Selecting the Optimal Radiation Modality in Prostate Cancer

Luca F. Valle, MD[1,2*]; Amar U. Kishan, MD[1,4*]; Antonio Franco, BS[3]; Ting Martin Ma, MD, PhD[5]; John Nikitas, MD[1]; Matthew Farrell, MD[1]; Albert J. Chang, MD, PhD[1]; Nicholas G. Nickols, MD, PhD[1,2,4]; and Michael L. Steinberg, MD[1]

[1]University of California Los Angeles, Department of Radiation Oncology, Los Angeles, California

[2]Greater Los Angeles Veterans Affairs Healthcare System, Department of Radiation Oncology, Los Angeles, California

[3]California University of Science and Medicine, Colton, California

[4]University of California Los Angeles, Department of Urology, Los Angeles, California

[5]University of Washington, Department of Radiation Oncology, Seattle, Washington

**Drs Valle and Kishan contributed equally to the manuscript.*

Corresponding author:
Luca F. Valle, MD
Department of Radiation Oncology
200 UCLA Medical Plaza, Suite B265
Los Angeles, CA 90095-6951
Email: lfvalle@mednet.ucla.edu
Tel: (310) 825-9775

Abstract: There are numerous radiation modalities for the definitive treatment of localized prostate cancer. Classic clinical trials have established the basic tenets of treatment approaches, and emerging data have generated new potential avenues of treatment that optimize the therapeutic ratio by increasing prostate cancer tumor control while minimizing treatment-related toxicity. In the definitive setting, the selection of the optimal radiation therapy approach depends largely on the appropriate up-front risk stratification of men with prostate cancer, with greater intensification of treatment and greater integration of multimodality therapies for men with higher-risk disease. Hormonal therapy should be selectively deployed based on prognostic information derived from the National Comprehensive Cancer Network risk group and biologic tumor aggressiveness informed by genomic classifiers. Moreover, treatment intensification and target volume delineation are increasingly informed by molecular imaging and multiparametric magnetic resonance imaging. Herein, we perform a critical appraisal of the literature focusing on the optimal selection of radiation therapy modality for localized prostate cancer. Collaboration among medical oncologists, surgeons, and radiation oncologists will be critical for coordinating evidence-based radiation therapies when clearly indicated and for supporting shared decision-making when the evidence is incomplete.

Keywords
Genomics, hormone therapy, localized prostate cancer, molecular imaging, radiotherapy

Introduction

Prostate cancer (PCa) is the most common noncutaneous solid

malignancy in men and the second leading cause of cancer death for men[1] in the United States. Most men harbor only localized disease at the time of diagnosis, for which definitive treatment is highly effective.[2] Evidence-based therapies for localized PCa include both systemic hormonal therapies that suppress androgen activity and local therapies that directly address disease in the prostate, including radical prostatectomy (RP) and definitive radiation therapy (RT).[3]

Treatments for localized PCa are broadly grouped into those deployed in the definitive setting vs the postoperative setting following RP. In the definitive treatment setting, these treatments include RT and systemic therapy. RT includes external beam RT (EBRT) and brachytherapy (BT), whereas systemic therapy includes first- and second-generation hormonal therapies. These are all used in various evidence-based combinations and sequencing. In contrast, postoperative treatment paradigms tend to focus on the integration of EBRT with hormonal therapy.

Thanks to improved prognostic stratification in both the definitive and postoperative settings, we are better able to identify patients who are most likely to benefit from intensification of treatment because their PCa harbors aggressive features. This article provides an overview of the latest data supporting the optimal integration of radiation modalities and hormonal therapies for the treatment of patients with localized PCa. It also highlights how recent publications are seeking to further refine risk stratification approaches to improve the appropriate integration of multimodality therapies for localized PCa.

