An audit of referral and treatment patterns of high-risk prostate cancer patients in Alberta

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Cite as: *Can Urol Assoc J* 2016;10(11-12):410-5. http://dx.doi.org/10.5489/cuaj.3910

Abstract

Introduction: We aimed to determine the impact of clinical practice guidelines (CPG) on rates of radiation oncologist (RO) referral, androgen-deprivation therapy (ADT), radiation therapy (RT), and radical prostatectomy (RP) in patients with high-risk prostate cancer (HR-PCa).

Methods: All men >18 years, diagnosed with PCa in 2005 and 2012 were identified from the Alberta Cancer Registry. Patient age, aggregated clinical risk group (ACRG) score, Gleason score (GS), pre-treatment prostate-specific antigen (PSA), RO referral, and treatment received were extracted from electronic medical records. Logistic regression modelling was used to examine associations between RO referral rates and relevant factors.

Results: HR-PCa was diagnosed in 261 of 1792 patients in 2005 and 435 of 2148 in 2012. Median age and ACRG scores were similar in both years (p>0.05). The rate of patients with PSA >20 were 67% and 57% in 2005 and 2012, respectively (p=0.004). GS ≤6 was found in 13% vs. 5% of patients, GS 7 in 27% vs. 24%, and GS ≥8 in 59% vs. 71% in 2005 and 2012, respectively (p<0.001). In 2005, RO referral rate was 68% compared to 56% in 2012 (p=0.001), use of RT + ADT was 53% compared to 32% (p<0.001), and RP rate was 9% vs. 17% (p=0.002). On regression analysis, older age, 2012 year of diagnosis and higher PSA were associated with decreased RO referral rates (odds ratios [OR] 0.49, 95% confidence interval [CI] 0.39–0.61; OR 0.51, 95% CI 0.34–0.76; and OR 0.64, 95% CI 0.39–0.61), respectively [p<0.001]).

Conclusions: Since CPG creation in 2005, RO referral rates and ADT + RT use declined and RP rates increased, which demonstrates a need to improve adherence to CPG in the HR-PCa population.

Introduction

Prostate cancer (PCa) is the most common cancer among men in North America. According to Canadian Cancer Statistics, approximately 21 600 men will be diagnosed with PCa and 4000 men will die in 2016 due to PCa, accounting for 10% of cancer mortality in men.[1]

Treatment is guided by risk stratification, which uses Gleason score (GS), prostate-specific antigen (PSA), and clinical exam (T-stage) to classify patients into high-, intermediate- and low-risk groups. High risk disease (HR-PCa) represents 20–30% of all patients and is defined as ≥T3a, GS ≥8, or PSA >20.[2,3]

Four randomized, controlled trials (RCTs) established the combination of radiation therapy (RT) and androgen-deprivation therapy (ADT) as a standard treatment for men with HR-PCa. These trials showed that RT + ADT is associated with higher overall survival rates compared to RT or ADT alone.[4-7] However, several retrospective studies suggested that radical prostatectomy (RP) may provide comparable outcomes to RT + ADT, but no RCT has compared them directly.[8-10] Therefore, the optimal treatment approach to HR-PCa remains controversial. Urologists are usually the first specialists to see these patients and may or may not elect to refer patients for a discussion of RT + ADT.

In Alberta, Canada, an interdisciplinary team including urologists, as well as radiation and medical oncologists, developed an evidence-based clinical practice guideline (CPG) for the management of PCa in January 2005.[11] The guideline, which has been regularly updated, recommends that patients with HR-PCa be referred to a radiation oncologist (RO) prior to surgery and that the preferred treatment is RT + ADT. These recommendations are consistent with other national and international guidelines.[12-14] This is a report on the impact of the CPG on clinical practice since its publication.

We hypothesized that RO referral rates would increase from 2005 to 2012. The primary and secondary endpoints are RO referral rate and treatment received by patients in 2005 and 2012, respectively.

Methods

All men with a new diagnosis of prostate adenocarcinoma of age ≥18 years in 2005 and 2012 were identified through the Alberta Cancer Registry, which included all patients diagnosed in the province of Alberta, Canada. HR-PCa was defined as GS ≥8 on biopsy, or pre-treatment PSA >20 ng/ml. Clinical T-stage was excluded from risk stratification due to the subjectivity of digital rectal examination, lack of documentation, and inter-observer variability. Patient demographics, pre-treatment PSA value, GS on biopsy, occurrence and date of RO referral, PSA at time of RO referral, primary treatment modality (RT + ADT, RT, ADT, RP or nothing), and pathological characteristics at RP were collected from electronic medical records. Aggregated Clinical Risk Grouping (ACRG) — a classification system for risk adjustment that assigns individuals a single risk group score (10–100) based on both historical clinical and demographic characteristics to serve as a proxy for pre-diagnosis patient comorbidity[15] — was also collected. ACRGs were derived from the Data Integration, Measurement and Reporting (DIMR) unit in the year prior to PCa diagnosis to avoid interaction of the PCa diagnosis on the score. Patients who received non-curative RT or those with documented metastasis on clinical exam, computed tomography (CT), or bone scan (which was routinely done for these patients at diagnosis) were excluded.

