Assessing guideline impact on referral patterns of post-prostatectomy patients to radiation oncologists

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Cite as: *Can Urol Assoc J* 2016;10(9-10):314-8. http://dx.doi.org/10.5489/cuaj.3539

See related commentary on page 319.

Abstract

Introduction: Adjuvant radiotherapy (aRT) can improve biochemical progression-free survival in patients with high-risk features (HRF) after radical prostatectomy (RP). Guidelines from Alberta and the Genitourinary Radiation Oncologists of Canada (GUROC) recommend that patients with HRF be referred to radiation oncologists (RO) based on the findings from three randomized, controlled trials (RCT). Our study examines the impact of these recommendations both pre- (2005) and post- (2012) publication of RCT and GUROC guideline establishment.

Methods: Patients undergoing RP during 2005 and 2012 were identified from the provincial cancer registry. Charts were retrospectively reviewed and variables of interest were linked to the registry data. RO referral patterns for each year were determined and variables influencing referral (extracapsular extension, positive margin, seminal vesicle invasion, and post-RP prostate-specific antigen [PSA]) were compared.

Results: Median time to referral was 26.4 months in 2005 compared to 3.7 months 2012 ($p<0.001$). Among patients referred post-RP, a higher proportion was referred within six months in 2012 (21%) as compared to 2005 (13%) ($p=0.003$). Among eligible patients in 2012, 30% were referred for discussion of aRT compared to 24% in 2005 ($p=0.003$). There was a marked drop in patients referred for salvage radiation therapy beyond six months and a rise in the number of patients who are never referred.

Conclusions: Despite an increase in referral rates to RO post-RP from 2005–2012, more than 50% of those patients with HRF did not receive a referral. Initiatives aimed at improving multidisciplinary care and guideline adherence should be undertaken.

Introduction

In 2015, 24 000 new cases of prostate cancer diagnosis are anticipated in Canada (Canadian Cancer Stats 2015). Of these patients, approximately 50% will undergo radical prostatectomy (RP).[1] Despite improvements in surgical techniques, some patients will have high-risk features (HRF) (i.e., positive margins [M+], extracapsular extension [ECE], and seminal vesicle invasion [SVI]) post-resection without biochemical evidence of disease. Phase 3 randomized, controlled trials (RCT) have shown that adjuvant radiation therapy (aRT) for patients with HRF improves biochemical relapse-free survival and recurrence-free survival.[2-4] The update of the Southwest Oncology Group (SWOG) 8794 trial with median followup of 12.9 years has also shown an improvement in metastasis-free survival and overall survival.[5] Similarly, the 10-year followup data from the European Organization for Research and Treatment of Cancer (EORTC) 22911 trial confirms biochemical progression-free survival benefit and reports a clinical progression-free survival benefit with patients who underwent aRT.[6]

Following publication of these trials and a meta-analysis,[7] the Genitourinary Radiation Oncologists of Canada (GUROC) issued a consensus statement advising a consultation with a radiation oncologist (RO) early in the postoperative period to discuss benefits and side effects of aRT in those with HRF.[8] The American Urological Association (AUA) and American Society for Therapeutic Radiation Oncology (ASTRO) have also issued similar recommendations in their guidelines.[9] Furthermore, the American Society of Clinical Oncology has also endorsed these recommendations.[10]

The Alberta Health Services Cancer Control clinical practice guidelines, initially published in 2005 and updated yearly thereafter, reflect the phase 3 RCT evidence and recommendation of GUROC.

The goal of this study is to assess referral pattern to RO post-RP in order to determine the impact of published recommendations and compliance with our provincial guidelines.

Methods

All men who were ≥18 years of age and received a diagnosis of prostate adenocarcinoma in Alberta in 2005 (n=1794) and

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2012 (n=2149) were identified through the Alberta Cancer Registry, gold-certified by the North American Association of Central Cancer Registries, using discharge abstract database (DAD) with an error rate of <5%.[11] Only patients who underwent RP were included in the study cohort (n=658 in 2005; n=485 in 2012). Patients were excluded if they were treated out of province or if they had incomplete/inaccessible medical records (final cohort: n=374 in 2005; n=476 in 2012). Patient characteristics, disease characteristics, pathological characteristics, and referrals to RO were confirmed through manual chart review. Patients were considered to have HRF post-RP if they had ECE, M+, or SVI. Patients were considered to have had a RO referral if there was any evidence in their medical record of an appointment with a RO.

