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Review Article

Irradiation of localized prostate cancer in the elderly: A systematic literature review

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ABSTRACT

Purpose: To analyze the literature that addresses radiation therapy for intermediate and high-risk prostate cancer (PC) in the elderly.
Patients and methods: A PubMed literature search was conducted including articles from 01/01/2000 to 30/06/21, with the following keywords: PC, radiotherapy/brachytherapy and elderly. The analysis mainly focused on the issue of under-treatment in the elderly and the benefit/risk balance of irradiation.
Results: Of the 176 references analyzed, 24 matched the selection criteria. The definition of "elderly patient" varied from 70 to 80 years. The analysis was impacted by the inhomogeneous primary end points used in each cohort. Age was often an obstacle to radical treatment, with a subsequent risk of under-treatment, particularly in patients with a poorer prognosis. However, comparable elderly oncological outcomes were compared to younger patients, both with external beam radiotherapy alone or combined with brachytherapy boost. Late toxicity rates are low and most often comparable to younger populations. However, a urinary over- toxicity was observed in the super-elderly (>80 years) after brachytherapy boost. The use of ADT should be considered in light of comorbidities, and may even be deleterious in some patients.
Conclusion: Due to the increase in life expectancy, the management of PC in the elderly is a challenge for patients, clinicians and health insurance payers. Except for unfit men, elderly patients remain candidates for optimal curative treatment (i.e. regardless of age) after oncogeriatric assessment. More solid data from prospective trials conducted specially in this population will provide better guidance in our daily clinical practice.

Introduction

Prostate cancer (PC) is the second most common cancer in the world and the most common cancer in people over 70. The incidence increases with age and people over 70 represent about 50% of new patients [1]. The estimated PC incidence rate in 2040 is 2.43 million new cases (against 1.41 million today + 42%) and will double in the over 70 s with 1.44 million new cases (709,000today) [2]. Because of the aging and longevity of the population, clinicians have increasingly to implement the most relevant treatment for elderly PC. It is therefore a growing public health issue.

At the beginning of the 90 s, Balducci et al. was already making PC the model for geriatric cancer. He emphasized the ever-present challenge of prolonging survival without compromising the quality of life (QoL) of older patients [3]. Since 2000, there has been a growing interest in the management of seniors, highlighted by the increasing

Abbreviations: ACE-27, Adult Comorbidity Evaluation 27; AD, Alzheimer's disease; ADT, androgen deprivation therapy; ASCO, American Society of Clinical Oncology; bNED, Biological non-evidence of disease; BRFS, biochemical relapse-free survival; BT, brachytherapy; CCI, Charlson comorbidity index; EBRT, External beam radiation therapy; G, grade; GI, Genito-urinary; GI, Gastro-intestinal; HDR, high dose-rate; IGRT, Image Guided Radiation Therapy; IMRT, intensity modulated radiation therapy; LDR, low dose-rate; LE, life expectancy; MA, median age; MFU, median follow-up; NCCN, National Comprehensive Cancer Network; OS, overall survival; PC, prostate cancer; PCSM, prostate cancer specific mortality; PCSS, Prostate cancer specific survival; QoL, quality of life; SBRT, stereotactic body radiation therapy; SEER, Surveillance, Epidemiology, and End Results; SIOG, International Society of Geriatric Oncology; 3DCT, 3D conformal radiotherapy.

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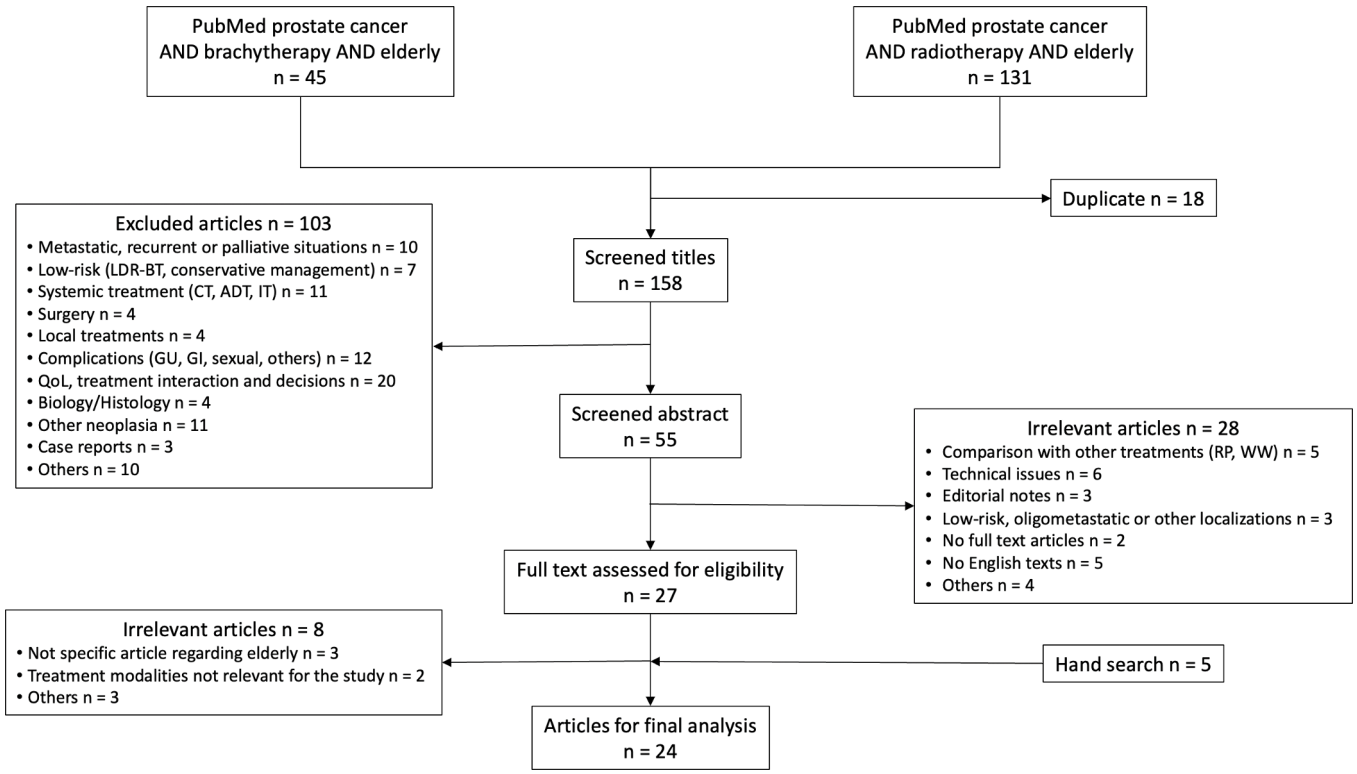