Statistical analyses were performed using SigmaPlot (San Jose, CA, U.S.). Logistic regression modelling was used to determine the association between RO referral rate, the use of RP and ADT use and the described variables. Chi-square was used to compare categorical variables. This study was approved prior to conduct, by the Alberta Privacy Office after using the ARECCI Ethics Screening tool.[16]

Results

Patients

In 2005 and 2012, 1792 and 2148 patients received a new diagnosis of PCa in Alberta, respectively. HR-PCa was identified in 261 (14.5%) patients in 2005 and 435 (20.3%) in 2012. Median age and ACRG were similar between the time cohorts. GS ≤6 was found in 13% vs. 5% of patients, GS 7 in 27% vs. 24%, and GS ≥8 in 59% vs. 71% in 2005 and 2012, respectively (p<0.001). PSA scores varied (p=0.004) between 2005 and 2012. PSA >20 was noted in 67% of HR-PCa patients diagnosed in 2005 and 57% of those diagnosed in 2012. Clinical tumour stage (cT) was similar between cohorts (p=0.332). Table 1 summarizes the characteristics of those with HR-PCa.

Table 1. High-risk prostate cancer patients' clinical characteristics

	2005 (n=261)	2012 (n=435)	p value
Median age (range), years	71 (47–93)	72 (43–95)	0.270
ACRG, n (%)			0.200
10–30	111 (42.5)	155 (36.5)	
31–50	42 (16.1)	68 (16.0)	
51–70	106 (40.6)	192 (45.2)	
71–100	2 (0.8)	10 (2.4)	
Unknown	0	10	
Gleason score, n (%)			<0.001
≤6	31 (13.2)	17 (4.6)	
7	64 (27.4)	89 (24.1)	
≥8	139 (59.4)	263 (71.3)	
Unknown	27	66	
PSA, n (%)			0.004
<10	55 (21.9)	99 (23.0)	
10–20	28 (11.2)	88 (20.4)	
>20	168 (66.9)	244 (56.6)	
Unknown	10	4	
T-stage, n (%)*			0.332
T1	53 (20.9)	91 (21.8)	
T1a**	2 (0.8)	5 (1.2)	
T1b**	7 (2.8)	18 (4.3)	
T1c	44 (17.4)	68 (16.3)	
T2 (including those NOS)	135 (53.6)	242 (58.0)	
T2a	18 (7.1)	30 (7.2)	
T2b	31 (12.3)	36 (8.6)	
T2c	44 (17.4)	39 (9.4)	
T3 (including those NOS)	59 (23.3)	73 (17.5)	
T3a	27 (10.7)	44 (10.6)	
T3b	16 (6.3)	11 (2.6)	
T4	6 (2.4)	11 (2.6)	
Unknown	8	18	

*All included patients had clinical N0 (no lymph node metastasis) and M0 (no distant metastasis); **patients with cT1a and T1b were diagnosed following a surgical procedure for non-malignant causes (e.g., transurethral resection of prostate). ACRG: Aggregated Clinical Risk Group; NOS: not otherwise specified; PSA: prostate-specific antigen.

Referral rates

Referral rates to RO decreased from 68% in 2005 to 56% in 2012 (p=0.001). Among patients treated with RP, 4.3% received an RO referral prior to RP in 2005 compared to 21.6% in 2012 (p=0.02). After RP, 52% of patients in 2005 and 28% in 2012 received RO referral (p=0.02). Table 2 summarizes RO referral rates.

