Identifying the use and barriers to the adoption of renal tumour biopsy in the management of small renal masses

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Abstract

Introduction: Renal tumour biopsies (RTBs) can provide the histology of small renal masses (SRMs) prior to treatment decision-making. However, many urologists are reluctant to use RTB as a standard of care. This study characterizes the current use of RTB in the management of SRMs and identifies barriers to a more widespread adoption.

Methods: A web-based survey was sent to members of the Canadian and Quebec Urological Associations who had registered email address (n=767) in June 2016. The survey examined physicians' practice patterns, RTB use, and potential barriers to RTB. Chi-squared tests were used to assess for differences between respondents.

Results: The response rate was 29% (n=223), of which 188 respondents were eligible. A minority of respondents (12%) perform RTB in >75% of cases, while 53% never perform or perform RTB in <25% of cases. Respondents with urological oncology fellowship training were more likely to request a biopsy than their colleagues without such training. The most frequent management-related reason for not using routine RTB was a belief that biopsy won't alter management, while the most frequent pathology-related reason was the risk of obtaining a false-negative or a non-diagnostic biopsy.

Conclusions: Adoption of RTBs remains low in Canada. Concerns about the accuracy of RTB and its ability to change clinical practice are the largest barriers to adoption. A knowledge translation strategy is needed to address these concerns. Future studies are also required in order to define where RTB is most valuable and how to best to implement it.

Introduction

Increased use and improved accuracy of abdominal imaging over the last decade has increased the number of small renal masses (SRMs) being diagnosed.[1,2] While the majority of solid renal tumours measuring ≤4 cm are malignant, up to 30% are benign.[3] Additionally, most malignant SRMs are low-grade and have low metastatic potential.[3] Initial definitive treatment of SRMs may represent overtreatment in many cases.

To justify and hopefully reduce overall treatment, with its associated burden of care, renal tumour biopsy (RTB) has been proposed as a safe, accurate, and reliable method to identify the histology of SRMs before treatment.[4-7] Although the use of active surveillance for SRMs is increasing, this strategy in surgical candidates could be refined based on RTB results. RTB could be helpful in identifying higher metastatic potential tumours better suited for definitive treatment or by identifying histologically benign tumours that do not require a followup protocol as stringent as do malignant tumours.[8] Thus, although debatable, RTB can influence management. However, in spite of the potential benefits, many urologists are still reluctant to adopt RTB as a standard of care for SRMs.[9] Consequently, most SRMs are still treated[10] and RTBs remain underused.[11,12] Reasons for slow adoption of routine RTB are not well-understood, but may include concerns regarding non-diagnostic rates, discordance with final pathology, safety, and a lack of perceived impact on clinical management.[9] These potential concerns have not been well-supported by studies reported over the past few years.[5,6]

The objectives of this study were to characterize the uptake of RTB in Canada for the management of SRMs and to assess whether utilization rates varied between types of practice and training. Lastly, we aimed to better characterize the barriers to a greater adoption.

Methods

Following approval from the University Health Network Research Ethics Board, a pilot questionnaire was developed and tested in 20 urologists in May 2016. All items were then

revised according to the responses in the pilot survey. The survey questions were formatted as either multiple-choice, rating scale, or short answer. An electronic survey was then generated (www.surveymonkey.com)[13] and distributed via email. The survey was distributed to all active members of the Canadian Urological Association (CUA) and the Quebec Urological Association (QUA). Two emails (one initial and one reminder) containing a link to the survey were sent out to all 767 members on June 13 and 22, 2016. Members of both associations were invited to answer a questionnaire in their language of preference (available in French and English). The survey contained questions regarding the physicians' practice patterns, RTB use, and potential barriers of RTB (Supplementary Table 1). We excluded non-urologists, pediatric urologists, urologists who did not manage SRMs, and physicians who gave incomplete demographic information or who did not answer questions beyond the demographic ones.