Very–Low-Risk and Low-Risk Prostate Cancer

Men at the lowest end of the PCa risk spectrum have disease that is characterized by low prostate-specific antigen (PSA) values, low PSA density, a low burden of PCa in sampled biopsy cores, an International Society of Urological Pathology (ISUP) grade group of 1, and a low T category. The ProtecT trial[4] enrolled men predominately in these low-risk groups and demonstrated survival equivalence among active surveillance, definitive therapy with RP, and definitive therapy with RT, although approximately 50% of men who initially chose active surveillance ultimately received treatment, and the rate of metastatic disease was higher in the active surveillance arm.[2]

In terms of radiation modality for low-risk disease, EBRT and BT are both evidence-based options that boast similarly high oncologic endpoints. For men desiring a more surgical radiotherapeutic intervention for the definitive management of their PCa, BT leverages implanted radioactive isotopes to precisely deliver radiation to the prostate, with a steep falloff in radiation that limits the dose to surrounding organs at risk. These isotopes can be inserted through the permanent implantation of low-dose-rate (LDR) seeds or through the surgical implantation of temporary catheters that allow high-dose-rate (HDR) sources to deposit radiation. A recent study comparing patient-reported quality-of-life (QOL) outcomes among EBRT, LDR BT, and HDR BT demonstrated that urinary symptom scores in both the short- and long-term were worse with LDR BT.[5] Thus, the HDR approach may be the BT modality of choice for men opting for surgical radiation management with BT, given its more favorable toxicity profiles.

Regarding EBRT, all men in historical PCa trials of EBRT received conventionally fractionated RT, in which small doses of radiation from 1.8 to 2.0 Gy per fraction are delivered daily over 8 to 9 weeks. Advancements in our understanding of PCa biology have elucidated the low alpha/beta ratio of PCa, which suggests improved radiobiological responses to ionizing radiation in treatments delivered with larger radiation doses per fraction. A number of studies, including the CHHiP, PROFIT, and RTOG 0415 studies, have shown that moderately hypofractionated RT using 60 Gy in 20 fractions[6,7] or 70 Gy in 28 fractions[8] is noninferior to dose-escalated conventionally fractionated regimens, even in the absence of hormonal therapy.

Pushing the envelope further, ultrahypofractionated RT regimens (ie, stereotactic body RT [SBRT]) limit the delivery of RT to just 5 concentrated sessions rather than the historical 40 to 45 sessions. These regimens have recently become more widespread, ushered in by randomized[9] and consortium-based[10] data that demonstrate the noninferiority of SBRT compared with more traditional regimens. The abbreviated nature of SBRT has been shown to be a more convenient and patient-centered radiotherapeutic treatment option that is cost-effective.[11] This approach leads to value-driven savings for the healthcare system[12] in the current fee-for-service reimbursement environment of the United States.

Given the high radiation doses delivered per treatment, SBRT requires a highly sophisticated degree of targeting accuracy and precision. Although it is traditionally delivered only under computed tomography (CT) guidance, advanced imaged-guided techniques, such as magnetic resonance imaging (MRI) guidance, have garnered much interest in recent years. MRI-guided RT (MRgRT) offers many advantages, such as superior soft tissue resolution and better visualization/delineation of targets and surrounding critical organs at risk, as well as real-time tracking/gating of the target during delivery.[13] These advantages enable the use of reduced planning margins and eliminate the need for fiducial marker/electromagnetic beacon placement, which requires an invasive procedure. Reduced planning margins should, in theory,

lead to reduced toxicity. A recent randomized trial called MIRAGE (NCT04384770) demonstrated a significant reduction of both physician-scored and patient-reported acute gastrointestinal (GI) and genitourinary (GU) toxicities with MRgRT compared with CT-guided SBRT.[14] It remains to be determined whether this toxicity advantage will persist in the long term. Although less rigorously explored, MRgRT can also facilitate online adaptive RT, in which daily variations in anatomy are accounted for by same-day recontouring and replanning radiation treatments before each fraction. From a financial standpoint, it has been postulated that MRgRT (specifically MRI-guided SBRT) can be cost-effective for PCa treatment based on the reduction in toxicity alone.[15]

A complementary strategy to reduce toxicity from both conventional and hypofractionated approaches involves the insertion of a rectal spacer. Rectal spacers consist of an absorbable polyethylene glycol hydrogel that is injected into the perirectal space to temporarily increase the distance between the anterior rectal wall and the prostate. In appropriately selected patients without posterior extension of their tumor, there is increasing evidence that the use of a rectal spacer may diminish radiation toxicity, improve patient-reported outcomes, and reduce costs, with minimal risk when deployed in the EBRT[16] and BT[17] settings. In a randomized controlled trial, Mariados and colleagues[16] demonstrated reduced rectal irradiation, reduced rectal toxicity, and improved bowel-related QOL in men with T1 to T2 disease who received a rectal spacer, with a high success rate for hydrogel placement. A recent systematic review reached similar conclusions, showing that use of a rectal spacer decreased the rectal dose across the majority of studies, regardless of RT type, and that the dosimetric advantages associated with rectal spacer placement also improved late GU and GI toxicities.[18] However, in the setting of already-low rectal toxicity from the aforementioned rapidly advancing radiation delivery technology (ie, MRgRT), the absolute gain from rectal spacers is likely to be small.[19] Thus, the merits of this additional procedure should be balanced against the known potential risks of spacer-related complications (including rectal wall infiltration and abscess) when counseling patients about the use of rectal spacers.