Fig. 1. Flow chart.

number of "elderly" publications noticed in Pubmed [4–5].

In addition to performance status, clinical, biochemical and histo-prognostic factors, elderly patients represent a heterogeneous population with specific features related to age (comorbidity factors, polymedication, cognitive declines…) [6]. Indeed, age-related co-morbidities affect life expectancy (LE) and can be considered a competitive risk of death with a potential deleterious impact on treatment tolerance. It is therefore important to carefully analyze the benefit/risk balance of more aggressive treatment in older adults.

In order to help physicians in elderly patient management, the International Society of Geriatric Oncology (SIOG) and the American Society of Clinical Oncology (ASCO) published recommendations and recent studies. They signal the importance of oncogeriatric assessment for personalized approaches and toxicity treatment management [7–12]. In addition, the elderly have histological criteria that are often pejorative (stage, histological grade) [13]. Indeed, although $>$ 75 year (y) old men represent 25% of the patients, they account for more than half of prostatic specific deaths [14] assuming the risk of potential under-treatment in patients with poor prognostic factors [15–18].

Nevertheless, the management of PC in the elderly remains complex and controversial, due to a lack of solid data (they often remain under-represented in the majority of studies). Prospective trials enrolled mainly patients $<$ 75y and extrapolated results to the elderly, acknowledging that the oncological outcome and toxicity profile could be different, especially in frail patients.

In this review, we analyzed the literature available related to radiation therapy for localized PC in the elderly, with a particular focus on intermediate and high-risk patients.

Material and methods

A literature search was made based on PubMed, from 01/01/2000 to 06/30/2021. In a first step, two searches with MeSH criteria were performed: "Prostatic neoplasms/radiotherapy (Major Topic) AND Aged" and "Prostatic neoplasms/Radiotherapy (Mjr) AND Brachytherapy AND Aged". Each of the searches returned 4424 and 1450 results respectively. We then narrowed the search to the following keywords 1) "Prostate cancer AND Elderly AND Radiotherapy" and 2) "Prostate Cancer AND Elderly AND Brachytherapy" present in the title and/or abstract. The selected articles had to report on localized PC (ideally intermediate and/or high-risk), on treatment with radiotherapy and/or brachytherapy (BT), and focus on elderly patients. Selected references had to be full-length articles written in English.

Exclusion criteria were: non-localized or recurrent PC, active surveillance, focal treatment, systemic therapy, surgery alone, complications alone, biology, other neoplasia, case report and anything non-specific to radiotherapy and/or the elderly.

The studies were analyzed according to PRISMA criteria. After the stepwise selection, the manuscript was organized in order to answer the following most relevant questions:

- Are elderly patients undertreated?
- What is the benefit/risk balance of radiation therapy in the elderly in regard to oncological outcomes (external radiotherapy, BT and androgen deprivation therapy (ADT)), tolerance (toxicity and QoL), and influence of comorbidities?

Results

The two searches carried out, from 01/01/2000 to 06/30/2021, with the above-mentioned key words: 1)"Prostate cancer AND Elderly AND Radiotherapy" and 2)"Prostate Cancer AND Elderly AND Brachytherapy", present in the title and/or abstract, found 131 and 45 results respectively. Among these 176 results, 24 articles were selected for the final analysis. The flowpath of the article selection process is presented in Fig. 1. Among the 24 selected articles, 22 were retrospective studies and 18 were multicenter analyses.

Are older adults undertreated?

