Background for the proposal of SIOG guidelines for the management of prostate cancer in senior adults

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Contents

1. Introduction ................................................................. 69
2. Epidemiology of prostate cancer ........................................... 70
3. The evaluation of health status in senior adult cancer patients .................................................. 71
   3.1. Comprehensive geriatric assessment ......................................... 71
   3.2. Patient subgroups defined through health status evaluation ........................................... 73
      3.2.1. Evaluation of comorbidities .................................................. 73
      3.2.2. Evaluation of dependence .................................................. 73
      3.2.3. Other components of health status to consider ......................... 73
      3.2.4. Health status evaluation summary ..................................... 73
   3.3. Possible interventions in senior adult patients ........................................... 75
4. Localised prostate cancer .................................................... 76
   4.1. Staging procedures ....................................................... 76
   4.2. Prognostic factors .......................................................... 76
   4.3. Treatment of localised prostate cancer ....................................... 78
      4.3.1. Radical prostatectomy ...................................................... 79
      4.3.2. Special considerations for patients with prior trans-urethral resection of the prostate ............. 81
      4.3.3. External beam radiation therapy ........................................ 81
      4.3.4. Brachytherapy ............................................................ 81

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Abstract

Background: The incidence of prostate cancer increases with age, with a median age at diagnosis of 68 years. Owing to increased life expectancy, the management of prostate cancer in senior adult men (i.e., aged 70 years or older) represents an important public health concern and a major challenge for the future. No specific guidelines have previously been published on the management of prostate cancer in older men. The SIOG has developed a proposal of recommendations in this setting.

Methods: A systematic bibliographical search focused on screening, diagnostic procedures, treatment options for localised, locally advanced and metastatic prostate cancer in senior adults was performed. Specific aspects of the geriatric approach were emphasised, including evaluation of health status (nutritional, cognitive, thymic, physical and psycho-social) and screening for vulnerability and frailty. Attention was drawn to the consequences of androgen deprivation and complications of local treatment, mainly incontinence. The collected material has been reviewed and discussed by a scientific panel including urologists, radiation oncologists, medical oncologists and geriatricians from both Europe and North America.

Results: The consensus is to use either European Association of Urology or National Comprehensive Cancer Network clinical recommendations for prostate cancer treatment and to adapt them to health status based on instrumental activities of daily living (IADL) and activities daily living (ADL), comorbidity evaluation by Cumulative Illness Scoring Rating-Geriatrics and screening for malnutrition. Patients in Group 1 (no abnormality) are ‘fit’ and should receive the same treatment as younger patients; patients in Group 2 (one impairment in IADL or one uncontrolled comorbidity or at risk of malnutrition) are ‘vulnerable’ and should receive standard treatment after medical intervention; patients in Group 3 (one impairment in ADL or more than one uncontrolled comorbidity or severe malnutrition) are ‘frail’ and should receive adapted treatment; patients in Group 4 (dependent) should receive only symptomatic palliative treatment.

Conclusions: Treatment of prostate cancer in senior adults should be adapted to health status. Specific prospective studies in this setting are warranted.

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Keywords: Clinical management; Elderly; Guidelines; Localised disease; Metastatic disease; Prostate cancer; Comorbidity

1. Introduction

Prostate cancer is predominantly a disease of senior adults (i.e., men aged 70 years or older), yet, no specific guidelines exist for this population. Existing guidelines for the management of prostate cancer make little reference to senior adult patients and age-related factors that may affect treatment decisions. Some of them (e.g., National Cancer Centre Network [NCCN] and European Association of Urology [EAU] guidelines) refer to the concept of life expectancy, which depends on many components of a patient’s well-being and is often misinterpreted by physicians. This is perhaps owing to the under-representation in clinical trials of senior adult patients with cancer [1], and the subsequent lack of data from which to develop evidence-based recommendations. In this respect, it is pertinent to note that many of the pivotal clinical studies that have formed the basis for current guidelines in prostate cancer were conducted in selected patient populations that, in terms of age and health status, are not representative of the general population with prostate cancer because of various protocol exclusions (i.e., upper age limits, comorbidities, poor performance status, physiological organ impairments and history of other cancer), different access to care and the misconception that senior adult patients are not suitable candidates for more aggressive therapy [2].

The guidelines presented here have been developed through consideration of the published data in senior adult patients with prostate cancer and highlight age-related issues
that may affect screening and treatment decision-making. Where possible, recommendations have been made together with suggestions for further research. Aging is a highly heterogeneous process and each patient should be treated as an individual and not solely according to chronological age. The objective of the International Society of Geriatric Oncology (SIOG) prostate cancer guidelines for senior adults is to promote the highest possible standards of care for senior adult men with prostate cancer, and to support treatment decisions that are likely to provide optimal clinical outcomes in these patients.

2. Epidemiology of prostate cancer

The most recent GLOBOCAN statistics [3] estimated that in 2002, there were 679,023 new cases of prostate cancer worldwide, ranking prostate cancer as the fifth most common cancer in adults and the second most common cancer in men (11.7% of all new cancer cases, excluding skin) after lung cancer. A total of 221,002 men died from prostate cancer in 2002, representing 5.8% of all cancer deaths in men. Prostate cancer is the most prevalent cancer in men, with an estimated (based on 5-year survival) 2,369,000 men worldwide living with the disease [3]. The real prevalence, based on a longer survival period, is by far much higher. Age-standardised incidence and mortality rates for prostate cancer vary significantly between countries (Fig. 1) [3], the incidence being highest in North America, Australia/New Zealand, and Northern and Western Europe. Hence, prostate cancer is the most frequently diagnosed male cancer in US and in Europe [4,5] and represents the second and third cause of cancer-related death in men in these regions, respectively [4,5]. Much of this large variation between countries is likely to be linked to policies regarding screening (for example, prostate-specific antigen [PSA] testing is more prevalent in more developed countries), but more importantly, to environmental factors (diet, sun exposure, etc.). The mortality–incidence ratio is generally much lower (i.e., survival is better) in developed countries with a high incidence of prostate cancer, although it is unclear to what extent earlier detection and improved treatment contribute to this discrepancy [3].