Continuous and categorical variables were reported using medians (interquartile range [IQR]) and proportions, respectively. Chi-squared tests were used to assess differences between specific groups of respondents (types of practice and fellowship training). To test whether different patient and tumour characteristics were associated with the likelihood of recommending a RTB, we performed paired McNemar's tests to determine whether responses within respondents differed based on presence or absence of each factor. Univariate and multivariate conditional logistic regression models, adjusted for interactions between variables and accounting for repeated subjects, were used to analyze the impact of age, comorbidity status, and renal function on the likelihood of requesting a RTB. A Bonferroni correction (adjusted p value=0.025) was applied for multiple groups comparison, when required. All other statistical tests were two-sided and p values <0.05 were considered statistically significant. Statistical analyses were conducted in the R statistical environment, version 3.2.3 (R core team).[14]

Results

In total, 223 members responded to the survey, resulting in a response rate of 29.1%. From these, we excluded 12 because they did not provide data on their type of profession, 11 because they did not answer any questions other than the demographic ones, and another 12 because they did not manage SRMs. Therefore, our study included 188 individuals. Demographic data is presented in Table 1. Of the eligible respondents, 69 (36.7%) practiced in an academic centre, while 119 (63.3%) practiced in a non-academic one. The median (IQR) number of new SRMs patients managed annually by the included respondents was 20 (12.5–30).

Table 1. Demographic data of the included respondents (n=188)

Variables	n (%)
Current profession	
Adult urology	178 (94.7)
Urology resident/fellow	10 (5.3)
Years in practice	
0–5	52 (27.7)
6–10	38 (20.2)
11–15	24 (12.8)
>15	72 (38.3)
Practice under supervision	2 (1.1)
Fellowship training	
Urologic oncology	48 (25.5)
Endourology/minimally invasive surgery	43 (22.9)
Other fellowship	27 (14.4)
No fellowship training	70 (37.2)
Type of practice	
Academic hospital	69 (36.7)
University-affiliated hospital	44 (23.4)
Community or rural hospital	75 (39.9)
Annual number of new SRMs consultation, mean ± SD	26±27
1–10	40±21.3
11–20	61±32.4
21–30	45±23.9
>30	42±22.3

SD: standard deviation; SRMs: small renal masses.

Renal tumour biopsy use

Of the eligible respondents, a minority (11.7%) performed a RTB in greater than 75% of cases, while 53.2% never performed or performed RTB in less than 25% of cases. There was no significance difference in the perceived use of RTB according to the type of urologic practice (Table 2). However, physicians with a urologic oncology fellowship were significantly more likely to request a biopsy than endourologists (Bonferroni adjusted p=0.01) and physicians without fellowship training or with a non-oncology/non-endourology fellowship (Bonferroni adjusted p=0.003) (Table 3).

When performed, nearly all respondents indicated that RTB was performed by a radiologist (96.2%) and most used needle core biopsy (68.6%) or a combination of fine-needle aspiration (FNA) and core biopsy (18.6%). The majority also indicated that biopsies were performed on an outpatient basis (92%). There was with no major differences in these parameters according to the type of practice, but some variation was observed according to the type of centre (Tables 2, 3).

Patient and tumour factors associated with recommending a biopsy

Several patient and tumour characteristics were associated with increased likelihood of recommending a biopsy (Table 4A). Physicians were more likely to recommend a biopsy for patients with a known family history of renal cell carcinoma,

Table 2. Renal tumour biopsy utilization: Overall and per type of practice

Questions	Overall (n=188)	Academic (n=69)	Non-academic (n=119)	p
In what proportion of patients with SRM do you request a RTB to inform treatment?				0.2
Never	13 (6.9)	2 (2.9)	11 (9.2)	
≤25% of cases	87 (46.3)	30 (43.5)	57 (47.9)	
26–50% of cases	40 (21.3)	14 (20.3)	26 (21.9)	
51–75% of cases	26 (13.8)	12 (17.4)	14 (11.8)	
76–100% of cases	22 (11.7)	11 (15.9)	11 (9.2)	
What type of biopsy is typically performed at your centre?				0.01
Fine needle aspiration (FNA)	7 (3.7)	4 (5.8)	3 (2.5)	
Needle core biopsy	129 (68.6)	54 (78.3)	75 (63.0)	
Both FNA and core biopsy punctures	35 (18.6)	10 (6.9)	25 (21.0)	
Biopsies are not performed or I am unsure	17 (9.0)	1 (1.5)	16 (13.5)	
Who typically performs these RTBs?				0.07
Radiologist	180 (95.7)	67 (97.1)	113 (95.0)	
Urologist	1 (0.5)	1 (1.5)	0 (0)	
Urologist/radiologist	1 (0.5)	1 (1.5)	0 (0)	
Biopsies are not performed at our centre	6 (3.2)	0 (0)	6 (5.0)	
Following RTB, patients are typically:				0.04
Hospitalized overnight	8 (4.3)	0 (0)	8 (6.7)	
Discharged on the same day (outpatient)	173 (92.0)	68 (98.6)	105 (88.2)	
Other	7 (3.7)	1 (1.4)	6 (5.0)	