Clinicians, still today, rely more on chronological age and therefore LE is often underestimated in seniors. However, selected healthy elderly patients could benefit as much from definitive treatment as younger ones. This is particularly true for intermediate (especially unfavorable intermediate) and high-risk individuals, whose PC specific mortality is higher. Nevertheless, studies suggest that older adults may not receive treatments that can improve survival. Bratt et al. conducted a study matching each case of high-risk prostate cancer with five cancer-free controls of similar age to calculate a 10-y LE stratified by age and comorbidities [19]. The authors reported that only 10% of 75-80y patients without comorbidities (Charlson score 0), with high-risk cancer, whose 10-year LE was 52%, received local treatment (prostatectomy or radiotherapy). These results appear significantly lower than those observed in younger patients with the same LE (<65y with a Charlson score of 3), 52% of whom received radical treatment [19]. Similar results were reported by Yang et al. in a cohort of 411,443 intermediate to high-risk patients [20]. Indeed, the authors confirmed the inverse relationship between age and radical treatment in high-risk patients but also in intermediate-risk patients, with a parallel increase in single-agent hormone therapy. However, the authors noticed that definitive treatment also had a beneficial effect on overall survival (OS) even in the super-aged (>80y), with a gain of 12% (86% vs 98%) at one year [20]. Fortunately, in recent years, we report an increase in local treatment in older adults with a positive impact on specific mortality. As recently described by Aas et al., curative treatment in high-risk patients over 70 has increased almost 6-fold (15 to 51%) in 10 years with a parallel decrease in specific mortality [21]. The absence of curative treatment unequivocally increased specific mortality by a factor of 3 and also overall mortality by a factor of 2 [21]. These studies suggest a benefit in terms of specific and overall survival for elderly patients with few or no comorbidities who are offered optimal treatment. However, these encouraging results in terms of oncological outcome should be tempered by the lack of data on the proportion of treatments carried out (surgery or radiotherapy), their respective modalities and tolerance profile, which is underestimated in these studies.

The question of optimal treatment in the elderly also arises with BT intensification. In a retrospective study of 764 patients > 65y (median age (MA) 73 years) with high-risk disease, without cardiovascular or corrected cardiovascular comorbidities, Hoffman et al. demonstrated a benefit in prostate cancer specific mortality (PCSM) after a combination of BT, external beam radiotherapy (EBRT) and androgen deprivation therapy (ADT) (2.2%) versus BT alone (6.7%), with no significant increase in other causes of mortality, particularly cardiovascular (23.6 vs 20.4%, p = 0.631) [22]. Studies have also compared EBRT alone versus EBRT + BT boost in elderly populations, providing similar results with a benefit in biochemical relapse, specific and overall survival. Stromberg et al, evaluated in 443 high-risk patients > 70y the oncological outcome after EBRT alone vs BT + EBRT [23]. The authors reported a significant benefit with BT boost at 5 years for biological non-evidence of disease (bNED) (47.5% vs. 79.4%, p < 0.001), prostate cancer specific survival (PCSS) (91.4% vs. 94.6%, p = 0.06) and OS (72.9% vs. 87.7%, p < 0.001). Similarly, Kent et al, confirmed that for intermediate and high-risk patients, EBRT + BT boost led to a gain in biochemical control at 5 years (84% vs 82%), increasing at 15 years (68% vs 54%, p = 0.03), slightly better than previously described due to younger patients and better conducted ADT (6and30monthsrespectivelyforintermediate-and-high-risk) [24]. These studies suggest that optimal treatment with BT intensification in high-risk, "fit" elderly patients has to be discussed. However, missing information regarding patient comorbidities and heterogeneous irradiation techniques have to be taken into account.

In this context, elderly patients, especially with high-risk prostate cancer, tend not to be treated with the recommended optimal therapies, thereby potentially impairing oncological outcomes; a benefit in both CSS and OS has moreover been demonstrated, especially in "fit" patients with no or few comorbidities.

Benefit-risk balance of radiotherapy in the elderly

Oncological outcomes (Table 1)

External beam radiation treatment (EBRT). Among the selected studies, in elderly patients treated with EBRT, bNED ranges between 63% and 96%, while OS varies from 77% to 92%. These results may vary depending on treatment period and radiation technique used (box-technique, 3D, or IMRT), median follow-up (MFU), number of patients, their age as well as their characteristics. In 2003, Villa et al., reported the results of 183 patients over 70 (MA 75 years) with localized T1-T3N0M0 PC who underwent EBRT delivering a total dose of 70 Gy to the prostate using either box or 3D, combined with neoadjuvant ADT (60.9%) [21]. At 5 years, the rates of bNED, PCSS and OS were 63.2%, 93.7% and 90.6% respectively [25]. For patients > 80y (23pts), the oncological outcome appeared poorer with a 3-year bNED, PCSS and OS rates of 75.2%, 66.6% and 62.5% respectively. Nguyen et al. analyzed the oncological outcome of a small multicenter cohort of 65 all-risk older patients (>80y), with comorbidities requiring treatment (50%), treated with 3D (27 pts: 45 Gy to the pelvis; and 38 pts: with 69.5 Gy to the prostate) [26]. The authors reported a 5-year bNED rate of 73% and OS of 77%. Geinitz et al. compared the oncological outcome between a cohort of 80 patients > 75y versus a younger group of 221 pts treated with 3D (70 Gy to the prostate without lymph node irradiation) combined with neoadjuvant ADT (5 months) for intermediate and high-risk PC [27]. The authors observed a better bNED in the > 75y patient group (76% vs. 61%, p = 0.042), with no significant difference for OS (92% vs. 90%, p = 0.877). More recently, and in contrast to previous studies, Okonogi et al. compared IMRT at 78 Gy (+ADT of 17 months median duration) in 23 patients > 80y versus 171 younger, intermediate- or high-risk patients. Despite a shorter MFU and patients with a poorer prognosis, the results are similar or even better than those already reported: 3-y bNED of 96% (vs 97.3% <80y) and a 3-y OS of 92% (vs 99.4% <80y) [28].

