Does prolonging the time to renal cancer surgery affect long-term cancer control: a systematic review of the literature

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Background: *Prolonged surgical wait times have significant effects on a patient's psychological well being and a negative impact on quality of life but the effect on long-term cancer control is controversial. We conducted a systematic review of the renal cancer literature to examine the best available evidence addressing the following key questions:*

- *What is the reported time interval for renal cancer patients from the initial surgical consultation until the day of renal cancer surgery?*
- *Are there recommendations/guidelines in the urological cancer literature and, if so, how do the Canadian times compare?*
- *Is there a known association between duration of wait time beyond the recommended standard and clinical outcome (i.e., recurrence-free survival, overall survival)?*

Methods: *A structured literature search PubMed, Embase, the Cochrane Database and Google Scholar from January 1965 to October 2005 was conducted for published studies and international guidelines/consensus documents that evaluated surgical wait times for renal cancer. Data extracted from eligible studies included median or mean time to renal cancer surgery from diagnosis or referral, and key patient outcomes, such as survival rate or adjusted hazard ratios (HR).*

Results: *Only three studies evaluating wait times for renal cancer surgery were identified. Differences in study data availability, method of analysis and wait time definitions precluded statistical pooling of the findings. Wait times from various points of patient contact ranged from a median delay of 26 days (diagnosis to radical surgery, i.e., nephrectomy) to 82 days (general practitioner referral to radical surgery). One study reported a mean of 23.6 days between referral for surgery to hospital admission for nephrectomy. In the Canadian epidemiological study, which focused on all types of urological cancer, median wait time was 64 days from referral to surgery. This was in contrast to national and international guidelines, which recommended a maximum waiting time between 2 and 4 weeks for all cancer surgeries. There were no epidemiological studies evaluating the association between surgical delay and clinical outcomes such as overall survival.*

Conclusions: *In Canada, it appears that current wait times for urological surgeries, such as for renal cancer, are beyond the threshold recommended by national and international expert bodies. Then again, the association between surgical delay and overall survival appears to be unexplored. Research in this area is urgently needed. Notwithstanding, the surgical wait times (SWAT) initiative was developed to provide the necessary guidance and recommendations on these issues to the federal and provincial governments. Through a partnership of the key stakeholders, it is the vision of SWAT to ultimately improve the care and quality of life of bladder cancer patients and their families.*

Key Words: renal cancer, surgery, wait time, delay

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Introduction

Cancer of the kidney is estimated to be the fifteenth most common cancer in the world and the seventh most common in Canada.[1,2] Four thousand five hundred new cases are expected to be diagnosed in Canada in 2005, with a ratio of occurrence in men to women of about approximately 5 to 3.[2] Described as having a "fairly good prognosis", the number of deaths from renal cancer is one-third of the number of newly diagnosed cases.[2]

Kidney cancer can originate from various cell types and can present at a variety of stages. Most of the cancers, i.e., 80%-85% of all malignant kidney tumors, originate in the renal cortex.[3,4] Surgery is the primary treatment for all types and grades of kidney tumors.[5] Unfortunately, tumor resection is not always curative and additional treatments, such as radiation or chemotherapy, have shown limited effectiveness.[3-6] Nonetheless, the 5-year relative survival rates (as reported for the United States) have significantly increased from 52% in 1974-1976 to 64% in 1995-2000.[7]

How quickly a patient progresses from their first visit to the family doctor, to complain of symptoms suggestive of some sort of urological problem, through to specialist referral, diagnosis and treatment is not well documented. The Progress Report on Cancer Control in Canada notes: "Excessive waiting is attributable to increased incidence and prevalence of cancer, insufficient facilities (operating rooms, radiotherapy equipment), human resource shortages, inefficient health care delivery systems, increased screening, new clinical care indications, or a combination of these factors".[8] Although suggestions or recommendations for shortened and "timely" access to health care have been made, data to substantiate these recommendations is not offered .

The impact of surgical delays remains controversial and appropriate wait time for treatments are currently unknown. Determining whether a delay is appropriate or not, or whether a delay affects patient outcome, is especially problematic, considering the various stages of cancer and possible co-morbid conditions with which patients may present.

