Treatment options for localized prostate cancer

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EDITOR'S KEY POINTS

- No one treatment of localized prostate cancer has proven to be clearly superior. For many patients, making the treatment decision can be challenging. Family physicians are often helpful in providing information and guiding patients through the decision-making process.
- This article describes the treatment options available for men with early stage prostate cancer: radical prostatectomy, prostate brachytherapy, external beam radiation therapy, and active surveillance.
- The use of decision aids in early stage prostate cancer can increase overall patient knowledge, reduce patients' anxiety, and increase their involvement in the decision-making process, and physicians might find them useful when supporting patients who are facing decisions about early stage prostate cancer treatment.

POINTS DE REPÈRE DU RÉDACTEUR

- Aucun traitement du cancer localisé de la prostate ne s'est à lui seul révélé clairement supérieur. Pour de nombreux patients, le choix du traitement peut être difficile. Les médecins de famille apportent souvent une aide précieuse dans la communication de renseignements et l'orientation des patients dans le processus décisionnel.
- Cet article décrit les options de traitement à la disposition des hommes atteints d'un cancer de la prostate à un stade précoce: la prostatectomie radicale, la curiethérapie de la prostate, la radiothérapie de la prostate et la surveillance active.
- Le recours à des aides à la décision à un stade précoce du cancer de la prostate peut accroître les connaissances générales du patient, réduire son anxiété et augmenter sa participation au processus décisionnel; les médecins peuvent les trouver utiles dans l'assistance aux patients aux prises avec une décision au sujet du traitement à choisir pour le cancer de la prostate à un stade précoce.

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Abstract

Objective To describe treatment options for clinically localized prostate cancer: radical prostatectomy, prostate brachytherapy, external beam radiation, and active surveillance.

Quality of evidence Prostate-specific antigen (PSA) outcomes presented are from non-randomized, cohort, and other comparisons trials (level II evidence). We describe PSA outcomes from Canadian centres when they are available. One small randomized controlled trial (level I evidence) in localized prostate cancer is available to compare radical prostatectomy with brachytherapy.

Main message Treatment choice in prostate cancer is based on initial PSA level, clinical stage of disease, and Gleason score, together with baseline urinary function, comorbidities, and patient age. In this article, we describe patients' eligibility for and the common side effects of all treatment options. Prostate brachytherapy and active surveillance have evolved as new standard treatments of localized prostate cancer. We give a brief overview of the brachytherapy procedure, side effects, and PSA outcomes across Canada, as well as active surveillance guidelines.

Conclusion Prostate cancer treatment requires a multidisciplinary approach, with input from both urology and radiation oncology. Input from family physicians is often as important in helping guide patients through the treatment decision process.

Options de traitement du cancer localisé de la prostate

Résumé

Objectif Décrire les options de traitement du cancer de la prostate cliniquement localisé: la prostatectomie radicale, la curiethérapie de la prostate, la radiothérapie externe et la surveillance active.

Qualité des données Les paramètres de l'antigène prostatique spécifique (APS) sont tirés d'études non randomisées, de cohortes et d'autres études comparatives (données probantes de niveau II). Nous décrivons les paramètres de l'APS provenant de centres canadiens lorsqu'ils sont disponibles. Il existe une petite étude randomisée contrôlée (données probantes de niveau I) sur le cancer localisé de la prostate, qui compare la prostatectomie radicale et la curiethérapie.

Message principal Le choix du traitement du cancer de la prostate se fonde sur le niveau initial de l'APS, le stade clinique de la maladie et le score de Gleason, ainsi que sur la fonction urinaire de base, les maladies concomitantes et l'âge du patient. Dans cet article, nous décrivons les critères d'admissibilité des patients aux différentes options thérapeutiques ainsi que les effets secondaires communs. La curiethérapie de la prostate et la surveillance active sont devenues les nouveaux standards de traitement du cancer localisé de la prostate. Nous donnons un bref aperçu de la procédure de la curiethérapie, de ses effets secondaires et des résultats sur le plan de l'APS au Canada, ainsi que des lignes directrices à suivre pour la surveillance active.

Conclusion Le traitement du cancer de la prostate exige une approche multidisciplinaire comportant l'intervention à la fois d'un urologue et d'un radio-oncologue. Les contributions d'un médecin de famille sont souvent importantes pour aider à orienter le patient dans le processus décisionnel de l'option thérapeutique.