The consistent results of these studies, most of which are getting old and use 3D, suggest a legitimate benefit in treating elderly patients with radical radiotherapy. This is even truer now, particularly with the advent of new techniques such as IMRT or stereotactic body radiation therapy (SBRT) that allow dose escalation [29].

Brachytherapy (BT). Studies have investigated the benefit of prostate BT (Low -LDR- or high dose-rate -HDR- BT) in the elderly and confirm its efficacy in this population with a bNED at 5 years ranging from 79.4% to 91.3% and an OS ranging from 79% to 97.8%.

In 2009, Stromberg et al. compared 3 treatment regimens in a cohort of 443 intermediate- and high-risk patients > 70y: EBRT (46 Gy) + HDR boost (16.5 Gy in 3 fractions), IMRT (75.6 Gy) or EBRT (66.6 Gy) only on the prostate [23]. With a MFU of 6.5 years, the findings were in accordance with BT and IMRT with a 5-y bNED respectively of 79.4, 73.5 and 47.5% (p < 0.001), a 5-y OS of 87.7%, 88.1%, and 72.9% (p < 0.001) while no significant difference was observed for PCSS (94.6%, 97.2%, and 91.4%) [23]. Yamazaki et al. conducted 2 retrospectives studies including all PC risks, comparing young vs old patients (>75y [25], then > 80y [26]. The authors described different treatment irradiation techniques: EBRT, BT alone (HDR or LDR) and LDR-BT + EBRT. No significant difference for bNED was observed between the 2 age groups (89.8% vs 90.6% at 7 years (>75y) and 91.3% vs 85.9% at 5 years (>80y)). In the first study (>75y), bNED was significantly higher after BT compared to IMRT, particularly for high-risk patients (91.2% vs 73.6%; p = 0.0195) [30]. In the second study (>80y), the authors reported similar 5-y OS in > 80y (MA 81y) and younger patients (MA 71y): 97.8% vs 96.4% (p = 0.4202) [31].

Contrary to previous outcomes, Valdivieso et al. explored the 10-year

oncological outcome in patients > 80y, after BT with or without EBRT and/or ADT. In this SEER database cohort of 2701 pts, 77% presented an intermediate- or high-risk PC (most patients with a Charlson comorbidity index (CCI) score of 0). Among them, only 47% had all 3 treatment modalities. Because of a 10-y OS of 47%, the authors estimated that one out of two patients might be overtreated [32].

The elderly showed similar biochemical controls to younger patients, but discordant results remain, particularly regarding the OS benefit in the super-elderly (octogenarians and nonagenarians), where comorbidity data are lacking; more attention should be paid to their physiological age and wishes.

Androgen deprivation therapy (ADT). ADT is a potential issue in the elderly because of the multiple, mainly bone health, metabolic, cardiovascular and cognitive side effects [33,34]. The use of EBRT + ADT is a legitimate concern in this population, in order to optimize the oncological benefit without inducing or aggravating pre-existing comorbidities. Bekelman et al. explored, in a large SEER Medicare database cohort of 31,451 pts (intermediate and high-risk), the efficacy of ADT + RT vs ADT alone using a propensity score analysis. The cohort itself was subdivided into 3 groups: randomized clinical trial, elderly (14,340 pts > 75y) and screen-detected group. The combination of ADT + RT was associated with reduced cause-specific mortality (9.8% vs 5%) and all-cause mortality (33.2% vs 54.5%) at 7 years in the 3 treatment groups, including the elderly group [35].

Nguyen et al. reported the outcomes of 206 pts (MA 72.4y), with intermediate to high-risk PC treated with EBRT (70 Gy) vs EBRT + ADT (6 months) [29]. The authors showed a significant decrease in 8-year mortality with ADT (16.5% vs 41.4%) in the elderly with no/mild comorbidities but a deleterious effect in those who presented moderate/severe comorbidities [36].

Dell'Oglio et al. reported the results of competing-risks multivariable analyses of a cohort of 3,692 patients > 80y with clinical T1-T2 and high histological grade, or clinical T3-T4 with any histological grade, that underwent EBRT ± ADT. The authors did not observe significant differences in either cancer-specific mortality (12.7% vs 13.9%, p = 0.4) or other cause mortality (55.5% vs 61.6% p = 0.051) while a combination of ADT/EBRT resulted in a significant cost increase [37].

Thus, in elderly patients with a moderate or poor prognosis, while the combination of ADT + RT shows a benefit in mortality compared to ADT alone, the results are more controversial compared to EBRT alone. In elderly with no or few comorbidities, the findings are identical, suggesting a benefit similar to younger patients. On the other hand, in subjects with moderate or severe comorbidities or in the super-aged, the results are not the same, and even suggest a deleterious effect. However, these studies, lack data on the modalities of irradiation (dose, volume, technique), the addition of BT, geriatric data (to evaluate frailty in older adults) and obviously the relative side effects of EBRT and ADT. In clinical practice, an individualized patient-centered approach is needed to identify patient comorbidities and frailty that might reverse the ADT benefit.