Table 2. Radiation oncology referral rates and treatment characteristics

	2005 (n=261) n (%)	2012 (n=435) n (%)	p value
Received RO referral	178/261 (68.2)	243/435 (55.7)	0.001
Treated with RP	23/261 (8.8)	74/435 (17.0)	0.002
Received RO referral	13/23 (56.5)	37/74 (50.0)	0.585
Before RP	1/13 (7.7)	16/37 (43.2)	0.02
After RP	12/13 (92.3)	21 (56.7)	
Received adjuvant radiotherapy	11/23 (47.8)	19/74 (25.7)	0.045
Treated with radiotherapy and ADT	138/261 (52.9)	139/435 (32.0)	<0.001
Treated with radiotherapy alone	3/261 (1.1)	9/435 (2.1)	0.367
Age in years, median (range)	76 (65–77)	69 (54–80.7)	0.407
Clinical risk group			0.944
10–30	1 (33.3)	3 (33.3)	
31–50	0	1 (11.1)	
51–70	2 (66.7)	5 (55.6)	
71–100	0	0	
Unknown	0	0	
Gleason score			0.762
≤6	0	0	
7	0	2 (22.2)	
≥8	2 (100.0)	7 (77.8)	
Unknown	1	0	
PSA			0.801
<10	1 (33.3)	5 (55.6)	
10–20	1 (33.3)	2 (22.2)	
>20	1 (33.3)	2 (22.2)	
Unknown	0	0	
Treated with ADT alone	44/261 (16.9)	164/435 (37.7)	<0.001
Received RO referral	19/44 (43.2)	46/164 (28.0)	0.054
No apparent treatment	53/261 (20.3)	51/435 (11.7)	0.002
Received RO referral	6/53 (11.3)	12/51 (23.5)	0.1
Age in years, median (range)	79 (60–93)	75 (43–94)	0.12
Clinical risk group			0.082
10–30	18 (34.0)	13 (28.3)	
3–50	6 (11.3)	7 (15.2)	
51–70	29 (54.7)	21 (45.7)	
71–100	0 (0.0)	5 (10.9)	
Unknown	0	5	
Gleason score			0.203
≤6	7 (24.1)	4 (10.5)	
7	5 (17.2)	12 (31.6)	
≥8	17 (58.6)	22 (57.9)	
Unknown	24	13	
PSA			0.169
<10	4 (8.0)	8 (17.0)	
10–20	3 (6.0)	6 (12.8)	
>20	43 (86.0)	33 (70.2)	
Unknown	3	4	

ADT: androgen-deprivation therapy; PSA: prostate-specific antigen; RO: radiation oncology; RP: radical prostatectomy.

Treatments

In 2005, 53% of the HR-PCa patients were treated with RT + ADT compared to 32% in 2012 (p<0.001). The RP rate was 9% in 2005 compared to 17% in 2012 (p=0.002). RPs were performed by 10 surgeons in 2005 vs. 20 surgeons in 2012. Robotic-assisted surgery, which was not available in 2005, was performed in approximately 25% of HR-PCa patients who underwent RP in 2012. Laparoscopic RPs were performed only in 2005 (about 10% of RPs). The remainder were retropubic RPs in both years. Adjuvant RT (defined as RT received within six months post-RP with undetectable PSA and no evidence of clinical recurrence) was used in 48% and 26% of patients in 2005 and 2012, respectively (p=0.045). ADT alone was received by 17% in 2005 compared to 38% in 2012 (p<0.001). RT alone was received by 1% and 2% in 2005 and 2012, respectively (p=0.36). Patients receiving RT alone had similar CRG scores, GS, and PSA values between years (all p>0.05). In 2005, 20% of patients had no apparent treatment compared to 12% in 2012 (p=0.002). Table 2 summarizes the different treatments received by patients.

Treatments in patients with both high-risk features (PSA >20 and GS ≥8)

In 2005, 49.0% of patients with both high-risk features (PSA >20 and GS ≥8) were treated with RT + ADT compared to 37.0% in 2012 (p=0.188). Among these patients, the RP rate was 2.0% in 2005 compared to 1.4% in 2012 (p=0.775), with no adjuvant RT being delivered. ADT alone was received by 32.7% in 2005 compared to 53.4% in 2012 (p=0.024) and no patients received RT alone. In 2005, 16.3% of these patients had no apparent treatment compared to 8.2% in 2012 (p=0.168). Table 3 summarizes the different treatments received by this subset of patients.

Univariate and multivariate correlates with RO referral

Univariate analysis identified older age (p<0.001), more recent year of diagnosis (p=0.001), and higher PSA (p<0.001) as being associated with lower referral rates. Higher GS was associated with higher referral rates (p=0.029). On regression analysis, older age (odds ratio [OR] 0.49, 95% confi-

Table 3. Radiation oncology referral rates and treatment characteristics in patients with both high-risk features (PSA >20 and Gleason score ≥8)