To address the issue of wait times for the key urological disease sites: prostate, bladder, kidney and testes - a Canadian surgical wait times (SWAT) initiative was undertaken. The SWAT initiative is composed of a steering committee and a scientific advisory committee. The SWAT initiative, whose members consist of urological oncologists, surgeons and methodologists, is mandated to review the current literature on the surgical wait times for urological cancers and then develop a consensus document that can serve as a guide for patients, physicians and other key stakeholders in the Canadian health care system. To begin this process, a review of renal cancer literature was performed to determine the recommendations currently available regarding appropriate wait times for surgery, and to quantify the overall risk of disease recurrence and overall survival in patients who have wait times beyond a recommended threshold. In this paper, the results of the systematic review of the literature addressing the key questions in renal cancer are described.

Methods

Objectives

A systematic literature review was conducted to obtain the best available published articles in the medical literature to address the following questions:

- What is the reported time interval for renal cancer patients from the initial surgical consultation until the day of renal cancer surgery?
- Are there recommendations/guidelines in the urological cancer literature and, if so, how do the Canadian times compare?
- Is there a known association between duration of wait time beyond the recommended standard and clinical outcome (i.e., recurrence-free survival, overall survival)?

Data sources, study selection and data extraction and synthesis

A structured literature search was conducted of PubMed, Embase, Cochrane Database and Google Scholar to obtain published epidemiological studies and international guidelines/consensus documents that evaluated surgical wait times for cancer of the kidney from January 1965 to October 2005. The following inclusion criteria were used: 1) The document was available as a full report; 2) The document was developed in North or South America, Western Europe, Australia or New Zealand; 3) Patients undergoing renal cancer surgery must have been considered; 4) The primary outcome of interest for epidemiological studies was the association between surgical wait times from the initial surgical consultation until the day of surgery and clinical outcomes. Care was undertaken to avoid the inclusion of duplicate publications.

Searches of the listed databases, as well as of government reports, took place between June and October 2005. Information was extracted from full copies of all primary study reports and included tables

that summarized key study characteristics and data. Key findings from each study were documented in summary tables. Studies evaluating the natural history of renal cancer were considered and particular note was made of those that placed patients into risk groups.

Results

Surgical wait time

Three studies reporting wait times for renal cancer surgery were identified. Differences in available study data, method of analysis, wait time definitions and grades of disease precluded statistical pooling of the data. Wait time definitions consisted of the following time intervals: from general practitioner (GP) referral to surgery, from referral to surgery, and from diagnosis to surgery. The findings are listed in Table 1.

There was one published epidemiological study from Canada.[9] It evaluated wait times for urological cancers in the province of Ontario, without specifying the types. The small cohort of 58 cases from the first half of the year 2000 had a median wait time of 64 days between referral and surgery. Recently, the Fraser Institute released a document on wait times in Canada, using a survey-based approach, for all medical procedures (surgery, radiation therapy, etc).[10] For all Canadian provinces, they report that wait times between GP referral to specialist and from specialist to treatment have increased between 1993 and 2005, but have fallen slightly between 2004 and 2005. Using the responses from 179 urologists from across Canada (without a further breakdown by disease site), the 2005 median wait period between GP referral and treatment was 12.8 weeks, 7.5 weeks between GP to specialist consultation and 5.3 weeks from consultation to actual treatment.[10]

The other two studies in this review were from the United Kingdom. The median wait time from GP referral to nephrectomy was reported as 82 days by Subramonian et al (from before December 2000), with a median of 26 days elapsing between disease diagnosis and nephrectomy.[11] Nutall et al, in their review of registry data for radical nephrectomy practices in England between 1995 and 2002, reported that the wait time between the decision to admit a patient for surgery and their date of admission was a mean of 23.6 days (SD = 26.8 days).[12] The yearly mean wait times were also reported and showed a significantly increasing trend over the data collection period (P for trend < 0.001): 21.2 ± 26.7 days in 1995-1996 to 27.0 ± 29.5 days in 2001-2002.