The purpose of this article is to describe the treatment options available for men with early stage prostate cancer: radical prostatectomy (RP), prostate brachytherapy (PB), external beam radiation therapy (EBRT), and active surveillance (AS). Family physicians are often asked to participate in the discussion with prostate cancer patients regarding available treatment options. Herein, we provide an update for Canadian family physicians on all treatment options for localized prostate cancer, including PB and AS, 2 new standard treatment approaches. We provide eligibility criteria, treatment toxicity, and disease and quality-of-life (QOL) outcomes.

Treatment choice in prostate cancer is based on the well established prognostic factors: initial PSA level, clinical TNM (primary tumour, regional lymph nodes, and distant metastasis) stage, and Gleason score (GS), along with general considerations such as baseline urinary function, comorbidities, and age. Family physicians' role in counseling patients with localized prostate cancer about treatment options has become increasingly difficult and complex.

Quality of evidence

Two recently published randomized controlled trials (RCTs) of prostate cancer screening[1,2] have not only increased controversies surrounding prostate cancer screening, but have also increased demands[3] for all radical treatment options. Unfortunately, there are very few randomized studies to compare treatments in localized prostate cancer.

There is only 1 RCT (level I evidence) in localized prostate cancer to compare 2 different treatment options—RP and PB—with each other.[4] Level II evidence (non-randomized comparison and cohort studies) is available for all treatments. A large, recently published systematic review compares all treatment options in prostate cancer and provides some insights into the comparative effectiveness of prostate cancer treatments using current modern literature results (848 articles and more than 50 000 patients).[5]

Variations in outcomes in oncology between institutions are owing to differences in techniques, patient selection, and experience. We believe patients should be informed about expected outcomes of treatment based on the results at the institutions where they will be treated. Therefore, we have focused our outcomes review on disease outcomes from Canadian urology and radiation oncology centres when possible, as this might be more relevant to Canadian family physicians and their patients. In the following section, we describe each treatment option, eligibility criteria, common side effects, treatment outcomes, and QOL.