	2005 (n=49)	2012 (n=73)	p value
	n (%)	n (%)	
Received RO referral	31/49 (63.3)	44/73 (60.3)	0.550
Treated with RP	1/49 (2.0)	1/73 (1.4)	0.775
Received RO referral	0/1 (0.0)	1/1 (100.0)	0.157
Before RP	0/1 (0.0)	1/1 (100.0)	0.157
After RP	0/1 (0.0)	0/1 (0.0	
Received adjuvant radiotherapy	0/1 (0.0)	0/1 (0.0)	
Treated with radiotherapy and ADT	24/49 (49.0)	27/73 (37.0)	0.188
Treated with radiotherapy alone	0/49 (0.0)	0/73 (0.0)	
Treated with ADT alone	16/49 (32.7)	39/73 (53.4)	0.024
Received RO referral	6/16 (37.5)	15/39 (38.5)	0.950
No apparent treatment	8/49 (16.3)	6/73 (8.2)	0.168
Received RO referral	1/8 (12.5)	1/6 (16.7)	0.825
Age in years, median (range)	78 (61–83)	76 (68–89)	0.457
Clinical risk group			0.279
10–30	0	1 (20.0)	
31–50	2 (25.0)	1 (20.0)	
51–70	6 (75.0)	2 (40.0)	
71–100	0	1 (20.0)	
Unknown	0	1	

ADT: androgen-deprivation therapy; PSA: prostate-specific antigen; RO: radiation oncology; RP: radical prostatectomy.

dence interval [CI] 0.39–0.61; p<0.001), more recent year of diagnosis (OR 0.51, 95% CI 0.34–0.76; p=0.001), and higher PSA (OR 0.64, 95% CI 0.39–0.61; p<0.001) were associated with lower referral rates, but that higher GS (OR 1.77, 95% CI 1.36–2.3; p<0.001) was significantly associated with higher referral rates. Patient comorbidity, as determined by ACRG scores, did not influence referral rates on univariate or multivariate analysis (Table 4).

Discussion

To date, no published data have reported on RO referral patterns for patients with HR-PCa in North America. Despite the evidence that approximately 90% of PCa patients have a performance status that would permit RT,[17] observed RO referral rates in our study were low, even for patients with both high-risk features (PSA>20 and GS ≥8). The lower overall RO referral rate in 2012 compared to 2005 was associated with decreased use of RT + ADT and increased rate of RP. The availability of the robotic-assisted surgery technique in 2012 might have contributed to the observed increase in RP rate, as it might be a more acceptable option to the patients than the classical technique (retropubic RP) despite early published reports that show no difference between techniques in oncological and toxicities outcomes.[18,19] For comparison, in a study that included 1593 HR-PCa patients from the Cancer of the Prostate Strategic Urological Research Endeavor (CaPSURE) database, the rates of RP and RT use were 36% and 22%, respectively.[20] In patients who received RT, ADT was used in 52%. Data for referral rates to RO were unavailable in the CaPSURE study. The higher RP rate compared to RT with or without ADT might reflect the fact that enrolling physicians in CaPSURE were urologists.

The debate about RT + ADT vs. RP to treat HR-PCa patients is yet to be resolved; it would require a well-powered, RCT with long-term followup directly comparing RT + ADT and RP, and addressing all the challenges that such a trial would introduce. Four major phase 3 RCTs (EORTC 22911, RTOG 8531, SPCG-7, and NCIC PR3) have shown that the combined modality of RT + ADT is superior to RT or ADT alone.[4-7] On the other hand, large retrospective studies with long followup times demonstrated equivalence of RP to RT + ADT.[8-10,21-26] A meta-analysis showed a modest improvement in cancer-specific survival with RP compared to RT + ADT.[21] However, this finding was based on two small retrospective studies and the authors of the meta-analysis were concerned about the limited quality of most studies included in the meta-analysis.[22,23] In contrast, Boorjian et al reported similar 10-year cancer-specific survival in patients treated with RP or RT + ADT.[8] Overall, the retrospective data that compared outcomes of RP to RT + ADT suffered from selection bias, variable length of ADT use, and contamination of the RP cohort by adjuvant and salvage therapies.

In our study, we found that patients who received adjuvant RT following RP decreased in 2012 compared to 2005, which may indicate better selection of a subgroup of patients with HR-PCa for RP in whom adjuvant RT was possibly not indicated. This might have resulted in limiting the overall treatment cost and the overall treatment toxicities. In order to select patients with higher-risk disease, we analyzed a subgroup of patients with both high-risk features (PSA >20 and GS ≥8) and found that rates of RT + ADT or ADT alone in these patients were higher than rate of RP (81.7% vs. 2% in 2005 and 90.4% vs. 1.4% in 2012). None of the two patients who were initially treated with RP in both years received adjuvant RT. Generally, there are no recognized HR-PCa patient subsets in the literature that may benefit more from one treatment (RT + ADT or RP) over the other. However, some reports suggest that patients with PSA >20 may have worse outcomes with RP compared to RT + ADT and rates of adjuvant and salvage therapies after RP increase with higher GS and clinical stage.[24,27] This may indicate that the benefit from local treatment only without ADT is limited in these patients. Given the potential need for adjuvant RT

