not blinded	Low risk	Low risk Primary outcome - DFS	Low risk
Ravaud [10] 2016 S-TRAC	Sunitinib versus placebo	Low risk Stratified by risk group, ECOG score and country	Low risk	Low risk	Low risk Primary outcome - DFS	Low risk
Haas [9] 2016 ASSURE	Sunitinib versus sorafenib versus placebo	Low risk Stratified by histology, type of surgery and risk group	Low risk	Low risk	Low risk Primary outcome - DFS	Low risk
Rini [14] 2014 INTORACT	Temsirolimus + bevacizumab versus interferon alpha and bevacizumab	Low risk Stratified by baseline prognostic group and prior nephrectomy	Low risk for overall survival <b>High risk</b> for other outcomes - Open label	Low risk	Low risk Primary outcome - PFS	Low risk
Motzer [13] 2013	Tivozaniv versus sorafenib	Low risk Stratified by geographic region, number or prior treatments for metastatic disease and number of metastatic sites	Low risk for overall survival <b>High risk</b> for other outcomes - Open label	Low risk	Low risk Primary outcome - PFS	Low risk
<b>Upper Tract Urothelial Cancer</b>						
Birtle [21] 2018 POUT ABSTRACT	Chemotherapy versus surveillance	<b>Unclear</b> Abstract	<b>Unclear</b> Abstract	<b>Unclear</b> Abstract	<b>Unclear</b> Abstract; Primary outcome - DFS	<b>Unclear</b> Abstract

Abbreviations: DFS, disease-free survival; ECOG, Eastern Cooperative Oncology Group; ITT, intention to treat; PFS, progression-free survival



**Appendix 5: AMSTAR 2 tool.**

## Evaluation of included systematic reviews using AMSTAR 2.

ITEM	BAI [11]	GREGG [19]	HSU [23]	LEOW [18]	YANG [20]
1. Did the research questions and inclusion criteria for the review include the components of PICO?	Y	Y	Y	Y	Y
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	PY	N	Y	PY	PY
3. Did the review authors explain their selection of the study designs for inclusion in the review?	N	Y	Y	Y	Y
4. Did the review authors use a comprehensive literature search strategy?	Y	N	PY	N	PY
5. Did the review authors perform study selection in duplicate?	Y	N	Y	Y	Y
6. Did the review authors perform data extraction in duplicate?	Y	N	Y	Y	Y
7. Did the review authors provide a list of excluded studies and justify the exclusions?	N	N	N	N	N
8. Did the review authors describe the included studies in adequate detail?	N	PY	PY	PY	N
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	PY	N	PY	N	PY
10. Did the review authors report on the sources of funding for the studies included in the review?	N	N	N	N	N
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	N	N	Y	Y	N
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Y	N	Y	Y	N
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	Y	N	Y	Y	N
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Y	Y	Y	Y	N
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	N	N	Y	Y	N
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Y	N	Y	Y	Y

Abbreviations: N=no; PY=Partial yes; Y=yes