RTB: renal tumour biopsies SRMs: small renal masses.

Table 3. Renal tumour biopsy utilization: Overall and per fellowship training

		Type of fellowship training			
Questions	Overall (n=188)	Urologic oncology (n=48)	Endourology /MIS (n=43)	Other fellowship/ none (n=97)	p
In what proportion of patients with SRM do you request a RTB to inform treatment?					
Never	13 (6.9)	0 (0)	3 (7.0)	10 (10.3)	0.01*
≤ 25% of cases	87 (46.3)	14 (29.2)	23 (53.5)	50 (51.6)	
26–50% of cases	40 (21.3)	15 (31.3)	7 (16.3)	18 (18.6)	
51–75% of cases	26 (13.8)	11 (22.9)	3 (7.0)	12 (12.4)	
76—100% of cases	22 (11.7)	8 (16.7)	7 (16.3)	7 (7.2)	
What type of biopsy is typically performed at your centre?					
Fine needle aspiration (FNA)	7 (3.7)	0 (0)	3 (7.0)	4 (4.1)	0.7†
Needle core biopsy	129 (68.6)	42 (87.5)	29 (67.4)	58 (59.8)	
Both FNA and core biopsy punctures	35 (18.6)	6 (12.5)	6 (14.0)	23 (23.7)	
Biopsies are not performed or I am unsure	17 (9.0)	0 (0)	5 (11.6)	12 (12.4)	
Who typically performs these RTBs?					
Radiologist	180 (95.7)	46 (95.8)	43 (100)	91 (93.8)	0.07
Urologist	1 (0.5)	1 (2.1)	0 (0)	0 (0)	
Urologist/radiologist	1 (0.5)	1 (2.1)	0 (0)	0 (0)	
Biopsies are not performed at our centre	6 (3.2)	0 (0)	0 (0)	6 (6.2)	
Who typically performs these RTBs?					
Radiologist	180 (95.7)	46 (95.8)	43 (100)	91 (93.8)	0.07
Urologist	1 (0.5)	1 (2.1)	0 (0)	0 (0)	
Urologist/radiologist	1 (0.5)	1 (2.1)	0 (0)	0 (0)	
Biopsies are not performed at our centre	6 (3.2)	0 (0)	0 (0)	6 (6.2)	
Following RTB, patients are typically:					
Hospitalized overnight	8 (4.3)	0 (0)	2 (4.7)	6 (6.2)	0.1‡
Discharged on the same day (outpatient)	173 (92.0)	48 (100)	41 (95.4)	84 (86.6)	
Other/missing	7 (3.7)	0 (1.4)	0 (2.3)	7 (7.2)	

*Bonferroni adjusted p value urologic oncology vs. endourology=0.01; Bonferroni adjusted p value urologic oncology vs. other fellowship/none=0.003. †If category "biopsies are not performed or I am unsure" considered in the analysis, p =0.02. ‡If "Other/missing" considered in the analysis, p=0.04. RTB: renal tumour biopsies; SRMs: small renal masses.

a known hereditary syndrome, and if the patient's treatment preference was active surveillance or thermal ablation rather than surgery. Likewise, tumours that were solid, multifocal, and greater than 2 cm in maximal dimension were more likely to be biopsied than their counterparts. Physicians were also more inclined to biopsy low or minimally enhancing tumours more often than the highly enhancing ones. Endophytic tumours and the ones located near the hilum were less often biopsied than exophytic tumours.