Table 4. Multivariate/univariate analysis, effect of variables on radiation oncologist referral rates

				Multivariate	Univariate
Variable	**OR**	**5% CI**	**95% CI**	**p value**	**p value**
Year of diagnosis	0.513	0.344	0.764	0.001	0.001
Gleason score	1.775	1.366	2.306	<0.001	0.029
PSA	0.643	0.514	0.805	<0.001	<0.001
Clinical risk group	0.991	0.805	1.219	0.929	0.102
Age	0.492	0.393	0.615	<0.001	<0.001

CI: confidence interval; OR: odds ratio; PSA: prostate-specific antigen.

in HR-PCa patients treated with RP, this therapy should be discussed with patients when RP is proposed as a preferred treatment option.

An observation from our study was the rise in the use of ADT alone from 17% in 2005 to 38% in 2012 without evidence or guidelines to recommend ADT alone as an initial "curative" treatment plan. In addition, approximately 20% of HR-PCa patients in 2005 and 12% in 2012 received no apparent treatment. The median age for these patients was 79 in 2005 and 75 in 2012. The proportion of patients with important medical comorbidities as represented by an ACRG score >50 were 55% and 46% in 2005 and 2012, respectively. RO referral rates were 11% and 23%, respectively. These patients were likely deemed not fit for curative treatment by their urologists or ROs. Although patient clinical performance status is unavailable at the population level, ACRGs scores are a reasonable surrogate for traditional measures of comorbidity, such as the Charlson index. ACRGs not only categorize individuals' illnesses, but they also include their severity, which have been validated for other cancers and are similar in construct to the John's Hopkins' Aggregated Diagnosis Groups (ADGs).[28-30]

In addition to the inherent bias normally associated with retrospective studies, another limitation of this study is the missing GS data of 27 and 66 patients in 2005 and 2012, respectively. This is likely secondary to the absence of pathology in patients where the transrectal ultrasound-guided biopsy was deemed to be clinically unnecessary to establish the diagnosis or to determine the subsequent treatment, or associated with a high risk of complications in a less healthy cohort of patients. Patients were likely diagnosed with HR-PCa based on elevated PSA and clinical or imaging evidence consistent with PCa. Also, overall GS incorporated the tertiary Gleason pattern in 2012 patients only. This might have resulted in assigning higher GS to these patients, but should not have affected RO referral pattern. Furthermore, we did not obtain treatment costs and outcomes in this study.

Several reports measuring adherence to National Comprehensive Cancer Network (NCCN) guidelines have demonstrated a relationship between compliance and improved outcomes in a variety of malignancies, including melanoma,[31] colon cancer,[32,33] pancreatic cancer,[34] gastric cancer,[35] and others.[36-38] In an effort to improve adherence to CPGs, multidisciplinary cancer clinics (MDCs) were introduced, which showed higher concordance with published CPGs compared to non-multidisciplinary clinics.[39,40] While MDCs could offer an opportunity for patient-centred care, issues around cost and process remain health system challenges that need to be addressed.

The observed decline in RO referral and the increase in rates of RP and ADT use alone raise concerns that patients are likely being treated without being fully informed of their treatment options. In 2012, more than two-thirds of patients received a RP without being referred to RO. Best practice for patients, in our opinion, is provided within the context of a multidisciplinary approach, with patients being informed by the specialists who offer the treatment.

Conclusion

Despite guideline implementation in 2005, RO referral rates and RT + ADT use declined between 2005 and 2012 in Alberta. RP rates increased. These observations are discordant with guideline recommendations and suggest that greater efforts need to be undertaken to improve the multidisciplinary management of HR-PCa patients.

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

Acknowledgements: Presented, in part, at the annual scientific meeting of the Canadian Association of Radiation Oncologists, September 11, 2015, Kelowna, BC, Canada, and the annual scientific meeting of the American Society for Radiation Oncology, October 18, 2015, San Antonio, TX, United States.

The Albaha University (Albaha, Saudi Arabia) sponsored Dr. Alghamdi for his residency training at the University of Calgary. The authors thank members of the GU Tumour Group in Alberta, who treated the patients and provided constructive advice during the design and interpretation of this study.

All financial and material support for the conduct of this study and preparation of this manuscript was provided through operational funding by CancerControl Alberta, Alberta Health Services.

This paper has been peer-reviewed.

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