Wait time guidelines and recommendations from the literature

Many government health services agencies (in Europe, North America, Australia) have identified the need to shorten wait times for patients to receive treatment. However, documents generally refer to the "need" and the "plan" without providing a definite waiting time threshold. When they do, it is for specific diseases or interventions, such as cardiac surgery, breast cancer treatment, and radiotherapy for cancer; cancer surgery, let alone surgery for cancer of the kidney, is usually not on the "action list". One professional organization and two government bodies have developed recommendations for a maximum wait time for cancer

TABLE 1. **Reported wait times for renal cancer surgery in various countries**

Reference	Country	No. patients (n) and year	Wait time definition used	Median duration
Nuttall[12]	England	n = 17,308; 1995-2002	Referral to date of hospital admission for radical nephrectomy	(mean) 23.6 ± 26.8 d[a]
Simunovic[9]*	Canada	n = 58; Jan-May, 2000	Referral to surgery	64 d
Subramonian[11]	United Kingdom	n = 40; before Dec 2000	Diagnosis to radical surgery (nephrectomy)	26 d
Subramonian[11]	United Kingdom	n = 40; before Dec 2000	GP referral to radical surgery (nephrectomy)	82 d

[a]Wait time was reported as a "mean" with standard deviation, rather than as a "median". Numbers were from the Hospital Episode Statistics (HES) database of the Department of Health in England. Annual mean wait time was shown as having a significantly increasing trend over the data collection period (P trend < 0.001): 21.2 ± 26.7 days in 1995-1996 to 27.0 ± 29.5 days in 2001-2002.

*Considered all urological cancer surgeries.

surgery in general, Table 2.[13-15] The Canadian Society of Surgical Oncology (CSSO) and the United Kingdom National Health Service made similar recommendations, where the maximum wait time for referral from a general practitioner (GP) to an oncology specialist should be 2 weeks.[13,14] The position statement of the CSSO states that cancer patients should be seen in consultation within 2 weeks of referral and that surgery should be initiated within 2 weeks after preoperative tests.[13] The United Kingdom National Health Service specifies in its Cancer Plan that there should be a maximum wait of 2 weeks from the time of the GP referral to the time for a specialist's assessment, a maximum 1-month wait between diagnosis and treatment, and a maximum 2-month wait between an urgent GP referral and actual treatment.[14] The Saskatchewan Surgical Care Network's recommendations for delay between diagnosis and treatment lie between the other two guidelines' at 3 weeks.[15] These recommendations are for all cancer types, with no specific guidelines for renal cancer. Again, not renal cancer-specific, nor specifying the type of intervention, The Fraser Institute's results of their 2005 cross-Canada survey reported that specialists indicated the median reasonable wait time between specialist visit and treatment for urology cases should be an average of 3.3 weeks.[10]

Is there an association between waiting time and clinical outcome?

One of the main objectives of the current study was to evaluate the epidemiological literature that measured the association between prolonged wait times and patients' clinical outcomes. No studies falling within the search parameters were identified for renal cancer. Therefore, research in this area is urgently needed because such findings will help guide the determination of optimal wait times for patients scheduled to undergo renal cancer surgery.

Qualitative insights from experts in the field

We do not know which patients can safely wait for longer periods, or what the wait time threshold should be. Therefore, initiatives such as SWAT need to consider published epidemiological data, the reported impact of delays on patient quality of life, the various patient risk groups, and the health care resources available in order to develop reasonable waiting time benchmarks for cancer surgery in Canada. In the absence of research data and epidemiological reports, and where there is limited, ambiguous, and even controversial data, expert opinion is often sought. Some qualitative insights from various researchers are presented in Table 3.[16-20] The comments do not specifically address surgical delays, but most often relate to the natural history of renal cancers.

Discussion

We conducted a systematic review of the literature to identify current wait times for renal cancer surgery, recommendations on what the maximum wait time should be and to assess the possible association between surgical delays and patient clinical outcomes. Our

TABLE 2. **Recommended maximum wait times from the literature**

Reference	Wait time definition	Recommended maximum wait time	Type of surgery
CSSO[13]	Referral to consultation	2 weeks	All cancer surgeries
	Conclusion of preoperative tests to treatment	2 weeks	All cancer surgeries
NHS[14]	GP referral to specialist assessment	2 weeks	All cancer surgeries
	Diagnosis to treatment	1 month	All cancer surgeries
	Urgent GP referral to treatment	2 months	All cancer surgeries
SSCN[15]	Diagnosis to treatment	3 weeks	95% of all cancer and suspected cancer surgeries
	Diagnosis to treatment	18 months	All cases (including cancers)
Esmail[10]*	Specialist to treatment	3.3 weeks	Urology (not specified)

GP = general practitioner or family physician

*Numbers are from information received through a cross-Canada survey of urologists (without specifying a site or type of treatment). The recommended maximum wait time is described as: "Median Reasonable Wait for Treatment after Appointment with Specialist".