Prostate cancer is predominantly a disease of senior adult patients. During the years 1993–2001, age-specific incidence rates for prostate cancer rose steadily with advancing age in both more- and less-developed countries [6]. According to the Surveillance Epidemiology and End Results (SEER) registry that provides estimates for the US population only, during the years 2000–2005, the median age at diagnosis for patients with prostate cancer was 68 years; over 60% of new cases of prostate cancer were diagnosed in men ≥65 years of age and 25.7% in men ≥75 years of age (Fig. 2); over 90% of deaths owing to prostate cancer occurred in men ≥65 years of age. The real prevalence, based on a longer survival period, is by far much higher. Age-standardised incidence and mortality rates for prostate cancer vary significantly between countries (Fig. 1) [3], the incidence being highest in North America, Australia/New Zealand, and Northern and Western Europe. Hence, prostate cancer is the most frequently diagnosed male cancer in US and in Europe [4,5] and represents the second and third cause of cancer-related death in men in these regions, respectively [4,5]. Much of this large variation between countries is likely to be linked to policies regarding screening (for example, prostate-specific antigen [PSA] testing is more prevalent in more developed countries), but more importantly, to environmental factors (diet, sun exposure, etc.). The mortality–incidence ratio is generally much lower (i.e., survival is better) in developed countries with a high incidence of prostate cancer, although it is unclear to what extent earlier detection and improved treatment contribute to this discrepancy [3].
years of age and 71.2% in men ≥75 years of age (Fig. 3) [7]. In 2005, in the US alone, an estimated 1,377,594 men aged ≥70 years (i.e., 13% of the overall male population of that age) were living with an invasive prostate cancer, making this disease the most prevalent invasive cancer type in that age group [7,8]. The overall growth and ‘aging’ of the world’s population is expected to increase the burden of prostate cancer—particularly in senior adults. In more developed regions of the world, the proportion of men aged ≥70 years is expected to increase from 0.8% in the year 2000 to 17.2% by 2050 [8] (Fig. 4). Qualitatively, similar changes are underway in less-developed regions (refers to figures). The introduction of PSA screening has dramatically changed the presentation of prostate cancer, with patients now presenting at a younger age and with lower grade/organ-confined disease

3. The evaluation of health status in senior adult cancer patients

3.1. Comprehensive geriatric assessment

Aging is a highly individual process and as such, a “comprehensive geriatric assessment (CGA)” was developed to assess the various biological and clinical correlates of aging on an individual basis. CGA is a “multidisciplinary evaluation in which the multiple problems of older persons are uncovered, described, and explained if possible, and in which the resources and strengths of the person are catalogued, need for services assessed, and a coordinated care plan developed to focus interventions on the person’s problems” [11]. CGA is a comprehensive process that includes diagnostic procedures, specific treatment plans and geriatric intervention. The domains typically assessed during a CGA and the corresponding screening tools are indicated in Table 1 [12–20]. They include cognition, comorbidity, emotional conditions, function, geriatric syndromes, pharmacy, nutrition and socioeconomic conditions. Familial antecedents are also important to consider. A number of randomised, controlled trials using CGA in senior adult patients have demonstrated a benefit of CGA on survival, quality of life (QoL), institutionalisation rates and many other outcomes [21]. These findings have been confirmed by meta-analyses [22,23]. Since the mid-1990s, attempts have been made to integrate CGA into the geriatric oncology setting. However, it
remains unclear which is the best form of CGA to use, exactly how it should be integrated into current oncology practice, and which parameters should be included in the oncology setting [21]. Relatively few studies have specifically examined the benefit of CGA in geriatric oncology [24–26], but the evidence generally supports the effectiveness of such an approach [27–29]. In patients with cancer, CGAs may permit the identification of conditions – for example depression or malnutrition – that can decrease a patient’s ability to tolerate cancer therapy, and which can be reversed after treatment with appropriate interventions [12].

Based on a systematic review of the literature, a SIOG task force has developed recommendations on the use of CGA in senior adult patients with cancer [11]. The SIOG task force recommended that a CGA, with or without screening, and with follow-up, should be used in cancer patients ≥70 years of age in order to detect unaddressed problems, improve their functional status, and possibly also improve their survival. However, the task force felt that at the time of the review (publications were included up to early 2003), there was not sufficient evidence to recommend any specific tool or approach above others, advising that general geriatric experience should be used. This conclusion has not changed to date because no large scale study has shown that any particular tool should be used as a standard approach. The SIOG task force analysis revealed strong evidence that a CGA detects problems missed by a regular assessment both in the general geriatric population and in cancer patients. There was also strong evidence that a CGA improved function and reduced the hospitalisation rate of senior adults. There was heterogeneous evidence that a CGA improved survival and is cost-effective [21]. A summary of the SIOG task force’s clinical recommendations (which are based on a number of questions) is detailed below:

1. **Is there clinically usable biological or other evidence for “degrees of aging”?** The best biological and clinical markers to use in senior adult cancer patients remain undetermined. Some biological markers (e.g., albumin, haemoglobin and creatinine clearance) can provide prognostic information and can be suggestive of a patient’s ability to tolerate cancer therapy, and which can be reversed after treatment with appropriate interventions [12].