All data was collected in accordance with the Health Information Act of Alberta after ethical review using the ARECCI method.[12]

Statistical analyses were performed using SPSS V.22 (IBM, Armonk, NY, U.S.) or SigmaPlot (San Jose, CA, U.S.). T-test or Mann-Whitney U test were used for monovariable comparisons of quantitative data points. Chi-square or Fisher's exact test were used for monovariable comparisons of qualitative data points. A linear regression logistic multivariable model was constructed to assess association of variables with referral within six months post-RP.

All financial and material support to conduct this study and prepare this manuscript were provided through operational funding by CancerControl Alberta, Alberta Health Services.

Results

In 2005 and 2012, 1794 and 2149 men were diagnosed with prostate cancer, respectively. A total of 658 (36.7%) patients underwent RP in 2005 compared to 485 (22.6%) in 2012 (p<0.001). It is worth noting that the decrease in prostatectomy use in 2012 is likely the result of increased use of active surveillance in patients with low-risk disease. In addition, prostate brachytherapy developed as an alternative to prostatectomy in Alberta; the number of prostate brachytherapy in Alberta increased from 138 implants in 2005 to 307 implants in 2012.

Clinical records of 374 patients who underwent RP in 2005 and 476 in 2012 were available for analysis. Table 1 summarizes the patient, disease, and pathological characteristics. In both years, age and prostate-specific antigen (PSA) at diagnosis were similar (p>0.05). However, a significantly higher proportion of men with Gleason score (GS) ≥8 underwent RP in 2012 compared to 2005 (p<0.001). There was significantly higher proportion of patients with positive surgical margins and detectable PSA post-RP in 2005 compared to 2012 (p<0.001).

In 2005, 163 (43.6%) patients were referred to a RO as compared to 133 (27.9%) in 2012. Overall median time to referral was longer in 2005 compared to 2012 (26.4 vs. 3.7 months; p<0.001). Patients with ECE, M+, and SVI also had longer median referral time in 2005 compared to 2012: 24.4 (0.5–99.0) vs. 3.3 (0.3–22.7) months; 20.7 (0.5–99.0) vs. 2.9 (0.5–22.0) months; and 14.9 (0.5–99.0) vs. 3.3 (0.8–22.7) months, respectively. Fig. 1 displays the referral distributions.

Fig. 2 and Table 2 describe timing of referral (within six months of RP, after six months of RP, or never referred) to a RO if patients had HRF. There were more patients referred within six months of RP in 2012 as compared to 2005, but significantly less were referred after six months and a large proportion were never referred in 2012 (p<0.001). Subgroup analysis of patients

Table 1. Patient, disease, and pathology characteristics by year of diagnosis

	2005 (n=374)	2012 (n=476)	p value
Age, median (range)	61.6 (37.8–79.0)	61.6 (35.9–84.2)	0.347
Gleason at diagnosis, n (%)			<0.001
≤6	224 (60.3)	137 (29.3)	
7	139 (37.5)	270 (57.7)	
≥8	8 (2.2)	61 (13.0)	
Unknown	3	8	
PSA at diagnosis, n (%)			0.205
<10	267 (79.7)	399 (84.5)	
10–20	53 (15.8)	57 (12.1)	
>20	15 (4.5)	16 (3.4)	
Unknown	39	4	
Extracapsular extension, n (%)			0.491
Present	86 (24.8)	126 (26.9)	
Absent	261 (75.2)	342 (73.1)	
Unknown	27	8	
Surgical margins, n (%)			<0.001
Positive	140 (40.2)	129 (27.4)	
Negative	208 (59.8)	342 (72.6)	
Unknown	26	5	
Seminal vesicle invasion, n (%)			0.080
Present	41 (11.8)	38 (8.1)	
Absent	307 (88.2)	430 (91.9)	
Unknown	26	8	
PSA post-surgery, n (%)			<0.001
Detectable	96 (29.4)	48 (11.7)	
Undetectable	231 (70.6)	363 (88.3)	
Unknown	47	65	
Lymph node status, n (%)			0.168
Positive	14 (4.4)	12 (2.6)	
Negative	307 (95.6)	454 (97.4)	
Unknown	53	10	

PSA: prostate-specific antigen.