TABLE 3. **Qualitative insights on the impact of wait time on clinical outcomes as noted by experts in the field**

Reference	Key opinion
Allen[16]	In patients referred under the 2-week-wait scheme with macroscopic hematuria, cancer is common…. The scheme as a whole is unlikely to improve cancer outcomes.
Kassouf[17]	As more of these small incidental renal tumors are being discovered, in addition to the aging of the population, treatment of these patients may raise questions. In a selected group of patients, particularly the elderly and patients with poor medical condition, observation may represent a valid option.
Mevorach[18]	Analysis of patients diagnosed prior to 1981 and cases detected subsequently reveals that there is no trend toward detection of lower stage cancer.
Nativ[19]	The most important variable affecting prognosis was tumor stage at diagnosis….
Rathmell[20]	Clinical observers have long noted the variable natural history of renal cell carcinoma, from indolent stability to rapid growth and death from metastases.

findings revealed that there is very little data published on wait times for the surgical management of renal carcinoma. Statistics Canada reports that for the year 2003, the median wait time for a specialist visit for a new illness or condition was 4.0 weeks and the median wait time for non-emergency surgeries was 4.3 weeks.[21] Using these estimates, it could be inferred that the median wait time between GP referral and surgery for renal cancer in Canada could be up to 8.3 weeks.

Recommendations for maximum wait times are few, and there are no standards for "acceptable" surgical delays. It is very difficult to conclude whether currently documented delays are reasonable and if they have a true negative impact on patient outcome. However, in addition to the potential clinical impact of a prolonged surgical delay, there is concern about the effect on patient health associated with the psychological stress from waiting. Widespread agreement exists that delays to surgery have significant effects on psychological well being, and reduced wait times may result in decreased psychological morbidity.[22,23] Furthermore, the issue of palliative surgery was not been addressed in this review.

One of the main causes of delayed treatment is delayed diagnosis, and the time it takes a patient to seek medical care is often a crucial variable. Encouraging patients to come for regular urological check-ups is beyond the scope of most health care systems. Nevertheless, some urologists have proposed the establishment of hematuria clinics, which could more quickly perform follow-up on patients with abnormal symptoms. This could increase the identification of new cancer cases, thereby shortening the hospital portion of waiting time.[24,25] Additional delays may be incurred by patients seeking a second opinion or by not following-up on referral.

Subramonian et al observed that the 2-week waiting rule from GP referral to specialist assessment will do nothing to improve other steps in the pathway to surgery.[11] Their study demonstrated that the longest wait time for all urological surgeries (except orchidectomy) is from diagnosis to surgery, which is the key time interval that needs to be shortened. Sikora et al, in their overview publication, Cancer Care in the NHS, write: "Perhaps the biggest disappointment has been the inability to reduce the delay from referral or diagnosis to first treatment".[26]

Overall, well-designed epidemiological studies are needed to examine the association between wait time and clinical outcomes, with the ultimate objective being the identification of a delay threshold, which would assist in the development of surgical guidelines for informed health policy decision-making. As a caution, the review conducted by Hanning et al on the initiative for reducing wait times for a variety of conditions and treatments, not including cancer, in Sweden should be considered.[27] The investigators found that surveyed physicians were initially very happy to implement shorter waiting times. Over time, there was increased demand, decreased health care expenditures and new patient priorities, all of which required some change in clinical practice. These changes "did not coincide with the physicians' professional values" resulting in their abandonment of the original agreement.