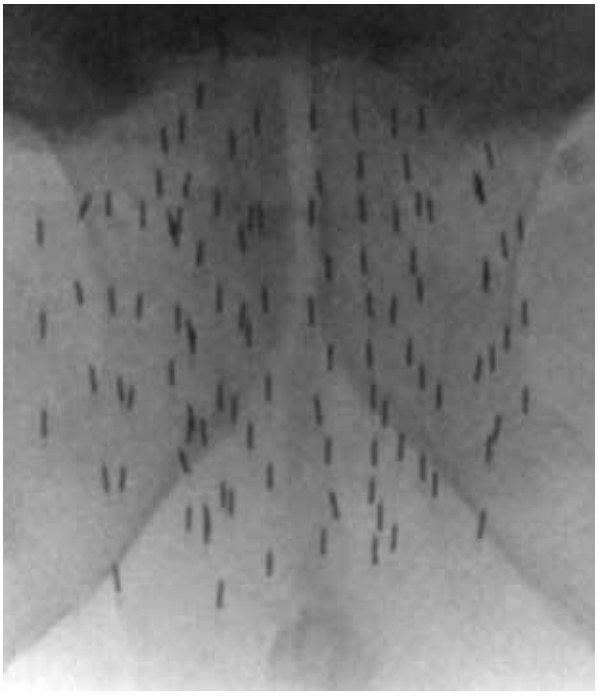
Main message

Radical prostatectomy. For 2 decades, RP has been the most commonly used treatment for healthy men younger than age 70 with localized prostate cancer. Use of PSA-based screening has increased the rate of organ-confined disease at the time of diagnosis, increasing the chances of successful outcomes after surgery. The best candidates for RP are those with organ-confined prostate cancer (low- or intermediate-risk disease, and selected patients with high-risk disease), younger than 70 years of age, who have a more than 10-year life expectancy and no or minimal comorbidities. In patients with pre-existing lower urinary tract symptoms due to benign prostatic hypertrophy, removal of the prostate often improves QOL. The complications of concern are incontinence and erectile dysfunction due to operative damage to the urinary sphincter and erectile nerves. In physician-reported series from single institutions, reported incontinence ranges from 0% to 12% at 6 to 24 months following surgery.[6] Patient-reported data suggest that at 24 months, 42% of patients have some leakage, 7% have frequent leakage, and 2% have no urinary control.[7] Minimally invasive surgical approaches, such as laparoscopic or robotic RP, offer potentially shorter recovery times but have not been shown to improve cancer control or side effects. Erectile function can be preserved in many men with normal preoperative function who undergo bilateral nerve-sparing RP. Surgical series report potency recovery in as much as 75% to 86% of men[8,9]; however, potency rates are 30% to 35% in surveys of tumour registry data.[10,11] Return of sexual function after surgery is usually gradual and might take 12 to 24 months. Penile rehabilitation is becoming the standard of care after surgery.[12] Long-term results of RP will depend on the skill and experience of the surgeon.[13,14]

Limited long-term results of RP in Canadian centres for patients with low- and intermediate-risk disease indicate 5-year PSA relapse-free survival (PRFS) of 65% to 92%[15-18] and 10-year PRFS of 75%.[16] A Canadian RCT of 3 versus 8 months of neoadjuvant hormones before prostatectomy was reported in abstract form only: 549 men were stratified by TNM stage, GS, and prebiopsy PSA level. Prostatectomy was completed in 502 men. After 7 years, overall, PSA relapse was 31.5% and not significantly different in the 2 treatment groups.[19]

Prostate brachytherapy. Prostate brachytherapy has acquired worldwide acceptance in the past 5 to 10 years. The term *brachytherapy* refers to the placement of radioactive sources inside or adjacent to a cancerous tumour. There are 2 forms of PB: low-dose-rate (LDR) brachytherapy where radioactive seeds are permanently implanted into the prostate (**Figure 1**) and high-dose-rate (HDR) brachytherapy where treatment is administered over about 10 minutes through temporary catheters that

Figure 1. Prostate brachytherapy seed implant as seen on fluoroscopy after the procedure



contain the radioactive sources. Low-dose-rate brachytherapy is most commonly used as monotherapy for patients with low- or intermediate-risk prostate cancer, or in combination with EBRT for patients with high-risk prostate cancer. High-dose-rate brachytherapy is usually used in combination with EBRT for intermediate- or high-risk disease. Both methods are emerging as the most effective radiation treatments of prostate cancer.[5] Prostate brachytherapy is available in several centres in Canada (British Columbia, Alberta, Manitoba, Ontario, Quebec, and New Brunswick).

Eligibility for LDR brachytherapy differs among provinces. In all Canadian brachytherapy centres, patients with Canadian consensus criteria (**Table 1**)[20-22] low-risk disease (clinical stage ≤ T2a, PSA level ≤ 10.0 ng/mL, or GS ≤ 6) are eligible for brachytherapy. In British Columbia, Manitoba, Quebec, and Alberta, intermediate-risk patients (clinical stage ≤ T2c, PSA level 10 to 20 ng/mL, or GS ≤ 7) are also eligible for PB. In Ontario, Quebec, and New Brunswick, HDR brachytherapy is used in conjunction with EBRT for high-risk patients. In British Columbia, where the HDR program has just begun, LDR brachytherapy is used in conjunction with EBRT for high-risk patients.

Low-dose-rate PB is a day-surgery procedure that takes about 1 hour. It is performed under general or spinal anesthesia (occasionally local). Patients are discharged home 2 to 3 hours after the procedure and

Table 1. Canadian consensus definition of prostate cancer risk stratification

RISK	DEFINITION
Low	≤ T2a* and iPSA level ≤ 10 ng/mL and GS ≤ 6
Intermediate	≤ T2c* and iPSA level 10-20 ng/mL or GS ≤ 7
High	≥ T3a* or iPSA level ≥ 20 ng/mL or GS 8-10

GS—Gleason score, iPSA—initial prostate-specific antigen, PSA—prostate-specific antigen.
*T1—tumour present, but not detectable clinically or with imaging (T1a—tumour was incidentally found in less than 5% of prostate tissue resected, T1b—tumour was incidentally found in greater than 5% of prostate tissue resected, T1c—tumour was found in a needle biopsy performed owing to an elevated serum PSA level); T2—the tumour can be palpated on examination, but has not spread outside the prostate (T2a—the tumour is in half or less than half of 1 of the prostate gland's 2 lobes, T2b—the tumour is in more than half of 1 lobe, but not both, T2c—the tumour is in both lobes); T3—the tumour has spread through the prostatic capsule (T3a—the tumour has spread through the capsule on 1 or both sides, T3b—the tumour has invaded 1 or both seminal vesicles); T4—the tumour has invaded other nearby structures.
Data from Lukka et al,[20] Greene et al,[21] and the Union for International Cancer Control.[22]