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   **2. What does a CGA detect in addition to oncological/medical assessments?** A CGA improves the likelihood of detecting parameters of a patient’s health status that can affect treatment outcome. If a CGA is not used, significant clinical information may be missed in the older cancer patient, but the best form of geriatric assessment is yet to be defined. In addition to the biological and functional elements mentioned above, screening for depression and cognitive impairment should be undertaken. Combinations of tools are frequently used in geriatric oncology and include ADL/IADL, the geriatric depression scale and Folstein’s mini-mental status.

   **3. What is the evidence for the effectiveness of CGA?** Use of some form of geriatric assessment and intervention can be expected to improve dependence status, QoL, rate of**
hospitalisation of cancer patients, and to be cost-effective. Any type of CGA intervention should include a follow-up, as this appears to be essential for the CGA to be effective. Frail and vulnerable patients appear to be ideal candidates for a CGA-based approach. A two-step approach including a screening step should be used.

4. Screening tools and alternative assessments. Screening for geriatric problems is recommended for use in patients with cancer who are ≥ 70 years of age; this should be considered a soft limit. A screening tool (see Table 1) can be used, and if positive, followed by a more complete geriatric evaluation (i.e., minimum data set or further assessment). Recently, a prospective trial was initiated in France that will compare a standard CGA in a geriatric setting with two screening tools (G8, an eight items screen and VES-13, Vulnerable Elders Score-13) in an oncology setting; results are expected in 2010. One of the most important questions to be answered pertains to the most appropriate definition of frailty. A number of different groups are researching on this subject [30]. The SIOG has had to delineate practical criteria to define frailty which could be used in the oncological and surgical settings.

Oncologists must be aware of the available resources and should activate the process, as senior adult patients, particularly those who are frail, vulnerable and/or disabled require more assistance and support compared with their younger counterparts. The SIOG task force conclusions on the role of CGA remain valid for senior adults with prostate cancer. Specific studies have shown that the relevant considerations for senior adult patients with prostate cancer do not differ from those for senior adults with other types of cancer [31].

3.2. Patient subgroups defined through health status evaluation

Frailty has been defined using a number of factors, the choice of which was based on the results of clinical trials. The factors to be considered are first, comorbidities and second, other factors that may affect health status in a stepwise fashion.

3.2.1. Evaluation of comorbidities

The impact of comorbidities on patient outcome has been specifically studied in patients with localised prostate cancer. Tewari and colleagues performed a multivariate analysis of prognostic factors for overall and prostate cancer-specific survival in patients with localised disease who were treated by radical prostatectomy [32]. The strongest predictive factor of non-prostate cancer death was the Charlson comorbidity index. The Charlson index is also a good prognostic tool for the development of post-operative complications [33]. In patients who are treated by radiation therapy for high-risk localised prostate cancer, the level of comorbidity is also helpful to select patients who may benefit from combined androgen deprivation therapy [34]. The combination of radiation therapy and androgen deprivation therapy resulted in a significant survival benefit compared to radiation therapy alone in patients with no or minimal comorbidity but showed no benefit in patients with moderate to severe comorbidity. The Charlson index focuses on 19 major comorbid conditions that significantly affect survival [35]. However, it provides only a partial evaluation of comorbidity as many diseases that have a lesser impact on survival (e.g., hypertension) are not rated. As such, use of the Cumulative Illness Score Rating-Geriatrics (CISR-G) – that also includes and rates non-lethal diseases according to their severity and level of control by treatment – may show a better discriminating value. The CISR-G has been validated in senior adults with cancer and its prognostic performance compares well with the Charlson index [36]. Although the CISR-G has improved clinical applicability, this tool has limitations as it does not permit separate screening of two comorbidities of the same organ [37].

3.2.2. Evaluation of dependence

Dependence is another key factor that contributes towards a poor health status. It can be evaluated using a number of different scales, the most important being the ADL and the IADL scales. The ADL [18] rates the patient’s ability to accomplish basic activities of daily living (bathing, dressing, toileting, transferring, continence and feeding). The IADL scale [19] rates activities that require a higher level of cognition and judgment (preparation of meals, shopping, light housework, financial management, medication management, use of transportation and use of the telephone). Fall and risk of falling are other components of dependence and may be caused by a number of different medical conditions including polypharmacy. Risk of fall can be screened by specific functional tests [38].

3.2.3. Other components of health status to consider

Malnutrition is another important component of health status and is a strong prognostic factor for poor outcome [39]. It is screened using the Mini-Nutritional Assessment tool that grades the nutritional state of senior adult patients [40]. Depression also contributes to frailty [41] and can be screened using the geriatric depression scale [42]. Lastly, cognitive impairment is also important to consider as it may be indicative of mental illness associated with a poor outcome and can lead to difficulties in decision-making as patients may not be able to participate in this process. It is screened using the Mini-Mental State tool [13]. Nevertheless, a complete understanding of the patient’s mental status requires a full neuro-psychological evaluation.

3.2.4. Health status evaluation summary

Treatment recommendations should balance the risk of death from prostate cancer in an individual patient with the risk of adverse events that can result of specific interventions. In this perspective, an assessment of the patient’s health status, including both patient and family history and past and
co-existent health problems is required. Health status influences the patient’s survival and may affect the patient’s ability to tolerate potential treatment-associated adverse events. There is a great variation in life expectancy among age groups which reflects variability of patient’s health status (Fig. 6) [43]. Hence, a ‘fit’ 80-year-old man may have a longer life expectancy (i.e., upper tertile in this age group) than a 70-year-old man with severe comorbidities (lower tertile in this age group). CGA permits a detailed evaluation of the health status of individual patients and helps to predict the probability of survival based on specific health status criteria [44]. The CGA permits the classification of cancer patients into four health status groups [12], the consideration of which can help to clarify treatment decisions. These patient groups are discussed below:

1. Patients who are fit: These patients have no serious comorbidity (CISR-G Grade 0 or 1 or 2), are functionally independent (no dependence in IADL and ADL) and have no malnutrition. Their health status is considered sufficiently well so that they are expected to tolerate any form of standard cancer treatment.