Natural history of renal cell carcinoma

Given the limited epidemiology data, a review of the natural history of renal cell carcinoma (RCC) is presented to aid in the development of waiting time benchmarks. RCC is the most common renal cancer, which is

TABLE 4. **Classification of renal cell carcinoma using the TNM system**

Renal carcinoma TNM	
T1:	Tumor 7 cm or less confined to the kidney
T2:	Tumor > 7 cm confined to the kidney
T3:	Tumor extends to vessels/ = adrenal gland, within Gerota's Fascia
T4:	Tumor invades beyond Gerota's Fascia
N1:	Single regional lymph node
N2:	> 1 regional lymph node
M1:	Distant metastasis

commonly described using the TNM system, Table 4. Ljungberg et al summarize that 30% of patients with RCC will have metastases at first diagnosis and that half of the remaining patients will develop metastases on follow-up.[28] Differences in outcome have been reported among patients with different histological types of RCC.[29,30] Advances in diagnosis, pathology and treatment have resulted in improved survival rates for patients: Pantuck et al of the University of California, Los Angeles, report a 5-year cancer specific survival rate for RCC after resection of 91% for stage I and 32% for stage IV cases.[31] It has also been reported that patients with RCC and end-stage renal disease (ESRD) who undergo nephrectomy have a significantly better survival rate compared to those who do not.[32]

In their review of small numbers of patients split into "young", those under 40 years of age, and "older" patients, aged 41 to 85 years, Goetzl et al did not find age to be a factor in the natural history and recurrence of renal cortical tumors after initial surgery.[33] As expected, where metastases are found at first presentation, there is a poorer prognosis,[34] and patients with higher stage disease are more likely to develop metastases.[35] Generally, after resection, follow-up frequency is recommended to be based on tumor staging.[36,37]

The concept of "watchful waiting" has been addressed by some clinicians for patients who are predominantly unwilling or unfit surgical candidates. Table 5 summarizes the findings from six such

TABLE 5. **Studies reporting on "watchful waiting" in renal cell carcinoma management**

Reference	**No. patients (RCC on biopsy)**	**Mean or average age (range)**	**Median tumor size (range)**	**Median tumor growth rate (range)**	**Median duration of follow-up (range)**
Kassouf[17] Montreal, Canada	24 (4)	68.3 years (29-83)	2.65 cm (0.9-10)	0.49 cm/year	24 months (8-86)
Lamb[42] United Kingdom	36 (23)	76.1 years (56-91)	6.0 cm (3.5-20.0)	0 cm/year (0.39)[b]	24 months (3-136)
Rendon[39]* Toronto, Canada	13 (5) (Mar 92-July 99)	69 years[c] (56-85)	13.6 cm^3[d]	0.216 cn/year[e] (0.24-8.16)[e]	42 months (5-57)
Sowery[40] Kingston, Canada	22 (2)	77 years (60-92)	4.08 cm[f] (2-8.8)	0.86 cm/year[g] (0.2-1.52)[g]	26 months
Volpe38* Toronto, Canada	29 (8) (Mar 90-July 02)	71 years (27-84)	7.0 cm^3[h] (0.4-31.6)[h]	(0.1 cm/year)[i]	27.9 months (5.3-143.0)
Wehle[41] United States	29 (4)	70 years (51-88)	1.83 cm[j] (0.4-3.5)	0.12 cm/year	32 months (10-89)

*Some of the authors are the same between these two studies. It is unclear whether the patients in the Rendon et al report are included in the Volpe et al paper.
[b]Mean growth rate
[c]Median age
[d]Mean volume at diagnosis
[e]Average growth rate (95% CI)
[f]Mean diameter
[g]Overall tumor growth (95% CI)
[h]Median volume
[i]The average growth rate was 0.1 cm/year, as the cubic root of the volume
[j]Average width

studies.[17,38-42] The numbers of patients are small and the range of findings is variable, in that some "tumors" were not biopsied or confirmed as RCC. Nonetheless, this approach seems to be viable in select patients: those who are asymptomatic, are elderly or are poor surgical candidates, those with small tumors (3 cm or 4 cm as a maximum diameter), and those with no identifiable metastases.

Although other modalities or technologies are in use or under study (e.g., immunotherapy, anti-VEGF, tyrosine kinase inhibitors),[20] surgical resection remains the standard treatment for RCC.

Conclusions

The findings of our systematic literature review revealed that the national and international guidelines are few, and those that exist recommend a maximum wait time between referral and surgery, without further specification, of about 4 weeks. Unlike other disease sites such a prostate and bladder cancer, there was no published data evaluating the potential impact of prolonged wait times on patient clinical outcomes in renal cancer. To address the important issues related to surgical delays, the SWAT initiative is mandated to provide the necessary guidance and recommendations to the federal and provincial governments. Through a partnership among key stakeholders, it is the vision of SWAT to ultimately improve the care and quality of life of cancer patients. □

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