Scenario questions: Interactions between factors associated with recommending a biopsy

Using a conditional multivariate logistic model, we identified that patients aged 70–75 years were more like to undergo biopsy than 50–65 years old, whereas patients aged ≥80 years were less likely to be biopsied. Patients with more medical comorbidities and decrease renal function were more likely to receive RTB than healthier patients (Table 4B).

When further evaluating the data, we identified several significant statistical interactions between the variables of age, comorbidity status, and renal function. When considering patients aged 50–65, poor renal function and the presence of multiple comorbidities increased the odds of requesting a RTB. In contrast, when considering patients 70–75 years old, only the renal function status correlated with requesting a RTB. Lastly, among patients >75, neither comorbidity nor renal function status influenced the likelihood of requesting a RTB (Supplementary Table 1).

Table 4A. Association of patient and tumour factors with likelihood of recommending biopsy

Variables	Likely to recommend RTB Yes, n (%)	p[a]
Patient characteristics		
Family history of RC		0.0002
Present	91 (50.0)	
Absent	65 (35.7)	
Risk of hereditary syndrome		<0.0001
Present	124 (68.1)	
Absent	62 (34.1)	
Patient's treatment preference		
Surgery	50 (27.5)	
Active surveillance	129 (70.9)	<0.0001[b]
Thermal ablation	153 (84.1)	<0.0001[c]
Tumour characteristics		
Tumour consistency		<0.0001
Solid	150 (82.4)	
Cystic	15 (8.2)	
Focality		0.0002
Unifocal	96 (52.8)	
Multifocal	129 (70.9)	
Tumour size		<0.0001
<2 cm	79 (43.4)	
2–4 cm	123 (67.6)	
CT enhancement		0.025
Low/minimal	100 (55.0)	
High	80 (44.0)	
Tumour location[†]		
Exophytic	100 (55.3)	
Endophytic	109 (60.2)	0.18[d]
Near hilum	63 (35.0)	<0.0001[e]

[a]p<0.05 indicates that the factor influences the decision to biopsy. [b]Surgery compared to active surveillance. [c]Surgery compared to ablation. [d]Exophytic compared to endophytic. [e]Exophytic compared to near the hilum. CT: computed tomography; RC: renal cancer; RTB: renal tumour biopsies.

Barriers of routine adoption of RTB

Several potential management-, pathology-, and radiology-related concerns were identified as barriers to routine adoption of RTB (Table 5). The most commonly reported management-related barrier was a belief that biopsy won't alter management (35.5%), while the risk of obtaining a false-negative or a non-diagnostic biopsy was the greatest pathology-related barrier. Of the four proposed radiology-related concerns, a lack of expertise with RTB was the most cited concern, but 43% of the respondents felt that none of the radiology-related items were major barriers to a more widespread adoption of RTB.

Discussion

In the absence of liquid biomarkers or better imaging, there isn't a more robust diagnostic test than RTB to determine histology and guide a more personalized management of SRMs. In spite of the evidence supporting the role of RTB

Table 4B. Factors associated with the likelihood of biopsy (scenario questions)

Factors	% of respondents that answered Yes	p[a]	Odd ratio (95% CI) – adjusted	p[b]
Age, years				
50–65	60.6		Ref.	
70–75	54.3		0.7 (0.5–0.9)	0.004
80+	27.9	<0.0001	0.14 (0.11–0.19)	<0.0001
Comorbidity status				
None	46.2		Ref.	
Multi	49.1	0.17	1.2 (0.97–1.5)	0.09
Renal function				
Normal	42.3		Ref.	
Poor	53.0	<0.0001	2.0 (1.6–2.4)	<0.0001

[a]p calculated from conditional logistic regression (accounting for repeated subjects). [b]Odds ratio and p calculated from a conditional logistic regression model including age, comorbidity status, and renal function as main effects only. CI: confidence interval.