2. Patients who are vulnerable: These are patients dependent in one or more IADL (but no dependence in ADL), or presenting one comorbid uncontrolled condition (CISR-G Grade 3) or at risk of malnutrition. Geriatric problems in this group should be reversible through geriatric intervention. These patients may benefit from additional geriatric intervention, and may receive standard cancer treatment after reversion of the geriatric problems.

3. Patients who are frail: These are patients dependent in one or more ADL, or with two or more uncontrolled comorbid conditions (i.e., at least two comorbidities CISR-G Grade 3 or one comorbidity CISR-G Grade 4), or showing major malnutrition. Patients in this group should benefit from geriatric intervention and can be given specific adapted cancer treatment.

4. Patients who are “too sick”: These patients have a very poor health status that results from a combination of different impairments. These patients can only receive therapy that is suitable for end-of-life palliation.

The following criteria have been chosen to define these health status groups:

- ADL measures a patient’s ability to accomplish basic activities of daily living: bathing, dressing, toileting, transferring, continence and feeding [18]. One ADL impairment is considered abnormal, except in considering incontinence in these patients with prostate disease.
- The IADL measures a patient’s ability to accomplish basic activities that require a higher level of cognition and judgment [19]. Nevertheless, considering the fact that the patients are men, only four items of the original IADL scale have been selected: financial management, medication management, use of transportation, and use of the telephone. One IADL impairment is considered abnormal.
- The CIRS-G measure used is a simplified version of the original description by Linn et al. [37], modified to permit easy, routine bedside use. Grade 2 comorbidity is controlled by first-line treatment; Grade 3 comorbidity is controlled by second-line or multidrug treatment and Grade 4 is an uncontrolled comorbidity.
- Nutritional status is estimated very simply by the variation of weight during the last 3 months: good nutritional status is a variation of less than 5% of weight, risk of malnutrition is a variation of weight between 5 and 10%, severe malnutrition is a weight loss more than 10% of body weight.
- The specific problem of dementia is not included in the classification, because it is more a limitation to decision-making than a limitation to treatment by itself. Patients who have signs of dementia must be discussed on an individual basis.
It is recommended that patients with prostate cancer who are aged $\geq 70$ years are screened very thoroughly for vulnerability and frailty [11,31]. Furthermore, it is recommended that the above classification that is based on a simple health status evaluation is used when considering appropriate prostate cancer treatment options, rather than chronological age. Nevertheless, it must be emphasised that health status screening is merely a tool that is used to determine which patients require CGA and geriatric interventions. The process of grouping patients has been studied [45], but the applicability of such an approach has never been validated prospectively. Thus, at present, CGA is merely a proposed tool to aid in the management of senior adult patients. It is anticipated that research will make this process evolve in the future. A general scheme for the decision-making process is provided in Fig. 7.

### 3.3. Possible interventions in senior adult patients

A number of physiological systems are affected as the body ages. Some of the main changes include reductions in organ function and changes in body composition, both of which can alter the pharmacokinetic and pharmacodynamic profiles of ingested drugs [46]. In patients with comorbid conditions, potential drug–drug interactions must be taken into account in order to minimise toxicity and reduce the potential for loss of treatment efficacy [47]. By the age of 75 years, the fat content of the body has approximately doubled; this enhances the distribution of fat-soluble compounds. In contrast, the volume of water in the body decreases with age, which reduces the distribution of water-soluble drugs [48]. Both plasma albumin levels and erythrocyte numbers may decrease with advancing age, thus increasing the proportion of unbound circulating drug, which may lead to impaired drug delivery and increased toxicity [49]. Chemotherapy can cause haematological toxicity and the usual course of action is to use haemopoietic growth factors. For example granulocyte-colony stimulating factors (G-CSFs) can be used as primary prophylaxis to prevent febrile neutropenia [50]. Agents that stimulate erythropoiesis can be used to reduce the need for transfusion and to treat anaemia in senior adult cancer patients [51,52].

The functional volume of the liver [53] and blood flow in the liver [54] decrease with age. In patients with poor liver function, chemotherapy dose adjustments may be necessary to avoid side effects, particularly for drugs that are eliminated by the liver, for example, taxanes [46]. Cytochrome P450 (CYP) enzymes may lose functionality over time [55]. Polypharmacy also affects the CYP pathway, as CYP3A4 is inhibited by many commonly prescribed medications. These factors may result in decreased first-pass metabolism of drugs, possibly influencing susceptibility to toxic effects. Excretion by the kidneys also declines with age [56] and this may be confounded by the presence of comorbid conditions. Careful dose adjustments may be warranted in patients with reduced renal function [57], particularly for renally excreted drugs with a narrow therapeutic index [58]. Concomitant use of nephrotoxic drugs to treat comorbidities should be avoided. It is mandatory to correctly evaluate creatinine clearance [59] and also, to adapt drug dosages to renal function [60]. Dementia is common in older patients. Data from the Canadian Study of Health and Aging have demonstrated that cognitively impaired patients have a reduced median projected survival of around 70 months.
compared with non-cognitively impaired individuals [61]. As such, the individual’s chance of surviving should be considered when choosing appropriate treatments. If chemotherapy is given in patients with dementia, support from a caregiver is needed [57] as some side effects of chemotherapy (e.g., diarrhea, dehydration, and febrile episodes) are exacerbated in this group and may result in delirium. Chemotherapies commonly associated with these side-effects should be avoided and, if used, particular attention should be given to the dose used and additional supportive measures such as hydration and growth factor administration [57]. Lastly, muscle weakness is another frequently observed and clinically significant side effect of chemotherapy in senior adult patients [62]. Physical therapy may be a suitable preventive intervention in patients who experience these symptoms.