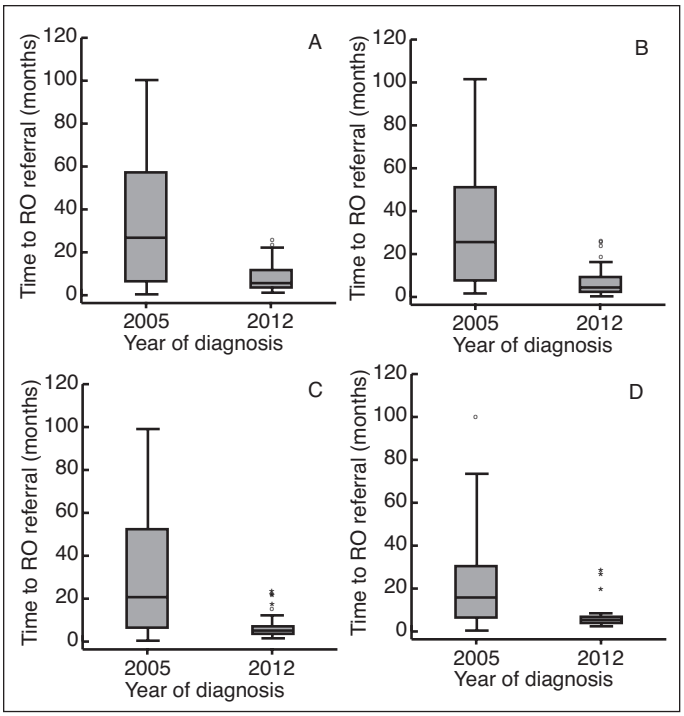

Fig. 1. Radiation oncologist referral from time of radical prostatectomy, median (range); ***(A)*** all patients, 26.4 (0.5–102.0) vs. 3.7 (0.3–26.1); ***(B)*** patients with extracapsular extension, 24.4 (0.5–99.0) vs. 3.3 (0.3–22.7); ***(C)*** patients with positive margins, 20.7 (0.5–99.0) vs. 2.9 (0.5–22.0); and ***(D)*** patients with seminal vesicle invasion, 14.9 (0.5–99.0) vs. 3.3 (0.8–22.7) months. Top line is maximum, bottom line is minimum, median is bolded with third and first quartile above and below (circles=outliers). RO: radiation oncologist.

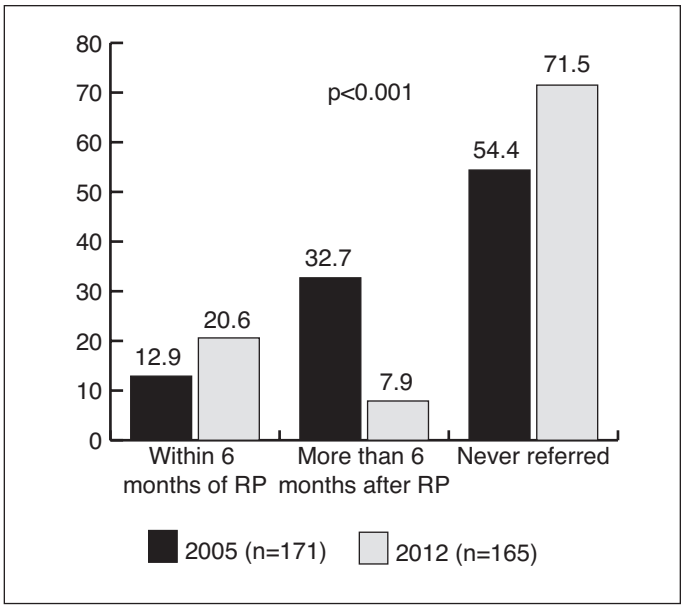

Fig. 2. Timing of referral to radiation oncologist for patients with at least one high-risk feature. RP: radical prostatectomy.

with HRF and those referred within six months showed that a higher proportion of these patients were referred in 2012 as compared to 2005, unless patients had all three HRF.

Fig. 3 displays patients who had HRF, undetectable PSA (<0.2 ng/ml), and were referred within six months post-RP (i.e., aRT). In 2012, only 30% of the patients were referred to RO for discussion regarding aRT. This is slightly higher than the 24% referred in 2005 (p=0.003). However, a significant proportion of patients were not referred in either of the two years examined (Fig. 3).