With regard to late GU toxicity rates and long-term QOL measures, there are no significant differences between SBRT and conventionally fractionated RT.[20] However, there may be germline genomic features inherent to each patient that drive whether they are more or less susceptible to late toxicities caused by ultrahypofractionated RT that we can use to personalize treatment recommendations. Kishan and colleagues developed a biomarker, based on 32 single-nucleotide polymorphisms that disrupt microRNA targets (mirSNPs), that showed an ability to predict late grade 2 or higher GU toxicity from prostate SBRT.[21] In theory, this biomarker could be used to counsel patients on whether an SBRT course would be appropriate for them or not. The fully accrued GARUDA trial (NCT04624256) is designed to validate this biomarker. More broadly, as more radiogenomic signatures are defined and validated, we may be able to better tailor RT fractionation to patient-specific genomic profiles.

Intermediate-Risk Prostate Cancer

For men with intermediate-risk PCa, who harbor more aggressive clinical features than the low-risk subset of patients, the same radiotherapeutic principles apply in that conventional fractionation, moderate hypofractionation, and ultrahypofractionation remain oncologically equivalent treatment options. However, it has been recognized that significant biological heterogeneity exists within intermediate-risk patients, such that some intermediate-risk patients may benefit from a multimodality addition of hormonal therapies to RT, whereas others might not. Importantly, hormonal therapies should be judiciously employed, given the significant effects they can have on QOL.[22] Thus, the appropriate duration of androgen deprivation therapy (ADT) and the subgroups of patients in which ADT is most beneficial remain controversial.

Intermediate-risk disease can be subclassified into men with unfavorable intermediate-risk disease and men with favorable intermediate-risk disease. This distinction is made primarily on the basis of the primary pattern of Gleason grading, the presence of multiple intermediate-risk factors, and evidence of 50% or greater involvement of the number of sampled cores. Emerging data suggest that hormonal therapies may be beneficial for patients with unfavorable intermediate-risk disease, whereas men with favorable intermediate-risk disease might reasonably be spared hormonal therapies. For example, a subset analysis of RTOG 9408, which originally examined the benefit of 4 months of ADT with RT, reported that ADT for favorable intermediate-risk disease did not reduce distant metastasis (DM), PCa-specific mortality (PCSM), or all-cause mortality. On the other hand, in unfavorable intermediate-risk disease, ADT did improve DM and PCSM at 15-year follow-up.[23]

If hormonal therapy is chosen for intermediate-risk disease, multiple studies have demonstrated that the ideal duration of ADT that balances oncologic outcomes and QOL is 4 to 6 months. EORTC 22991, a randomized trial of 245 patients, found that 74- or 78-Gy RT in conjunction with 6 months of ADT improved event-free

survival[24] vs RT alone. The PCS III study also found that 6 months of ADT improved freedom from biochemical failure,[25] whereas RTOG 0815 showed decreased rates of the more clinically meaningful endpoint of DM.[26] Several additional studies also found that extending the duration of ADT did not improve outcomes,[27,28] particularly when dose-escalated RT is employed.[29]

The timing of short-term ADT (STADT) also remains an important question for men receiving hormonal therapy with radiation. SANDSTORM was a pooled analysis of 12 randomized trials that demonstrated the superiority of concurrent/adjuvant ADT compared with neoadjuvant/concurrent ADT, specifically with regard to the substantive oncologic outcomes of metastasis-free survival (MFS; 10-year benefit of 8.0%, hazard ratio [HR], 0.65; 95% CI, 0.54-0.79), DM (HR, 0.52; 95% CI, 0.33-0.82), PCa-specific mortality (HR, 0.30; 95% CI, 0.16-0.54), and overall survival (OS; HR, 0.69; 95% CI, 0.57-0.83).[30] However, it is worth noting that these benefits were reserved for men receiving prostate-only RT, as no benefit was observed for men who also received whole-pelvis RT. Given what is understood about the protracted nature of RT-induced PCa cell death via mitotic catastrophe, an attractive biological explanation for the advantages of concurrent/adjuvant ADT may lie in prolonging the interruption of androgen receptor–mediated DNA repair during a period when repair of RT-induced DNA damage remains relevant.