4. Localised prostate cancer

Patients who are considered in this chapter are likely to be treated in the curative setting (i.e., local treatment with or without adjuvant treatment). This group generally includes patients with T1-3N0M0 disease. This section examines the importance of prostate cancer staging with respect to prognostic factors used to evaluate the risk of unfavourable oncological outcome, and to treatment decisions for localised disease. Guidelines used in this review include those of the EAU [63], the American Urological Association [64] and the NCCN [65]. The NCCN guidelines for the management of senior adult patients with cancer [66] have also been reviewed.

4.1. Staging procedures

Accurate tumour staging, in particular whether or not the tumour is confined to the prostate gland, is essential for treatment decision-making. The diagnosis is performed by prostate biopsies in a patient with abnormal digital rectal examination (DRE) and elevated serum PSA value. The method of prostate biopsy – target biopsies or random biopsies – is an unresolved question in senior adult patients. The Panel opinion is that it is desirable to refrain from performing random biopsies if a surgical treatment cannot be offered to those patients. The available methods for staging localised prostate cancer include DRE, serum PSA, transrectal ultrasonography (TRUS), and—in specific situations, computerised tomography (CT) scan and endorectal magnetic resonance imaging (MRI). Staging methods to evaluate the presence of distant metastases include CT scan, MRI and radioisotopic bone scan. It may not be necessary to perform an extensive staging in every patient with clinically localised disease (e.g., in patients at low-risk of developing distant metastases). The TNM staging of the American Joint Committee on Cancer and International Union Against Cancer is the most widely used and is now available on line [67]. A linear relationship has been reported between age and the risk of non-organ-confined disease in men presenting with PSA <10 ng/mL, with increasing age being associated with an increased risk [68]. In multivariate analysis, age was an independent predictor of non-organ-confined disease (p = 0.004).

4.2. Prognostic factors

Optimal treatment of prostate cancer requires an accurate assessment of the risk of unfavourable oncological outcome. The most widely used prognostic factors in prostate cancer are clinical T-stage, pretreatment serum PSA level, and Gleason score on prostate biopsy. They form the basis of a commonly used risk stratification tool developed by D’Amico et al. to evaluate the probability of biochemical relapse 5 years after curative therapy [69]. Patients in the low-risk group (<25% probability of PSA failure at 5 years) have a tumour stage of T1c–T2, a serum PSA level <10 ng/mL and a Gleason score ≤6; those in the high-risk group (>50% probability of PSA failure at 5 years) have a tumour stage ≥T2c, or a serum PSA level >20 ng/mL, or a Gleason score ≥8, and patients in the intermediate-risk group (25–50% probability of PSA failure at 5 years) are those with characteristics other than those listed above. This classification has been widely published and validated, and is cited in NCCN guidelines [65]. Prediction of pathological stage and outcome following various treatment modalities may also be obtained using nomograms (Table 2). These are algorithms that incorporate the interactive effect of multiple prognostic factors to predict pathological stage and oncological prognosis for an individual patient. A widely used nomogram developed by Partin et al. combines clinical T-stage, serum PSA level and biopsy Gleason score to predict extracapsular extension, seminal vesicle and lymph node invasion following surgical treatment [70,71]. Other models have been developed to evaluate the risk of disease recurrence following surgery, radiation therapy and brachytherapy [72–78]. It is noteworthy that these models do not generally predict cancer-specific mortality and that many men who experience PSA relapse following curative therapy will not live long enough to develop metastases or die from prostate cancer, particularly those who are of senior age. The predictive value of PSA kinetics is also being investigated. While the value of pretreatment PSA velocity in predicting outcome following curative therapy is controversial [79–81], there is consistent evidence that, in case of biochemical recurrence after radical prostatectomy or radiation therapy, PSA doubling time may be useful to identify patients at high-risk of dying of the disease [82–84]. For example, the predictive value of PSA doubling time has been evaluated in 381 senior adult patients (median age 73 years) who underwent radiation therapy for clinically localised prostate cancer [82]. Of the 118 patients considered at high-risk of biochemical relapse according to D’Amico classification, 45% were estimated to die from prostate cancer within 10 years after radiation therapy compared with 6% (p = 0.05) and 0% (p = 0.004) for patients with intermediate (n = 171) or low-risk (n = 90) disease. Conversely, 10-year
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<tr>
<th>Citation</th>
<th>Disease stage/therapy</th>
<th>Outcome</th>
<th>Clinical parameters</th>
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<tbody>
<tr>
<td>D’Amico et al. [72]</td>
<td>Localised/radical prostatectomy or external beam radiation therapy</td>
<td>Probability of post-treatment PSA failure</td>
<td>Pretreatment-PSA level</td>
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<td>Biopsy Gleason sum</td>
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<tr>
<td>Partin et al. [71]</td>
<td>Localised/radical prostatectomy (without neoadjuvant therapy)</td>
<td>Probability of organ-confined disease, extraprostatic extension, seminal vesical and lymph node invasion</td>
<td>Pretreatment-PSA level</td>
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<td>Biopsy Gleason sum</td>
</tr>
<tr>
<td>Kattan et al. [73]</td>
<td>Localised/3D conformal radiation therapy</td>
<td>5-Year probability of biochemical (PSA) recurrence</td>
<td>Pretreatment-PSA level</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Clinical stage</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Biopsy Gleason sum</td>
</tr>
<tr>
<td></td>
<td>± Neoadjuvant androgen deprivation Radiation dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kattan et al. [74]</td>
<td>Localised/permanent prostate brachytherapy</td>
<td>5-Year freedom from recurrence&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Pretreatment-PSA level</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Clinical stage</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Biopsy Gleason sum</td>
</tr>
<tr>
<td>Kattan et al. [75]</td>
<td>Localised/3D conformal radiation therapy</td>
<td>5-Year probability of metastasis</td>
<td>Pretreatment-PSA level</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Clinical stage</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Biopsy Gleason sum</td>
</tr>
<tr>
<td>Han et al. [76]</td>
<td>Localised/radical prostatectomy</td>
<td>3, 5, 7 and 10-Year probability of biochemical (PSA) recurrence</td>
<td>Pretreatment-PSA level</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Clinical stage</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Biopsy Gleason sum</td>
</tr>
<tr>
<td>Stephenson et al. [77]</td>
<td>Localised/radical prostatectomy</td>
<td>10-Year progression-free probability&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Pretreatment-PSA level</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Clinical stage</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Number of positive and negative biopsy cores</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Primary and secondary Gleason grade</td>
</tr>
<tr>
<td>Kattan et al. [78]</td>
<td>Localised/radical prostatectomy</td>
<td>10-Year freedom from biochemical recurrence</td>
<td>Pretreatment-PSA level</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Clinical stage</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Surgeon experience</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Biopsy Gleason sum</td>
</tr>
</tbody>
</table>