On univariable analysis, year of diagnosis (2012),as well as presence of ECE, M+, and SVI were found to be associated with referral to RO within six months (p<0.001). On multivariable analysis, only the year of diagnosis (p<0.001) and M+ (p<0.001) remained statistically significant.

Table 2. Referral of patients to RO within six months of RP if HRF were present (post-RP PSA excluded)

	2005	2012	p value
Extracapsular extension, n (%)	10 (23.8)	32 (72.5)	<0.001
Positive margins, n (%)	21 (34.4)	23 (79.3)	<0.001
Seminal vesicle invasion, n (%)	10 (38.5)	12 (80.0)	0.010
>1 pathological features, n (%)			
Two	5 (21.7)	16 (76.2)	<0.001
Three	7 (50.0)	7 (87.5)	0.079

HRF: high-risk factors; PSA: prostate-specific antigen; RO: radiation oncologist; RP: radical prostatectomy.

Discussion

In patients with HRF post-RP, risk of local recurrence is more than 60%.[5,6] Many international urologic and oncologic organizations have endorsed offering aRT to these patients, as it improves biochemical progression-free survival by 20–30%[2-4] and metastasis-free survival by 10%,[5] as well as clinical progression-free survival.[5,6] The impact on overall survival (OS) is uncertain, as the SWOG trial shows an improvement in OS,[5] while the EORTC trial does not.[6] A Cochrane review concluded that aRT improves OS and metastasis-free survival at 10 years.[13]

CancerControl Alberta has a process to develop treatment guidelines based on best available evidence. In 2005, guidelines recommended aRT for patients with M+, PSA <2 ng/ml, PSA doubling time >10 months, and GS ≤7. In 2012, these guidelines reflected RCT evidence and international consensus guidelines. The evidence and changes to guidelines are discussed at the annual provincial genitourinary meetings attended by urologists, radiation oncologists, and medical oncologists. The observed modest increase in the referral rates of patients with HRF seen in 2012 indicates ongoing dialogue among various healthcare members treating prostate cancer. Importantly, the observed increase in referral within six months of RP is potentially a result of guideline recommendations. However, a decline in referral rate greater than six months post-RP was noted (Fig. 2). This observation may be attributable to: (1) a higher number of

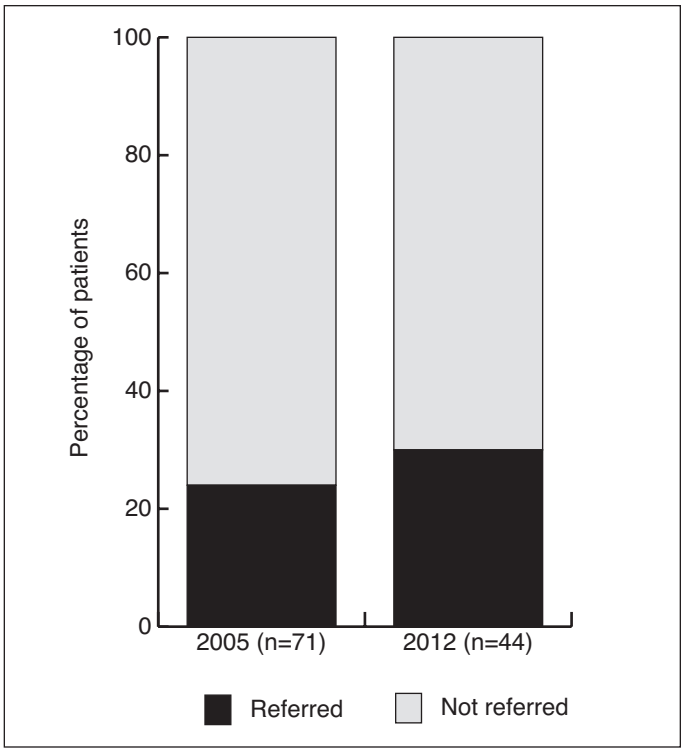

Fig. 3. Proportion of patients referred to a radiation oncologist for adjuvant radiotherapy consultation post-radical prostatectomy.*
*Presence of at least one high-risk feature, prostate-specific antigen <0.2 ng/ml, and referral within six months of radical prostatectomy.

patients being referred for salvage RT in 2005; and (2) inclusion of some patients referred for palliative RT many years post-RP in this cohort. This latter observation is supported by median time to referral, which was significantly longer for the 2005 cohort compared to the 2012 one.

