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## COMMENTARY

# Canadian guidelines for SRMs: How Canadian are they?

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Small renal masses (SRM) are encountered by most urologists as part of their routine clinical practice, which makes best practice statements or guidelines like those published in this month's *CUAJ* important in standardizing care.<sup>1</sup> While it is good for patients to have options, the management of SRMs has started to resemble that of localized prostate cancer – each patient and the treating physician have many potentially difficult choices to make, and there is an underlying concern for over-treatment.

The European Association of Urology (EAU) and the National Comprehensive Cancer Network (NCCN) have recently updated their kidney cancer guidelines including the management of SRMs.<sup>2,3</sup> The American Urological Association (AUA) published guidelines specifically on SRMs in 2009 and validated these in 2010.<sup>4</sup> Furthermore, the Kidney Cancer Research Network of Canada (KCRNC), which includes many of the same contributors who drew up these SRM guidelines, has developed best practice guidelines in the past.<sup>5</sup> The question therefore arises how these

new guidelines compare to other international guidelines, how they differ from the prior KCRNC consensus statement, and what makes them specifically Canadian. The answer to all these questions is: not much.

Specific Canadian content to the literature on the management of SRMs relates primarily to the utility of renal mass biopsy<sup>6-8</sup> and the adoption of active surveillance,<sup>9</sup> both of which we as a Canadian community of urologists would generally promote. However, neither of these components is emphasized particularly strongly in the current guidelines, reflecting a degree of uncertainty in their widespread adoption. With respect to these two issues, these guidelines do not read much differently than the AUA guidelines from 2010, which also recognize an increased role for biopsy and allow for active surveillance in older patients and those with significant medical comorbidities.<sup>4</sup> The EAU and NCCN guidelines do not really entertain the notion of SRM biopsy to decide on surgical intervention versus surveillance, but instead limit its scope to patients with metastatic disease, those on surveillance, or those undergoing ablation. The NCCN guidelines are more restrictive than these Canadian guidelines with respect to use of ablative procedures, and reserve these for patients who are explicitly not candidates for surgery. However, this represents a deviation of the

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- Not indicated for reducing the risk of developing skeletal-related events in pediatric patients.

### Contraindications:

- In patients with pre-existing hypocalcemia, which must be corrected prior to initiation

### Most serious warnings and precautions:

**Osteonecrosis of the jaw (ONJ):** In clinical trials, the incidence of ONJ was higher with longer duration of exposure. In patients with risk factors for ONJ, an individual risk/benefit assessment should be performed before initiating therapy with XGEVA. An oral exam should be performed and a dental exam with appropriate preventive dentistry is recommended prior to treatment with XGEVA, especially in patients with risk factors for ONJ. Avoid invasive dental procedures while receiving XGEVA. In patients who develop ONJ during treatment with XGEVA, a temporary interruption of treatment should be considered based on individual risk/benefit assessment until the condition resolves.

### Other relevant warnings and precautions:

- Do not use concurrently with Prolia
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- Hypocalcemia has been reported (including severe symptomatic hypocalcemia and fatal cases postmarketing). Monitor calcium prior to the initial dose, within two weeks after the initial dose, and if suspected symptoms of hypocalcemia occur. Administer calcium, magnesium and vitamin D as necessary. If hypocalcemia occurs while receiving XGEVA, additional short-term calcium supplementation and additional monitoring may be necessary.
- Caution on risk of hypocalcemia in patients with renal impairment
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### Fizazi, et al. study<sup>3</sup>

Phase 3, randomized, double-blind, double-dummy, active-controlled study. Patients with castrate-resistant prostate cancer and bone metastases (n=1901) received either 120 mg XGEVA<sup>®</sup> SC Q4W (once every 4 weeks) (n=950) or 4 mg zoledronic acid IV Q4W (n=951). The primary outcome measure was to demonstrate non-inferiority of time to first on-study SRE as compared to zoledronic acid. The secondary outcome measures were superiority of time to first on-study SRE and superiority of time to first and subsequent SREs. An SRE is defined as any of the following: pathologic fracture, radiation therapy to bone, surgery to bone or spinal cord compression.

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NCCN guidelines from the general consensus of the other guidelines rather than a deviation of the Canadian guidelines.

These Canadian guidelines take a weak stance on the European Organisation for the Research on the Treatment of Cancer (EORTC) prospective randomized trial demonstrating an overall survival advantage for radical nephrectomy over partial nephrectomy in 541 patients with a renal mass  $\leq 5$  cm in diameter.<sup>10</sup> The overall survival difference (81.1% vs. 75.7% at 5 years; hazard ratio 1.50 with 95% confidence interval 1.03–2.16) was significant on an intention-to-treat (ITT) analysis, but not when restricted to patients with pathologically confirmed renal cell carcinoma. Since the histologic diagnosis of renal cell carcinoma is not generally made until after partial nephrectomy because pre-operative biopsy has not been widely adopted, the ITT analysis is the clinically more relevant one. It appears easy to disregard this level one evidence without critical analysis of the results. While we are reluctant to give up the purported advantage of preserving renal function despite the results of this EORTC trial, should they not at least dissuade the urologist from performing technically very challenging partial nephrectomies? Interestingly, the NCCN guidelines do not even refer to this paper,<sup>2</sup> and the EAU guidelines completely disregard any controversy with the simple statement: “In a prematurely closed randomized study of RCC < 5 cm, comparing PN and RN, there was no difference in OS in the targeted population.”<sup>3</sup> At least the controversy has been acknowledged in the Canadian guidelines.

**Competing interests:** Dr. Black is currently a member of the advisory boards for AbbVie and Astellas. He is also a member of the Speaker's bureau for AbbVie. He is participating in clinical trials with Janseen, Ferring, Astellas, and Amgen and is receiving consulting fees from Cubist. He is also part of the clinical trial design team for Roche/Genentech.

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