<sup>a</sup> Defined as post-treatment administration of androgen deprivation therapy, clinical relapse or biochemical (PSA) failure.

<sup>b</sup> Defined as secondary therapy or clinical relapse or PSA relapse or aborted radical prostatectomy for lymph node metastases.
estimates to die from another cause were 27, 17 and 12% in patients at high-, intermediate- and low-risk, respectively. Nearly identical estimates of death from prostate cancer or from other cause were observed in men with biochemical relapse and having a PSA doubling time ≤ 12 months. Despite their old age, the cause of death in these patients with short PSA doubling time was nearly exclusively prostate cancer.

4.3. Treatment of localised prostate cancer

Evidence suggests that in both the USA (Fig. 8) and in Europe, only a minority of senior adults with localised prostate cancer receive curative therapy. The 2008 EAU guidelines recommend that “as a standard, an assessment of the patient’s life expectancy, overall health status and tumour characteristics is necessary before any treatment decision can be made”. It is also stated that “life expectancy, rather than patient age, should be the factor considered in treatment selection” [63]. The panel did not select a specific chronological cut-off point for treatment recommendations. Alibhai and colleagues evaluated treatment efficacy in men aged ≥ 65 years with localised prostate cancer by using a decision model that integrates the patient’s age, comorbidity, Gleason score, patient preference and treatment efficacy data (from three complementary data sources including modern radiation therapy results) [87,88]. The results showed that radical prostatectomy and radiation therapy significantly improved life expectancy and quality-adjusted life expectancy in older men with few comorbidities and moderately or poorly differentiated localised prostate cancer. As healthy men in their 70s or 80s with localised prostate cancer are often managed conservatively, it was concluded that “curative therapy should be seriously considered in men up to age 80 years who have high-grade disease”. In a population-based cohort study of men aged 75–84 years with clinically localised prostate cancer, it was reported that men receiving an aggressive treatment (prostatectomy or radiation therapy) were more likely to suffer from urinary and bowel dysfunction and were more bothered by erectile dysfunction than those managed conservatively [89]. The adjusted disease-specific mortality ratio was 0.43 (95% confidence interval [CI], 0.15–1.28), favouring aggressive treatment, however, the absolute 5-year disease-specific survival difference between both groups was rather small (98% versus 92%) because most deaths were from other causes. The authors concluded that when treating patients aged ≥ 75 years in whom aggressive treatment is associated with uncertain survival benefits, physicians should balance the expected survival outcome with the potentially harmful effects of treatment. A recently published observational study of 44,630 US patients aged 65–80 years with localised, well- or moderately differentiated prostate cancer, who either were managed conservatively, or received curative treatment (prostatectomy, radiation therapy or brachytherapy) [90] suggested a significant survival advantage for patients who received curative treatment (hazard ratio [HR] 0.75, 95% CI 0.66–0.72), including men aged 75–80 years at diagnosis. The survival benefit was in fact attributed to a reduction in non-prostate cancer mortality, and consequently, these results have been strongly challenged [91]. Results of a Canadian population-based cohort of 6183 men aged ≥ 70 years demonstrated that 40% of men selected for radical prostatectomy did not have adequate life expectancy to warrant attempted curative therapy and 70% of men who received radiation therapy died before reaching the 10-year marker [92]. These findings indicate the need for more stringent radiation therapy and prostatectomy selection criteria, including accurate health status assessment, to minimise overtreatment and its side-effects.

The influence of comorbidity on survival was studied by Tewari et al. [32]. The risk of non-prostate cancer mortality was three times higher in patients with severe comorbidity (Charlson score ≥ 2) compared with those with less severe comorbidity (Charlson score 0–1) (Table 3). This suggests that treatment decisions in senior adults should balance the
Table 3
Predictors of mortality in 1611 patients with localised prostate cancer: multivariate modelling [32].