Table 5. Barriers to more widespread adoption of renal tumour biopsy

Concerns	Statement reported as being a concern, n (%)	Statement reported as being the greatest concern, n (%)
Management-related concerns*		
– Current safety, accuracy and reliability of RTB are not replicable outside of centres with experience	75 (44.4)	41 (24.3)
– Biopsy results won't alter management	89 (52.7)	60 (35.5)
– Don't see need to biopsy because we have a low rate of overtreatment at our centre	66 (39.1)	16 (9.5)
– Patient's concerns regarding the safety and/or benefits of renal tumour biopsy	54 (32.0)	13 (7.7)
– None of the above is a barrier/other	n/a	39 (23.1)
Pathology-related concerns		
– Lack of concordance between renal tumour biopsy histology and surgical histology (malignant)	44 (26.5)	12 (7.2)
– Risk of false-negative or non-diagnostic biopsy	106 (63.9)	75 (45.2)
– Lack of grade concordance between renal tumour biopsy and surgical specimen	47 (28.3)	2 (1.2)
– Lack of evidence supporting concordance for benign histology between renal tumour biopsy and surgical pathology	56 (33.7)	22 (13.3)
– We don't have an expert uro-pathologist at our centre	44 (25.1)	10 (6.0)
– None of the above is a barrier	n/a	45 (27.1)
Radiology-related concerns‡		
– Lack of expertise with renal tumour biopsy at our centre	58 (35.4)	33 (20.1)
– Lack of access to interventional radiologists	49 (29.9)	27 (16.5)
– Risk of adverse events related to the procedure (including tumour seeding)	41 (25.0)	20 (12.2)
– Lack of infrastructure to carry out image-guided biopsies at our centre	32 (19.5)	13 (7.9)
– None of the above is a barrier	n/a	71 (43.3)

*Answers missing in 19 cases. †Answers missing in 22 cases. ‡Answers missing in 24 cases.
RTB: renal tumour biopsies.

in the management of SRMs,[5-7,15-18] our survey confirms that many urologists in Canada do not routinely use RTB as a means to guide treatment for SRMs. Only a quarter of respondents indicated that they requested a RTB in more than 50% of cases, while more than half indicated that they never performed or only performed RTB in less than 25% of cases. Adoption rates were higher among urologic oncologists than among endourologists or urologists with no fellowship training or with non-oncology/non-endourology fellowship training, but did not differ between academic and non-academic urologists.

Despite the limited adoption of RTB to guide management of SRMs, proponents of RTBs have to be encouraged by our findings, as the perceived use of RTB is higher than what had previously been reported in the literature. In 2012, Barwari et al surveyed members of the Endourological Society and reported that the majority of respondents (73%) never or rarely perform RTBs and that only 9% of them recommended a biopsy in more than 25% of cases.[11] Similarly, a Surveillance, Epidemiology, and End Results-Medicare (SEER) database study from 1992–2007 demonstrated that although there was a modest rise in the use of RTB, the increase was primarily observed among patients with metastatic disease and those receiving percutaneous thermal-ablative therapies. Among patients with localized disease, the utilization rates of RTB in SEER remained fairly stable throughout the study period, with RTBs being used in less than 20% of cases.[12]

This survey identified several patient and tumour characteristics that increased the likelihood that a physician recommends a RTB to inform treatment decision process. Not surprisingly, personal and familial history of cancer, treatment preference, and a myriad of tumour characteristics impacted the likelihood that a physician requested a RTB. The study also highlights the fact that the treatment decision for SRM is a complex one and that several patient and tumour characteristics need to be considered.

Lastly, the survey evaluated several key barriers that physicians felt were preventing a greater adoption of RTB. In spite of being legitimate concerns, many of the identified barriers (diagnostic yield, eligibility, safety, generalizability outside of single-centre studies, etc.) have previously been shown to be unfounded, while others remains to be further investigated (i.e., benign histology concordance, impact of RTB on management). Recent reports have demonstrated that RTBs are an accurate and reliable tool to guide management of SRMs.[5-7] Additionally, a meta-analysis by Marconi et al has demonstrated that initial RTBs yielded in diagnosis in >90% of cases and that they had a high concordance with surgical pathology (96%) for both histology and grade (66% and 87% when using a four- and two-tiered grading system, respectively).[5] Our group has also shown that a repeat biopsy has a similar diagnostic yield than the initial one, indicating that technical factors are often the reason for a non-diagnostic biopsy.[6] Despite these reports, nearly half of the respondents answered that the risk a false-negative or non-diagnostic biopsy was still a major deterrent to a more widespread adoption of RTB.