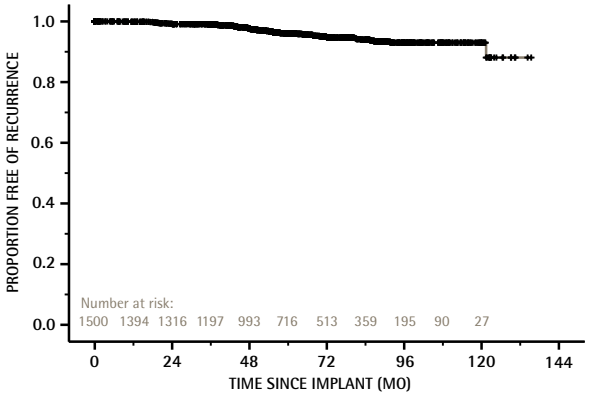
resume normal activities with minimal recovery time (1 or 2 days). Between 70 and 150 radioactive seeds are implanted into the prostate through the perineum, using 20 to 30 needles, each carrying 2 to 7 seeds.

To our knowledge, more than 12 000 patients have been implanted so far in all Canadian centres. As is the case for surgery, long-term results depend on quality-assurance standards. A 5-year PRFS rate of 95.6% has been published for the first consecutive 1006 low- and intermediate-risk patients treated in British Columbia (**Figure 2**, updated 10-year results).[23] In Ontario the reported actuarial 7-year PRFS rate was 95.2% for 776 men treated at Princess Margaret Hospital in Toronto for low-risk (85%) or intermediate-risk (5%) prostate cancer with a median follow-up of 54 months (**Figure 3**).[24] Data from Quebec showed a 5-year PRFS rate of 90.5% for both low- and intermediate-risk groups in 1723 patients from Hôtel-Dieu de Québec of the Centre hospitalier universitaire de Québec.[25,26]

Recovery time after the procedure is short; patients are able to resume usual daily activity within days. Most men experience moderate irritative and obstructive urinary symptoms lasting several months; more than 90% have minimal or no urinary symptoms in the long term.[27-29] Approximately 5% to 10% of patients will experience urinary retention and require Foley catheters; the urinary retention usually resolves within a few days. Mild self-limiting rectal irritation affects 20% to 30% of patients. Rectal bleeding occurs in 2% to 7% of patients.[30] Serious rectal injury requiring major surgical intervention such as colostomy is very rare (fewer than 1 of every 500 to 1000 patients). Erectile dysfunction rates after brachytherapy are favourable.[10,31,32] As with surgery, younger

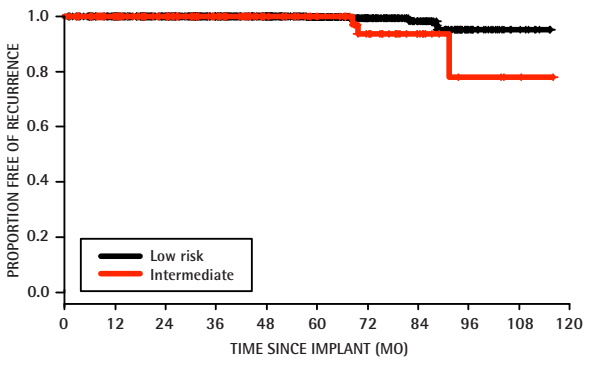
patients and those with better pretreatment function are likely to have better outcomes.[33,34] Oral cyclic guanosine monophosphate–specific phosphodiesterase inhibitors (sildenafil, vardenafil, and tadalafil) are helpful. A recent study from British Columbia of more than 1400 patients showed preserved erectile function rates 8 years after brachytherapy of 60% to 80% (in those aged younger than 60 years), 55% to 60% (in those aged 60 to 69 years), and 20% to 30% (in those older than 70 years).[34] The Toronto experience in 1111 men showed that 82.8% of men retained satisfactory erectile function beyond 5 years.[24,29,33] A recent *JAMA* publication reported erectile function outcomes after radical prostate cancer treatments in 1913 patients treated in 9 US university-affiliated hospitals.[11] Reported rates of erectile function at 2 years after prostatectomy, brachytherapy, and EBRT were overall 35%, 58%, and 37%, respectively. Pretreatment sexual health-related QOL score, age, race or ethnicity, body mass index, and treatment were all independent predictors of functional erections 2 years after treatment. Overall, multivariable logistic regression models predicting erectile function estimated 2-year function probabilities from as low as 10% or less, to as high as 70% or greater depending on the individual's pretreatment patient characteristics and the treatment received.[11]