<table>
<thead>
<tr>
<th>Predictor</th>
<th>All cause mortality</th>
<th>Prostate cancer mortality</th>
<th>Non-prostate cancer mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR (95% CI)</td>
<td>p</td>
<td>RR (95% CI)</td>
</tr>
<tr>
<td>Radical prostatectomy</td>
<td>0.41 (0.31–0.54)</td>
<td>&lt;0.001</td>
<td>0.35 (0.19–0.54)</td>
</tr>
<tr>
<td>Radiation therapy</td>
<td>0.90 (0.70–1.15)</td>
<td>ns</td>
<td>0.41 (0.22–0.74)</td>
</tr>
<tr>
<td>Age at diagnosis</td>
<td>1.04 (1.02–1.06)</td>
<td>&lt;0.001</td>
<td>1.04 (0.99–1.06)</td>
</tr>
<tr>
<td>Charlson score 2+</td>
<td>2.63 (2.08–3.32)</td>
<td>&lt;0.001</td>
<td>1.43 (0.79–2.56)</td>
</tr>
<tr>
<td>Biopsy grade</td>
<td>1.28 (1.08–1.53)</td>
<td>0.005</td>
<td>2.08 (1.41–3.06)</td>
</tr>
<tr>
<td>Log baseline PSA</td>
<td>1.55 (1.28–1.87)</td>
<td>&lt;0.001</td>
<td>2.51 (1.85–3.41)</td>
</tr>
<tr>
<td>Income in $10,000s</td>
<td>0.91 (0.85–0.98)</td>
<td>0.014</td>
<td>0.96 (0.84–1.11)</td>
</tr>
</tbody>
</table>

CI = confidence interval; ns = not significant; PSA = prostate-specific antigen; RR = risk ratio.

risk of dying of prostate cancer with the risk of dying from another cause (i.e., severity and number of comorbidities that contribute to the patient’s health status in general).

4.3.1. Radical prostatectomy

The main prostate cancer recommendations for radical prostatectomy are summarised in Table 4. Results of a randomised trial of 695 men (with a mean age of 65 years) with localised prostate cancer demonstrate that compared with conservative management, radical prostatectomy reduced prostate cancer mortality and risk of developing metastases, but that there was little or no further increase in benefit 10 or more years after surgery [93]. Other studies have reported 5-year PSA-free survival rates of 69–84% and 10-year PSA-free survival rates of 47–75% following RP [94–98]. The risk of death and of post-operative complications following RP is more a function of severity of comorbidities than of chronological age [33,99–101].

Urinary incontinence is a common complication of radical prostatectomy, with incidence being reported in the range of 3–74% [64]. Longitudinal follow-up indicates that incontinence rates progressively decrease between 3 and 24 months following surgery [102,103], however, the exact risk is difficult to evaluate because series differ in the definitions used, the type of surgical technique, time intervals considered since surgery and methods of quantification. Increasing age has been consistently identified has a risk factor of long-term incontinence following radical prostatectomy [33,104–106]. An analysis of 1291 men from the Prostate Cancer Outcome Study who underwent radical prostatectomy between 1994 and 1995, showed that age was significantly associated with the level of urinary control and frequency of incontinence after surgery [106]. At 24 months post-surgery, men aged 75–79 years had the highest level of total incontinence compared with those aged <75 years (13.8% versus 0.7–3.6%, \( p = 0.03 \)) (Table 5). Similarly, incontinence >2 times per day was more frequently reported in men aged 75–79 years than younger ones (40.8% versus 10.0–15.9%, \( p < 0.001 \)) (Table 5). Younger men also regained urinary function sooner than older men. Analysis of 11,522 men from the SEER-Medicare data base who underwent RP between 1992 and 1996, confirmed that long-term incontinence was signifi-

Table 4
Summary of guidelines for radical prostatectomy, highlighting references to age.

<table>
<thead>
<tr>
<th>Guideline, year</th>
<th>Guideline/recommendation</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUA, 2007 update [64]</td>
<td>Based on the panel's interpretation of the literature and panel opinion, the patient most likely to benefit from radical prostatectomy would have a relatively long life expectancy, no significant surgical risk factors and a preference to undergo surgery</td>
<td>Candidates for surgery should have: (1) An expected longevity longer than the expected morbidity of his cancer if left untreated (2) No significant surgical risk factors or serious comorbid conditions that would contraindicate an elective operation (NCCN) (3) A willingness to undergo surgery following a discussion of the risks, operative side effects, natural history and options</td>
</tr>
<tr>
<td>EAU, 2008 update [63]</td>
<td>Radical prostatectomy is a standard treatment in patients with stage T1b–T2b, N0–N1, M0 disease and a life expectancy &gt;10 years. Radical prostatectomy is optional in younger patients with stage T1a disease and a long life expectancy. Radical prostatectomy is optional for selected patients with limited ≤T3a, Gleason score ≤6, PSA level of &lt;20ng/mL and long life expectancy.</td>
<td></td>
</tr>
<tr>
<td>NCCN, 2009 [65]</td>
<td>Radical prostatectomy is appropriate for any patient whose tumour is clinically confined to the prostate, has a life expectancy of 10 years or more, and has no serious comorbid conditions that would contraindicate an elective operation.</td>
<td></td>
</tr>
</tbody>
</table>

NCCN = National Comprehensive Cancer Network; RP = radical prostatectomy.
cantly related to increasing age (24% in men ≥75 years versus 17–18% in those <75 years, \( p < 0.001 \)), but also demonstrated a relationship with the severity of comorbidities (ranging from 18% for Charlson 0–21% for Charlson ≥2, \( p = 0.03 \)) [33]. In a recent series of 3477 consecutive radical retropubic prostatectomies performed by a single surgeon between 1983 and 2003, return to full continence evaluated at least 18 months following surgery significantly decreased with age (40–59 years, 60–69 years, 93%, ≥70 years, 86%) [104]. Lastly, in a Swedish study of 376 men with localised prostate cancer who were randomly assigned to radical prostatectomy or watchful waiting (median follow-up of 4 years), urinary leakage more than once a week was more common in the group who underwent surgery (49% versus 21%; unadjusted relative risk 2.3; 1.6–3.2), but on average, well-being and subjective QoL were similar in both groups [107]. In this study, 45 patients received androgen deprivation therapy, which negatively affected self-assessed QoL compared with men assigned to watchful waiting. Quality of life was also associated with the number of physical symptoms, was lower with longer follow-up time in both groups, and was statistically significantly better in the watchful waiting group [108]. However, although many patients adapt to the adverse outcomes of surgery such as incontinence, individual patients’ responses to surgical results vary greatly [109], emphasising the importance of counselling regarding the potential benefits and harms of surgery and of treatment decisions being made on an individual level. In clinical practice, it is important to

Table 5
Distribution (%) of urinary function after radical prostatectomy by age and period [106].