Another common concern among urologists was that the safety, accuracy, and reliability of RTBs were not replicable outside of centres with experience. However, a recent Canadian-based, multicentre, retrospective study has recent-

ly disproved this concern, as the report demonstrated the safety (significant adverse events in <1%), reliability (histological and two-tiered grading system concordance with surgical pathology of 88% and 81%, respectively), and accuracy (diagnostic yield ≈90% diagnostic yield) of RTB outside of a single-institution series.[17]

Most proponents of RTB believe that biopsying SRMs will lead to a decrease in unnecessary interventions by avoiding treatment of benign SRMs and of low metastatic potential tumours.[19] However, this belief is not unanimously supported by the urologic community and it has not been validated in well-designed trials. As demonstrated by this report, many urologists believe that a key barrier to a more widespread adoption of RTB is that they do not alter patient management. Similar concerns have been voiced by a number of experts in the field.[9] Therefore, future studies evaluating the impact of RTB on SRM management will be key to determining the exact role of RTB in a SRM treatment decision algorithm.

This study is not devoid of limitations. Similar to Barwari's survey (10% response rate),[11] our response rate was also low, with a rate of only 29%. This response rate could potentially be explained by the fact that the survey was sent to the email addresses of CUA and QUA members regardless of their level of training, type of practice, and field of interest. It is probable that non-urologists or urologists that did not treat adult and/or renal cancer were less likely to respond to the survey. Additionally, although several key potential barriers were proposed, the current survey did not allow for free text and thus, other additional key concerns may not have been appropriately captured. Nevertheless, in an era where overtreatment is gaining worldwide attention,[20,21] this study provides insight on the use of RTB in the management of SRMs and on the potential barriers to its more widespread adoption. As demonstrated, many identified concerns have already been debunked and, therefore, there seems to be a dire need for knowledge transfer strategies to improve the adoption of RTBs.

Conclusion

The adoption of RTB as a diagnostic test to identify pretreatment histology of SRMs remains low in Canada. Several barriers to a greater adoption of RTB have been identified, with the main ones being concerns over its accuracy and its ability to change clinical practice. Several of the identified concerns have already been addressed by previous reports, while others remain to be further investigated. Knowledge translation strategies are needed to inform urologists of the potential benefits and limitations of RTB. Further research is also essential to address the remaining knowledge gap and to evaluate where RTB is most valuable and how to best implement this tool.

Competing interests: Dr. Richard has attended advisory boards for BMS and Sanofi; and has been a speaker for AbbVie, Astellas, and Jasssen. Dr. Lavallée has attended advisory boards for Ferring and Sanofi; and has received a grant from Sanofi. Dr. Evans has participated in clinical trials supported by Omnyx LLC. Dr. Finelli has attended advisory boards for AbbVie, Amgen, Astellas, Bayer, Janssen, Roche, and Sanofi. The remaining authors report no competing personal or financial interests.

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Supplementary Table 1. Scenario questions: Multivariate conditional logistic regression models evaluating the likelihood of requesting a RTB after adjusting for statistical interactions between terms*

	Age, years OR (95% CI)			Comorbidities OR (95% CI)		Renal function OR (95% CI)	
Variables	**50–65**	**70–75**	**≥80**	**None/ minimal**	**Multiple**	**Normal**	**Poor**
Age, years							
50–65				REF	REF	REF	REF
70–75		N/A		1.2 (0.8–1.7)	0.4 (0.3–0.6)	0.9 (0.6–1.3)	0.5 (0.3–0.7)
≥80				0.3 (0.2–0.4)	0.08 (0.05–0.12)	0.3 (0.2–0.4)	0.07 (0.05–0.11)
Comorbidities							
None/minimal	REF	REF	REF	N/A		REF	REF
Multiple	2.5 (1.7–3.7)	0.8 (0.6–1.2)	0.9 (0.6–1.3)			1.8 (1.3–2.5)	0.8 (0.6–1.1)
Renal function							
Normal	REF	REF	REF	REF	REF	N/A	
Poor	3.7(2.5–5.5)	2.0 (1.3–2.8)	1.1 (0.7–1.6)	3.0 (2.2–4.0)	1.3 (0.95–1.8)		

*Every presented OR (95% CI) is produced from separate models taking into account one interaction at the time while adjusting for the other variable. CI: confidence interval; OR: odds ratio; REF: reference.

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