Importantly, although the addition of hormonal therapies to definitive RT is chiefly thought to benefit men with unfavorable intermediate-risk disease, the MARCAP meta-analysis[31] pooled data from 10,853 patients at 12 centers and found that the addition of ADT to RT improved MFS (HR, 0.83; 95% CI, 0.77-0.89), as did prolongation of adjuvant ADT (HR, 0.84; 95% CI, 0.78-0.91), irrespective of RT dose, patient age, or National Comprehensive Cancer Network (NCCN) risk group. This suggests that even in the modern era of RT dose intensification, there still appears to be a relative benefit to adding ADT of any duration to RT for most men with localized PCa. However, the absolute benefit of ADT does diverge for intermediate-risk vs high-risk patients, with a calculated number needed to treat in order to avert 1 DM event at 10 years of 8.4 (95% CI, 6.0-13.8) for high-risk patients vs 18.0 (95% CI, 12.7-30.7) for intermediate-risk patients.

In addition to considerations regarding the use of hormone therapies for intermediate-risk PCa, increasing attention has turned to the integration of molecular positron emission tomography (PET) scans that incorporate PCa-specific radiotracers into the staging workup prior to the pursuit of definitive RT. This is particularly true for patients with unfavorable intermediate-risk and high-risk disease, for whom the superiority of PSMA PET compared with conventional imaging (CT and bone scan) was demonstrated in the ProPSMA study.[32] In addition to enhanced sensitivity (85% vs 38%) and specificity (98% vs 91%) with PSMA PET vs conventional imaging, changes in management were significantly more likely in men who underwent PSMA PET–based staging than in those who underwent conventional staging (28% vs 15%; *P*=.008). These changes could include intensification of definitive RT through the addition of pelvic lymph node volumes[33] or an increase in the duration or potency of concomitant hormonal therapies, particularly when disease outside of the prostate was identified with molecular PET. Whereas staging with PSMA PET is generally indicated for men with unfavorable intermediate-risk and high-risk disease, nomograms have been developed that predict the risk of upstaging via the detection of occult nodal and DM disease on PSMA PET.[34]

Ongoing clinical trials seek to harness precision medicine platforms to identify intermediate-risk patients who may benefit from de-escalation to RT alone vs those who benefit from treatment escalation with intensified ADT. For example, NRG-GU010/GUIDANCE (NCT05050084) seeks to risk stratify unfavorable intermediate-risk patients using the Decipher genomic test. Patients with a Decipher score of less than 0.4 are randomized to RT alone or RT plus 6 months of ADT with a primary endpoint of DM. A separate randomization for men with a Decipher score of 0.4 or higher will determine if patients should undergo an intensified regimen of RT plus 6 months of ADT along with a second-generation antiandrogen, darolutamide (Nubeqa, Bayer), or standard-of-care RT with 6 months of ADT alone, using MFS as a primary endpoint. An artificial intelligence–derived digital pathology–based biomarker has also garnered recent excitement following validation[35] of its ability to predict the benefit of ADT in a cohort of intermediate-risk patients enrolled in RTOG 9408. However, until such biomarkers can be prospectively validated, candidates for omission of ADT without significant compromise in oncologic outcomes are likely best identified by NCCN risk group classification, with omission preferred for favorable intermediate-risk patients and 4 to 6 months of concurrent/adjuvant ADT preferred for most unfavorable intermediate-risk patients.

High-Risk and Very–High-Risk Prostate Cancer

High-risk PCa is an aggressive biologic entity that carries a high risk of disease progression following definitive treatment. Thus, there has been substantial interest in

evaluating treatment intensification strategies and the interplay among intensification strategies for high-risk disease.