Toxicity profile (Table 2)

External beam radiotherapy (EBRT). No study reported grade (G) 4 or 5 toxicity. The most frequent late toxicities were hematuria, urethral stricture and rectal bleeding.

Villa et al. reported 68.8% acute toxicity with only 9.3% G2-3 (Genito-urinary (GU):7.5%, Gastro-intestinal (GI):3.1%). No patient > 80y old had G2-3 toxicity, certainly due to the small number of patients [23] and more 3D (than box technique). He described 19.7% late complications, of which 5.5% were G2-3 (GU:3.1%; GI:2.5%). 3D significantly decreased G2 GU toxicity rates, with no difference for GI toxicities. [25] Nguyen et al. reported 38% acute G2-3 GU and 21% GI toxicities. In particular, there was a significant difference in G2-3 GI toxicity with pelvic irradiation (37% vs 10.5%). Twenty-six percent of the patients experienced at least one late toxicity (GU or GI). [26].

Geinitz et al. and Okonogi et al., comparing geriatric populations (>75y and > 80y respectively) with younger patients, did not show any significant difference in either acute or late toxicity between the two populations. Okonogi et al. reported a cumulative incidence of GU toxicity of 4.8% vs 1.2% and GI toxicity of 13% vs 7% [28]. In the Geinitz et al. study, the only remaining significant factors for late G2-3 toxicity were the occurrence of acute G2-3 toxicity and a dose ≥ 70 Gy to the prostate (for rectal toxicity only). However, age or diabetes were not significant [27]. The only study carried out with modern EBRT (IMRT/Image Guided Radiation Therapy (IGRT)) by Okonogi et al. showed a correlation between late rectal toxicity and mean rectal values, and especially V70, but this was not found with GU toxicity and mean bladder dose. In this study, age, diabetes or anticoagulants were still not considered significant prognostic factors for late GU/GI toxicities [28].

These findings suggest an acceptable tolerance in the elderly, similar to younger patients. Age is not an independent factor. Furthermore, new irradiation techniques, such as IMRT/IGRT, make it possible better to preserve organs at risk, thus improving tolerance. However, it is important to note that toxicities are only ranged by grade, whereas lower toxicities can have important consequences in older adults (dehydration, hospitalization).

Brachytherapy (BT). In 2001, Stromberg et al. compared 90 pts > 70y with 102 younger, high-risk patients who had received EBRT + HDR-BT boost. With a MFU of 3.3 years, no difference was noted in acute toxicity or in late GI toxicity. (G2: 8% vs 3% p = 0.19) [31]. Nevertheless, the authors reported an increased late G2 GU toxicity (22% vs 8%; p = 0.005) [38]. In 2009, the same team reported in patients > 70y more G3 urethral strictures with HDR vs IMRT (9% vs 2%; p = 0.03) [23]. Yamazaki et al. in the 2018 study, reported similar late toxicities at 7 years between old (>75y) versus younger patients in terms of G ≥ 2 GU (13.6% vs 14%) and GI toxicities (3.1% vs 3.3%) but also underlined the increase of GU toxicity induced by BT vs IMRT [30]. In 2020, the authors confirmed their results with similar acute G ≥ 2 GU (9 % vs 14.3 %), GI toxicities (2 % vs 1 %) and late toxicities in > 80y and young people. However, late GI toxicities were increased by EBRT (vs BT ± EBRT) and GU toxicities increased in > 80y patients in the BT group. Consequently, age > 80y and BT emerged as independent factors of late G ≥ 2 GU toxicity [31].

Löser et al. reported low toxicity rates for patients > 75y treated with EBRT (50.4 Gy) + HDR (18 Gy). The authors presented results consistent with the previous ones with acute G ≥ 2GU and GI toxicities of 18.2% and 17.3% respectively, and late G ≥ 2GU and GI toxicities of about 3.3% respectively. IMRT notably allowed a decrease in reported toxicities (vs EBRT) [39].

Li et al. explored acute toxicities, especially those requiring admission to an emergency department within 30 days post-BT. Age was found to be an independent factor (50% higher rate mainly > 75y) [40]. Finally, Chen et al. in a large cohort of 5621 patients > 65y, highlighted age, comorbidities and the addition of EBRT as factors of post BT complications, for both GU and GI toxicities. Nevertheless, the modalities of BT or radiotherapy are not specified [41].

The results concerning toxicities remain discordant. Although they suggest similar acute toxicities overall compared to younger patients, it seems that age increases the risk of late toxicity, particularly urinary, in conjunction with BT. Consequently, the use of BT-boost should be analyzed in depth in terms of benefit/risk.