Figure 2. British Columbia Cancer Agency provincial brachytherapy program results: *Kaplan-Meier plot of PRFS as a function of time since implant for all men treated between July 1998 and July 2006 (N=1500); the Phoenix (nadir + 2 ng/mL) threshold was used to define biochemical recurrence; the 5-year Kaplan-Meier PRFS = 96.0% (SD 1.2%), the 7-year Kaplan-Meier PRFS = 93.9% (SD 1.8%), and the 10-year Kaplan-Meier PRFS = 93.0% (SD 2.0%).*



PRFS—prostate-specific antigen relapse-free survival.
Data from Morris et al.[23]

Figure 3. Results from Princess Margaret Hospital in Toronto, Ont: *Kaplan-Meier plot of PRFS as a function of time since implant for 776 men with iodine-125 PB for low-risk (85%) or intermediate-risk (5%) prostate cancer with more than 3 years' follow-up.*



PB—prostate brachytherapy, PRFS—PSA relapse-free survival, PSA—prostate-specific antigen.
Data from Crook et al.[24]

External beam radiation therapy. External beam radiation therapy is a well established treatment for localized prostate cancer. In combination with androgen deprivation therapy (ADT), it is a standard approach for intermediate- and high-risk prostate cancer. Multiple RCTs (level I evidence) demonstrate a clinical benefit, including improvement in disease-free and overall survival, with the addition of ADT.[35-37] Higher radiation doses, which can be delivered safely with technologic advances, are critical to achieving optimal tumour control.[38] External beam radiation therapy is suitable for patients in all risk groups and, unlike PB, there are very few contraindications for EBRT, which can be offered to men for whom general or spinal anesthetic is not suitable, or those with various serious comorbidities, a large prostate size (greater than 70 g), or high-risk disease. In general, EBRT alone, or in combination with ADT in patients with low- and intermediate-risk prostate cancer, provides PRFS of 70% to 90% with 5-year follow-up and 50% to 70% with 10-year follow-up.[5] While there are very few studies comparing the side effects of EBRT and PB, EBRT is generally associated with substantially fewer urinary side effects, but greater rectal toxicity.[39] External beam radiation therapy is commonly delivered over a period of 7 to 8 weeks of daily treatments. Combination of EBRT and brachytherapy is considered to be more effective than EBRT alone in some intermediate-risk patients and in high-risk patients.[5]

A matched-pair analysis by Pickles et al from the BC Cancer Agency (level II evidence), showed that men treated with PB had superior PRFS outcomes when compared with conventional-dose EBRT. Seven-year PRFS rates were 95% for PB and 75% for EBRT.[39] Unlike brachytherapy, patients treated with EBRT continue to experience more PSA failures with longer follow-up.[5]

Active surveillance. Active surveillance is a novel approach in which patients with minimal disease are closely followed, with treatment initiated only if the disease progresses. About 20% to 40% of prostate cancer detected by screening might not require any treatment, remaining asymptomatic until patients die of other causes.[40] However, men under AS require careful follow-up so that curative treatment can be offered in a timely fashion should tumour progression occur. Patients suitable for AS include those with clinically localized prostate cancer, PSA levels less than 10 ng/mL, 2 or fewer positive biopsy cores, and GS of 6 or less. Rebiopsy within 6 to 12 months of the initial biopsy is mandatory in order to exclude more extensive or aggressive disease that might have been missed. Repeated periodic biopsy is also a part of regular follow-up.