Treatment Intensification via Extended Duration of Hormonal Therapies

The value of long-term ADT (LTADT) of at least 18 months in duration has consistently improved OS in multiple large, randomized trials, including EORTC 22863,[36] RTOG 8531,[37] and DFCI 95-096.[38] Conversely, RTOG 8610 examined the effect of 4 months of ADT and found improved PCSM, DM, and biochemical recurrence compared with RT alone, although the improvements in OS did not reach statistical significance. These data suggest that although ADT is beneficial, 4 months may not be sufficient to improve OS in men with high-risk disease.

Adding further granularity regarding the ideal duration of LTADT, the PCS IV trial compared 18 vs 36 months of ADT and showed equivocal OS (86% vs 91%, respectively; *P*=.07), with the QOL analysis favoring the 18-month arm.[39] However, it is worth noting that adherence was very poor in the 36-month arm, which may have contributed to the equivocal results. Moreover, this trial was designed as a superiority trial, and the implications of a negative superiority trial are distinct from those of a noninferiority trial. Taken together, these data suggest that although 18 months of ADT yields superior oncologic outcomes compared with STADT in high-risk patients, longer durations of LTADT (36 months) might be similar in efficacy to shorter durations of LTADT (18 months) in the modern dose-escalated RT treatment era. However, other evidence suggests that 18 months may still be insufficient.[40] Recommendations for the duration of hormonal therapy duration must rely on shared decision-making between providers and patients that accounts for patient values and preferences.

Treatment Intensification via the Addition of Second-Generation Hormonal Therapies

There has also been interest in incorporating advanced antiandrogen therapy into the up-front treatment of high-risk PCa in conjunction with EBRT/ADT. In a recent meta-analysis of two phase 3 trials from the STAMPEDE platform protocol, 1974 high-risk patients (defined as having node-positive disease or the presence of ≥2 of the following features: T3/T4 disease, Gleason score 8-10, or PSA ≥40 ng/mL) undergoing local therapy predominately with RT were randomized to ADT alone; ADT with abiraterone and prednisone; or ADT with abiraterone, prednisone, and enzalutamide (Xtandi, Astellas).[41] At 6 years, the combination arms demonstrated improved MFS (HR, 0.53; 95% CI, 0.44-0.64; *P*=.0001; 82% vs 69%), OS, PCSM, biochemical recurrence rates, and PFS when compared with ADT alone. However, no benefit in MFS was seen with the addition of enzalutamide (HR, 1.02; 95% CI, 0.70-1.50; *P*=.91), although side effects were increased. These data suggest that the addition of abiraterone and prednisone to ADT and definitive RT should be considered for selected men with high-risk, node-negative disease who meet the STAMPEDE criteria, or men with node-positive disease at diagnosis.

Ongoing studies are employing the Decipher genomic test as a stratification method to inform management of patients with high-risk, localized PCa. The 2-pronged NRG-GU009/PREDICT-RT study (NCT04513717) seeks to deescalate therapy in patients with a Decipher score of less than 0.85 by randomizing them to 12 months instead of 24 months of ADT in conjunction with RT. In contrast, the role of treatment intensification will be evaluated for patients with a Decipher score of greater than 0.85, with patients randomized to the standard 24 months of ADT vs 24 months of ADT plus apalutamide.

Treatment Intensification via the Addition of Whole-Pelvis RT

Elective inclusion of pelvic lymph nodes in the radiation field for patients with intermediate- and high-risk PCa is controversial. The rationale for whole-pelvis RT is that the draining pelvic lymph nodes may harbor micrometastatic disease that is insufficiently controlled with ADT alone. Despite this rationale, 3 randomized clinical trials have failed to demonstrate a conclusive benefit from the addition of whole-pelvis RT to treatment.[42-44] The only prospective randomized trial to demonstrate a benefit from whole-pelvis RT has been the POP-RT trial, which limited enrollment to clinically node-negative men with a greater than 20% predicted risk of lymph node involvement by the Roach formula.[45,46] Eighty percent of patients had a negative PSMA PET prior to enrollment. Additionally, modern RT techniques enabled higher doses of radiation to be delivered to the prostate and pelvic nodes, and long-term ADT was used on all patients. This trial not only showed a 5-year absolute improvement of 13.8% in the primary endpoint of biochemical failure-free survival but also a 5-year absolute improvement of 7.1% in the exploratory endpoint of DM-free survival. Of note, there was a significant increase in cumulative grade 2 or higher late GU toxicity with whole-pelvis RT (20.0% vs 8.9%), whereas grade 2 or higher late GI toxicity was similarly low regardless of whether whole-pelvis RT was delivered. Therefore, the potential gain in outcomes needs to be balanced against an increase in late toxicity. Importantly, patients enrolled in this trial were exceptionally high-risk (78.3% T3-T4 and 49.2% ISUP grade group 4-5), and thus the benefit of whole-pelvis RT in a less-advanced cohort of patients

is debated. Nevertheless, it may be reasonable to consider whole-pelvis RT in men with very–high-risk PCa and a negative PSMA PET scan in parallel to the patient population studied in POP-RT.