Quality of life (Qol). "Primum non nocere". If the primary objective of a treatment is to improve prognosis, it must not be deleterious and burden the QoL, especially in the elderly, who may have multiple comorbidities already impacting their daily condition. Goineau et al. prospectively explored the different predictive factors of QoL deterioration in a cohort

of 208 pts ≥ 75y (MA 77y) with localized PC (mainly intermediate- or high-risk) treated with EBRT ± ADT (>50% had comorbidities) [42]. The authors observed that tolerance was good with QoL maintained in 75% of patients (severe loss in 8.8%). Unfortunately, none of the parameters analyzed were considered predictive factors for QoL deterioration (oncogeriatric assessment, tumor and treatment characteristics (ADT, pelvic field, operating field) with a view to identifying patients potentially at risk [42].

Irradiation appears to be well tolerated in the geriatric population and should not discourage curative management that can improve the LE of patients with a poor prognosis. However, longer follow-up is warranted to confirm these findings and to develop other evaluation scales.

Impact of comorbidities

The comorbidity impact on LE becomes even more important with age. Indeed, cardiovascular and also cognitive comorbidities can have an impact on survival outcomes (OS, CSS) in addition to toxicity, whether irradiation or ADT.

Firstly, prior cardiovascular morbidity factors may influence oncological outcomes and tolerance of irradiation ± ADT. Fiorica et al. reported the results of a retrospective study of intermediate- and high-risk patients > 75y who underwent EBRT ± ADT (6 months) [43]. The authors observed a better 5-yOS (86.9% vs 45.3%) in patients with an Adult Comorbidity Evaluation 27 (ACE-27) score of 0 (no) to 1 (mild comorbidities) and good performance status. A correlation was also reported between toxicities (acute and late) and comorbidities, with no associated impact of age [43]. Merrick et al. and Nanda et al. evaluated the impact of comorbidities during BT (±EBRT). Nanda et al. reported that pre-existing cardiovascular morbidity factors (stenting, coronary bypass surgery, medical treatment) significantly decreased prostate cancer-specific mortality from 12.7% to 2.1%. In this study, compared to healthy patients, PSA level was no longer considered an independent specific mortality prognostic factor in patients with cardiovascular comorbidities [44]. In Merrick et al's cohort of 145 all-risk patients > 75y, only hypertension, tobacco and diabetes were reported, and patients did not benefit from a standardized assessment of their comorbidities [45]. Although smoking and ADT had an influence on OS in univariate analysis, tobacco emerged as the only factor in multivariate analysis. Cardiovascular deaths were not correlated with the addition of ADT or its duration (from 3 to 36 months) [45]. Indeed, the higher risk of cardiac toxicity induced by ADT is controversial and occurs especially in patients with pre-existing cardiovascular comorbidities such as heart failure or myocardial infarction [46,47]. Metabolic consequences are better established with metabolic alterations such as insulin resistance and dyslipidemia [33,34]. These outcomes suggest a minimal screening for cardiovascular comorbidities before any potential treatment, whether EBRT, ADT or BT, in order to identify patients with a greater benefit without increasing toxicity.

We cannot consider elderly comorbidities without referring to cognition, which may influence both treatment and tolerance, especially ADT. Indeed, the impact of ADT on cognitive decline is contested. While Baik et al. identified no association between ADT (and its duration) and Alzheimer's disease (AD) in 1.2 million patients ≥ 67y, 35% of whom received ADT [48], Jayadevappa et al. reported an association between ADT and AD or dementia (with an increasing HR with ADT duration), in 154,089 patients, 62,330 of whom received ADT with a MFU of 8.3 years [49]. Assuming that there may be a higher cognitive risk, it is important to consider the patient's cognition status and duly to adapt treatment and/or its duration.

Discussion

The incidence of PC in people > 70y will double in the next 20 years, so their management is a serious challenge for clinicians, health care systems and insurance companies. However, there is a shortage of robust data on their management due to a lack of representativeness or specific analysis (in subgroups) in prospective or randomized prospective trials. The National Comprehensive Cancer Network (NCCN) guidelines recommend radical treatment by prostatectomy or radiotherapy (including BT) combined with ADT, particularly in the intermediate and high-risk populations [50]. NCCN suggest treatments for patients based on LE but no recommendation is specific to the geriatric population. Furthermore, standards of care are less applied to the over 75 s (51.9%), who are at high risk and have a poorer prognosis, leading to a risk of inadequate or under-treatment. In fact, this latter group receives more conservative treatment (i.e. no treatment or ADT alone) [51]. This was confirmed in 2017 by Yang et al. with the decrease in radical treatment as age increased and the parallel increase in ADT alone [20]. This is the result of the dominance of *chronological* over *physiological* age in clinicians' assessment of LE. This trend is improving with an increase in radical treatment [21], probably due to awareness of certain studies, a more global appreciation of the elderly and an increasing rejuvenation of populations [10,11,13,14].

Among the definitive treatments, the combination of BT, EBRT ± ADT has shown a benefit particularly in bNED and PCSS in intermediate to high-risk elderly patients, with no deleterious [22], and even a positive effect on OS [23,24].