Potential factors contributing to slow uptake of guideline recommendations

There are published models that estimate optimal radiotherapy referral and use.[14-16] These models would suggest 100% of patients with undetectable PSA and at least one HRF should be referred to RO for discussion of aRT. Unfortunately, the observed rate was 30% in 2012, only slightly higher than in 2005 (24%). Overall, the low referral rate in 2005 can be explained by lack of level I or other sufficiently good quality of evidence to support radiotherapy in this setting. With the arrival of new study results, the reason for suboptimal referral rates in 2012 is unclear. Potential explanations include: (1) patient and physician concern regarding radiotherapy toxicity; (2) lack of agreement among referring physicians that guideline recommendations are appropriate (gatekeeper effect); (3) lack of clear evidence regarding the optimal timing of radiotherapy post-RP; and (4) lack of perceived OS benefit.

Several publications have reported utilization rates of RT ranging from 1.8–11% post-RP for patients with HRF.[17-22] Sineshaw et al[23] looked at the National Cancer Data Base in the U.S. and found a significant drop in the utilization rate of postoperative RT in prostate cancer patients with adverse pathological factors between 2005 and 2011 from 9.1–7.3%. However, this study and the other cited publications do not report the referral rates to a radiation oncology department. To our knowledge, this is the first published report detailing referral rates at the population level. We believe it is important to identify the actual referral rate, rather than just RT utilization rate to assess the guideline implementation and adherence.

In our analysis the referral rate is higher than reported RT utilization rates likely due to denominator used to calculate the final rate. In previously published series, the denominator is usually total number of RPs, whereas we report on a subgroup of patients undergoing RP who have HRF and PSA <0.2ng/ml.

Can we do better? Are there strategies to improve guideline implementation and adherence?

Prior et al systematically reviewed published literature on effectiveness and implementation of clinical guidelines and reported compliance rates of 0–60%.[24] They found that strategies that involve passive dissemination were associated with the lowest compliance rates, whereas strategies that included multifaceted interventions, such as auditing, peer review, and feedback, had higher compliance rates. Others have also reported that active strategies, such as educational activities within institutions, supplementary professional information, and patient education improved guideline compliance.[25,26] Similarly, in the case of prostate cancer, in addition to publishing guidelines and consensus statements in peer-reviewed journals, the above strategies must be adopted to improve the referral of men with HRF for a discussion regarding aRT.

Furthermore, referring physicians must be brought on board. Management that includes aRT meets a medical need for patients and medical system. Showalter et al. constructed a decision analysis model based on the SWOG 8794 patient population and concluded that aRT is not only efficacious, but also cost-effective compared to observation post-RP.[27] These analyses are helpful not only for guideline formulation and decision-makers, but also provide additional evidence to referring physicians regarding benefit of aRT.

Limitations

We recognize that this study has limitations inherent to its design as a retrospective analysis. Furthermore, there are many patients for whom the pathological data was not available, especially those who were treated in 2005, a limitation of the data available in the electronic medical records at

that time. In addition, issues of access to care are important to consider; many patients would have been treated in non-urban, non-tertiary hospitals, thus limiting their access to cancer service delivery. So as to contextualize our data, we do not have the observed population level RT utilization rates to assess changes in trend of RT utilization pre- and post-publication of guidelines.

Nonetheless, this is the first and largest study to report on the population-based referral rates of patients with HRF to RO after RP. We have identified potential areas for improvements in dissemination and implementation of clinical guidelines.

Conclusion

RCTs and meta-analyses have shown men with HRF may benefit from aRT post-RP. Men undergoing aRT remain free of biochemical progression for a longer period of time and this may translate into improved local control, improved metastasis-free survival, and delay of androgen-deprivation therapies. Despite a modest increase in referral rates to RO post-RP from 2005–2012, more than 50% of patients sampled with HRF did not receive a RO referral. Initiatives to improve guideline compliance could include urologists and radiation oncologists working in a multidisciplinary care setting, clinician education, and additional strategies to improve interdisciplinary communication.

Competing interests: The authors report no competing personal or financial interests.

This paper has been peer-reviewed.

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