The recently published Toronto experience with AS showed that out of 453 patients under AS, only 30% required and received treatment within 6.8 years of follow-up[41]; however, their outcome was remarkably unsuccessful, with a PRFS rate of less than 50% at 3 years. The risk of losing the opportunity for cure with this approach has not been fully quantified. Healthy young men can be more assured of a successful outcome if they are treated sooner rather than later. The ongoing anxiety of harbouring untreated cancer might be unacceptable to some patients. Active surveillance will become more attractive when accurate prediction of the biologic behaviour of individual cancers becomes possible using modern tissue and serum biomarkers. International studies are actively accruing patients using this approach and results will be available in several years.

Watchful waiting is distinct from AS in that it is reserved for patients who are elderly or who have considerable comorbidities. Other treatment options such as high-intensity focused ultrasound and cryotherapy are not considered standard approaches for early stage prostate cancer.[42]

Comparison between RP and PB (level I evidence). One small Italian trial randomized 200 patients to receive RP or PB.[4] With a median follow up of 5 years, PRFS was the same in both groups (91%). At 6 months and 1 year follow-up, brachytherapy patients had more irritative urinary symptoms but better sexual function. After 5 years, RP patients had a higher incidence of urinary stricture (6.5% vs 2%) and urinary incontinence (18% vs 0%). Sexual function recovery was greater with brachytherapy in the first year after treatment (60% vs 40%); however, it was virtually identical (65% vs 68%) after 5 years between the 2 arms. There was no difference in overall QOL measures between the 2 groups of patients.

Quality of life. The largest QOL study prospectively measured outcomes reported at multiple centres before and after RP, PB, and EBRT. The study included 1201 patients and 625 spouses.[43] Each prostate cancer treatment was associated with a distinct pattern of change in QOL in the urinary, sexual, bowel, and hormonal domains. These changes influenced satisfaction with treatment outcomes among patients and their partners. Brachytherapy resulted in fewer effects on bowel and sexual function than surgery did; however, urinary irritation was more common than with surgery. In general, PB is associated with worse functional and symptom scores in the first year, but better scores and functional outcomes in subsequent years.[44] Prospective QOL measures in 190 patients with a minimum 5 years of follow-up, who had undergone either RP or brachytherapy (patients' choice),[29] showed better urinary function, sexual function, higher overall QOL, and overall satisfaction with brachytherapy versus RP.

Role of family physicians. No one treatment of localized prostate cancer has proven to be clearly superior. For many patients, making the treatment decision can be challenging. Men are often required to process a large amount of previously unfamiliar information and assess the risks and benefits of various treatments while limiting the possibility of regretting the decision at a later date.[45] Information given by urologists and radiation oncologists can be sometimes contradictory, confusing, and overwhelming. More so, such specialists are likely to recommend the treatment that they commonly provide. Patients are known to often rely on spouses, family members, friends, anecdotes, media, and the Internet to help make decisions.[46]

Previous studies have indicated that patients have poor knowledge and unrealistic expectations of treatment, and physician judgments concerning patient preferences are often inaccurate.[46] A Queen's University study of a cognitive-based decision aid for patients with early stage prostate cancer demonstrated wide variation in treatment attributes and issues important to patients during the decision-making process. The study also describes a high likelihood that the importance of various attributes and concerns is likely to change during the decision-making process.[45] Many studies, including a recent RCT,[47] have showed that the use of decision aids in early stage prostate cancer can increase overall knowledge, reduce patients' anxiety, and increase their involvement in the decision-making process. As decision aids are not routinely used in clinical practice, various models for their dissemination and knowledge translation are being developed.[46]

Family physicians can provide further support to patients and their partners, when appropriate. They might further explore various treatment attributes and patient preferences regarding different treatment options, and at the same time, limit the cognitive burden. Focused discussion on the most important issues for each individual patient is likely to increase

patient and partner involvement in the decision-making process. The Queen's University Decision Aid in Early Stage Prostate Cancer computer program download might be useful.[48]

Conclusion

Decisions regarding the appropriate choice of treatment in men with localized prostate cancer require input from urology and radiation oncology. Discussion of the various options can be complex, and reaching a decision on how to proceed is sometimes difficult. Family physicians are often helpful in providing further information, and helping guide patients through the decision-making process.

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Contributors

All authors contributed to the literature review and analysis, and to preparing the manuscript for submission.

Competing interests

None declared

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