In terms of treatment, EBRT seems to have encouraging results, with even a benefit in bNED in the cohort of Geinitz et al [27]. In terms of toxicity, the results are also comparable to those of younger patients, with a preservation of their QoL, although most of the studies reported 3D treatment, now largely surpassed by IMRT. The same data were observed after BT with similar outcomes compared to younger populations. However Valdivieso et al. observed that one in two patients > 80y may be overtreated with a 10-y OS of 47% [32]. Toxicity appears more debatable, with late GU toxicity seemingly increased in the elderly or super-elderly population (>80y) [31,38]. Chen et al. in their large cohort, reported age as an independent factor in the increase of post-BT GU and GI toxicity, without specifying the modalities (LDR, HDR, dose, volume, urinary implantation status…) [41]. Finally, although the combination of ADT + EBRT has been shown to be more effective compared with ADT [35], the outcomes must be weighed against associated comorbidities and age compared to EBRT alone [36,37]. Indeed, the benefit in terms of mortality with the addition of ADT was not found in patients > 80y or in patients with moderate or severe comorbidities, with even a deleterious effect in the latter. Moreover, tolerance (cardiovascular, bone, cognitive, etc.) was not precisely investigated in these studies, despite it being crucial in patients with comorbidities and often subsequent medications.

In this regard, it seems necessary to make an oncogeriatric assessment both in daily practice and in prospective clinical trials [52].

Although our aim is to provide an overview of radiotherapy for localized PC specifically in the elderly, our study presents certain limitations. First, methodologically, by limiting itself to key words in the title/abstract, it may not be complete and may not take into account certain papers, particularly prospective studies, which also include the geriatric population. Furthermore, the selected studies are mainly retrospective and therefore lack scientific evidence.

It is also difficult to draw conclusions from them, even if the results are consistent; they have to be weighted according to characteristics and evaluation criteria owing to the lack of homogeneity. Indeed, the analyzed series differed in terms of population, period of analysis, follow-up, design (comparative versus simply descriptive), treatment methods and analysis criteria. For example, some authors studied people > 70, >75 or even > 80y and some, their comorbidities (Charlson score, ACE 27 scale, or items like hypertension, diabetes, coronary disease), and may or may not have compared the elderly population with younger patients; these differences can modify the results. The irradiation technique may also differ, as well as the treated volume, dose and fractionation, and thus have an impact on the oncological outcome and toxicity profile. Indeed, most articles report conventional 3D, which also

Table 1
Literature analysis of oncological outcome after irradiation of prostate cancer in the elderly.

Authors	# pts	MFU (months)	MA (years)	ACU	Risk groups	Irradiation techniques	Median dose (Gy)	Oncological outcomes		
								bNED	CSS	OS
Villa et al. [25]	183	43	75	70	All	Box, 3D	70	63[c]	94[c]	90[c]
Geinitz et al. [27]	301	40	77	75	All	3D	70.2	76 vs 61[b]		92 vs 90[b]
Nguyen et al. [26]	65	65	81	80	All	Box, 3D	69.5	73[c]		77[c]
Okonogi et al. [28]	194	35	81	80	I/H	IMRT	78	96 vs 97[a]		92 vs 99[a]
Stromberg et al. [23]	437	78	75	70	I/H	3D	66.6	47.5[c]	91[c]	73[c]
						IMRT	75.6	73.5[c]	97[c]	88[c]
						3D + HDR-BT	46 + 2x11.5/3x5.5	79[c]	95[c]	88[c]
Yamazaki et al. [30]	1108	87	77	75	All	EBRT*	72/74	90 vs 91[d]		88 vs 97[d]
						LDR-BT	145			
						HDR-BT	45.5/49/54			
						EBRT + LDR-BT	110			
Yamazaki et al. [31]	2429	71.4	81	80	All	EBRT	72 to 74	91 vs 86[c]	100 vs 99[c]	98 vs 96[c]
						LDR-BT	145			
						EBRT + LDR-BT	110			
						EBRT + HDR-BT	31.5/39			
Valdivieso et al. [32]	2701	37	82	80	All	EBRT, BT, EBRT + BT	NA	98[c]		79[c]

pts: number of patients; MFU: median follow-up; MA: median age; ACU: age cut-off; bNED: biological non-evidence of disease; CSS: cancer specific survival; OS: overall survival; IMRT: intensity modulated radiation therapy; EBRT: external beam radiation therapy; HDR: high dose-rate; LDR: low dose-rate; BT: brachytherapy.
*EBRT: 3D or IMRT.
a: @ 3 years; b: @ 4 years; c: @ 5 years; d: @ 7 years.

Table 2
Literature analysis of toxicity after irradiation of prostate cancer in the elderly.