Treatment Intensification via Focal Dose Escalation

There has been interest in focal dose escalation for men with high-risk disease, which can be achieved via BT boosting or by simultaneous integrated external beam boosting. As described above, prostate BT enables significant escalation in prostate dose, with a sharp falloff to surrounding organs at risk. In the landmark ASCENDE-RT trial,[47-49] 398 men were randomized to either standard EBRT of 46 Gy to the pelvis followed by a dose-escalated EBRT boost of 78 Gy vs standard EBRT to the pelvis followed by an LDR BT boost. Approximately two-thirds of the men enrolled were high-risk, one-third were intermediate-risk, and all men received 12 months of hormonal therapy. At a median follow-up of 6.5 years, men who received a BT boost were twice as likely to be free of biochemical failure (HR, 2.04; *P*=.004), with 7-year biochemical PFS estimates of 86% vs 75%. Moreover, this benefit was appreciated in both the intermediate-risk and high-risk groups, but no difference in DM or OS was reported. The biochemical PFS benefits came at the expense of an increase in grade 3 GI and GU toxicity, and thus the balance between increased toxicity and biochemical control must be weighed individually by patients considering a BT boost. However, a further benefit of the BT boost is that it may enable a shorter ADT duration of 12 months for high-risk patients, given findings from a retrospective analysis[40] of high-risk patients demonstrating that EBRT/BT may allow for a curtailed duration of ADT without compromising outcomes.

Further benefits of BT boost in men at the highest end of the risk spectrum with Gleason 9 or 10 disease were demonstrated in a retrospective analysis of 1809 patients. Improvements in PCa-specific survival and DM-free survival were documented in men who received EBRT/BT/ADT, surpassing the outcomes with RP or EBRT/ADT in this high-risk population.[50] An open question is whether this local dose escalation is necessarily achieved by BT or whether dose escalation with advanced EBRT approaches, such as SBRT, can provide similar survival and DM-free benefits. Moreover, it is important to note that when comparing patients receiving EBRT/BT with the subgroup of EBRT patients who received optimal-duration ADT (ie, >24 months), the observed PCa-specific survival differences were no longer statistically significant. This suggests that if the ADT duration were to be optimized, the outcomes might be equivalent to those with EBRT.[51]

As an alternative to BT boosting, focal EBRT boosting of the dominant intraprostatic lesion(s) aims to capture some of the favorable dose-escalating properties of BT, and has similarly been shown to improve outcomes with conventional fractionation, including biochemical DFS,[52] at a median follow-up of 72 months. Importantly, these biochemical benefits manifested without increasing radiation-related toxicity in a randomized phase 3 setting, so this too should be considered when selecting a radiation boost modality for high-risk disease. The recently reported DELINEATE trial also demonstrated the safety and efficacy of focal boosting with a moderate hypofractionated treatment approach in 20 fractions.[53] Although a contemporary meta-analysis[54] and an early safety primary endpoint analysis from a prospective phase 2 trial[55] suggest that this practice is safe and effect for SBRT dosing as well, full reporting of prospective randomized studies is eagerly awaited.

Conclusions

Appropriate risk stratification of men with PCa is critical for deploying the optimal treatment approach, which often involves multimodality treatment with hormonal therapies. In addition to classically defined clinical risk features including PSA, ISUP grade group, and T category, genomic predictors and molecular imaging modalities are emerging as critical tools for more precisely allocating treatment intensification with multimodality therapies and treatment deintensification. Collaboration among medical oncologists, surgeons, and radiation oncologists will be critical for coordinating evidence-based radiation therapies when clearly indicated and for supporting shared decision-making when the evidence is incomplete.

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Declarations

This article does not contain any studies with human or animal subjects performed by any of the authors.

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