Authors	# pts	MFU (months)	MA (years)	ACU	Risk groups	Irradiation techniques	Median dose (Gy)	Toxicity (G ≥ 2)			
								GU (%)		GI (%)	
								A	L	A	L
Villa et al. [25]	183	43	75	70	All	Box, 3D	70	7.5	3.1	3.1	2.5
Geinitz et al. [27]	301	40	77	75	All	3D	70.2	Total late G3 toxicity from 0 to 4%			
Nguyen et al. [26]	65	65	81	80	All	Box, 3D	69.5	38	17[a]	21	6[a]
Okonogi et al. [28]	194	35	81	80	I/H	IMRT	78	–	4.8 vs 1.2	–	13 vs 7
Stromberg et al. [38]	192	39.6	73 vs 63	70	I/H	3D + HDR-BT	45 + 3x5.5–6.5 45 + 2x8.25–10.5	–	22 vs 8[b]	–	8 vs 3[b]
Stromberg et al. [23]	437	78	75	70	I/H	3D	66.6	Total late G3 toxicity: 12%			
						IMRT	75.6	5-y G3 urethral stricture: 9 (BT) vs 2 (EBRT)			
						3D + HDR-BT	46 + 2x11.5/ 3x5.5				
Chen et al. [41]	5621	24	72	65	All	–	–	–	10.3[c]	–	0.8[c]
Yamazaki et al. [30]	1108	87	77	75	All	EBRT*	72/74	–	13.6 vs	–	3.1 vs
						LDR-BT	145		14		3.3
						HDR-BT	45.5/49/54				
						EBRT + LDR-BT	110				
Yamazaki et al. [31]	2429	71.4	81	80	All	EBRT	72 to 74	9 vs	9.9 vs 9.4	2 vs 1	3.5 vs
						LDR-BT	145	14.3			2.5
						EBRT + LDR-BT	110				
						EBRT + HDR-BT	31.5/39				
Löser et al. [39]	134	25	76	75	All	EBRT*+HDR-BT	50.4 + 2x9	18.2	3.3	17.3	3.3
Li et al. [40]	9042	1	67	–	–	BT	–	Hospital encounters: 6% with 68.7% within 7 days and 52.8% urinary retention >75 years: 50% increased odds			

pts: number of patients; MFU: median follow-up; MA: median age; ACU: age cut-off; G:grade; GU: genito-urinary; GI: gastro-intestinal; A: acute; L: late; IMRT: intensity modulated radiation therapy; EBRT: external beam radiation therapy; HDR: high dose-rate; LDR: low dose-rate; BT: brachytherapy.
*EBRT: 3D or IMRT a: all grade late toxicity; b: grade 2 toxicity only; c: grade 3 toxicity only.

affects irradiation volumes and doses. In fact, most authors describe prostate irradiation without a pelvic field up to 70 Gy. Nowadays, IMRT is predominant and allows dose escalation as well as better preservation of organs at risk, which can influence results and tolerance. The same is true for BT (LDR or HDR, fractionation, dose) and ADT with its duration (from 4 to 31 months). Furthermore, the endpoints may also be different: bNED, PCSS, OS; also, in terms of GU and GI toxicities: acute, late, cumulative incidence, all grades, ≥G2. We also decided not to study irradiation techniques such as SBRT, although this is currently in vogue, allowing hypo-fraction and dose escalation by increasing the doses per fraction in tissue with a low alpha/beta ratio, and shortening the overall treatment time, an attractive and promising non-invasive option in the elderly, including the frail. Our study also fails to take into account the wishes and preferences of patients we routinely see in our clinical practice, which may have changed in recent years with the improvement in their health and QoL, and which may thus lead to under-treatment (for example, by refusing combination of ADT + EBRT). Nevertheless, this analysis sums up the most relevant Questions/Answers related to irradiation of localized prostate cancer in the elderly (Table 3).

Conclusion

Elderly patients with localized PC with poor prognostic criteria (intermediate and high-risk) are fully eligible for radical treatment such as

Table 3
Summary.

Questions	Answers		
Are elderly undertreated?	Despite a benefit in CSS and OS with optimal treatment (including BT boost), elderly patients, especially with high-risk PC, often received inadequate or under-treatment.		
Benefit/risk balance of radiotherapy?	Oncological outcomes	EBRT	bNED: 63 to 96% OS: 77 to 92% Results are comparable between younger and elderly population.
		BT	5-y bNED: 79.4% to 91.3% OS: 79% to 97.8% bNED for elderly patients appears similar to that of younger patients. OS benefit is discordant especially in super-aged (>80 years).
		ADT	EBRT + ADT > ADT Use of ADT in combination with EBRT has to be carefully discussed in elderly patients with moderate or severe comorbidities or the super-aged.
	Toxicity	EBRT	No Grade 4 or 5 reported. Toxicities are comparable to younger patients. Age does not appear an independent factor.
		BT	Acute toxicities: similar to younger population Late toxicities: seem to increase with age (especially GU toxicity).
		QoL	Irradiation is well tolerated (QoL maintained in 75%). No predictive factor for QoL deterioration
Impact of comorbidities?	Elderly comorbidities can influence oncological outcomes (OS and CSS) and treatment tolerance (EBRT and/or ADT), with a decrease in specific mortality and an increase of overall mortality. While metabolic consequences are well established, cardiovascular and cognitive ADT toxicities remain under investigation.		

PC: prostate cancer; CSS: cancer specific survival; OS: overall survival; bNED: biological non-evidence of disease; EBRT: external beam radiation therapy; BT: brachytherapy; ADT: androgen deprivation therapy; GU: genito-urinary; QoL: quality of life.

radiotherapy, which can be part of a multimodal treatment. Patients in good shape even benefit from optimal treatment with ADT and dose escalation by BT with acceptable tolerance. Age alone should not be a barrier to irradiation. It is obviously necessary to assess comorbidities and pre-treatment functional status, optimally with the help of careful oncogeriatric assessment, in order to judiciously identify patients with the greatest benefit at the lowest toxicity.

In the future, prospective data on older adults would help to guide our practices. We must keep in mind the best overall benefit for the patient and thus take into account his wishes and preferences.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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