<table>
<thead>
<tr>
<th>Age, year</th>
<th>Level of urinary control</th>
<th>Frequency of incontinence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total control</td>
<td>Occasional leakage</td>
</tr>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;60</td>
<td>90.9</td>
<td>6.8</td>
</tr>
<tr>
<td>60–64</td>
<td>88.4</td>
<td>9.8</td>
</tr>
<tr>
<td>65–74</td>
<td>83.8</td>
<td>11.3</td>
</tr>
<tr>
<td>75–79</td>
<td>86.4</td>
<td>9.6</td>
</tr>
<tr>
<td>12 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;60</td>
<td>42.0</td>
<td>48.5</td>
</tr>
<tr>
<td>60–64</td>
<td>31.1</td>
<td>53.4</td>
</tr>
<tr>
<td>65–74</td>
<td>33.8</td>
<td>47.6</td>
</tr>
<tr>
<td>75–79</td>
<td>35.4</td>
<td>28.2</td>
</tr>
<tr>
<td>24 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;60</td>
<td>47.6</td>
<td>46.4</td>
</tr>
<tr>
<td>60–64</td>
<td>34.0</td>
<td>55.8</td>
</tr>
<tr>
<td>65–74</td>
<td>38.1</td>
<td>50.4</td>
</tr>
<tr>
<td>75–79</td>
<td>48.0</td>
<td>11.1</td>
</tr>
</tbody>
</table>

Table 6
Summary of guidelines for radiation therapy, highlighting references to age.

<table>
<thead>
<tr>
<th>Guideline, year</th>
<th>Guideline/recommendation</th>
<th>Further comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUA, 2007 update [64]</td>
<td>The patient most likely to benefit from radiotherapy would have a relatively long life expectancy, no significant risk factors for radiation toxicity and a preference for radiotherapy</td>
<td>Well tolerated Insufficient follow-up to compare survival outcomes of EBRT and brachytherapy</td>
</tr>
<tr>
<td>NCCN, 2009 [65]</td>
<td>Treatment recommendations are based on anticipated life expectancies and risk of recurrence: [ \text{Low-risk of recurrence (stage T1 to T2a, low Gleason score [2–6], and PSA level &lt;10 ng/mL): RT (3D external beam or brachytherapy) is an acceptable strategy in patients whose age or comorbidity leads to a life expectancy &lt;10 years as well as patients with a life expectancy of ≥10 years} ]</td>
<td>Intermediate-risk of recurrence (stage T2b to T2c, Gleason score of 7, or PSA level 10–20 ng/mL): RT (external beam with or without brachytherapy) is a treatment option in men with a life expectancy &lt;10 years and those with a life expectancy ≥10 years</td>
</tr>
<tr>
<td>EAU, 2008 update [63]</td>
<td>Treatment decision should be based on TNM classification, Gleason Score, baseline PSA, age, comorbidity, life expectancy and QoL: [ \text{3D-CRT with or without IMRT is recommended for patients with T1c–T2c N0 M0 disease. There is fairly strong evidence that intermediate-risk patients (T2b or PSA 10–20 ng/mL, or Gleason Score 7) benefit from dose escalation. Transperineal intrastitial brachytherapy without permanent implants may be proposed to patients with cT1–T2a, Gleason score ≤7 (or 3 + 4), PSA ≤10 ng/mL, prostate volume ≤50 mL, without a previous TURP and with a good IPSS} ]</td>
<td>Transperineal intrastitial brachytherapy without permanent implants may be proposed to patients with cT1–T2a, Gleason score ≤7 (or 3 + 4), PSA ≤10 ng/mL, prostate volume ≤50 mL, without a previous TURP and with a good IPSS</td>
</tr>
</tbody>
</table>
consider that older patients who have a good mobility score and are physically active, are likely to suffer a similar level of incontinence to their younger counterparts. Conversely, older patients who live a sedentary lifestyle have a much higher chance of experiencing persistent incontinence after surgery. Pelvic floor muscle training, before or after radical prostatectomy, may assist the more rapid return to continence in senior adults, but data from clinical trials are needed to confirm this [110,111].

With all the above factors considered, it appears reasonable that senior adult patients who are candidates for radical prostatectomy should be considered to satisfy the following conditions: (1) patients who have poor-risk prostate cancer (i.e., having a high-risk of prostate cancer-specific death), (2) patients who are fit, either in the good health or vulnerable groups (i.e., having a high probability of survival at 5–10 years), and (3) patients with a low-risk of incontinence (good pelvic floor tone).

### 4.3.2. Special considerations for patients with prior trans-urethral resection of the prostate

Patients who have had trans-urethral resection of the prostate (TURP) for benign prostatic hyperplasia and have later developed prostate cancer may not be eligible for certain treatment options including brachytherapy. Use of permanent low-dose rate brachytherapy requires sufficient tissue to hold the radioactive seeds used in place. Conversely, the use of high-intensity focused ultrasound (HIFU) often requires an initial TURP. These considerations do not differ in older and in younger patients.

### 4.3.3. External beam radiation therapy

The main prostate cancer recommendations for external beam radiation therapy (EBRT) are summarised in Table 6. Results of a systematic review of EBRT trials in prostate cancer, which included a total of 152,614 patients have recently been published [112]. A single-institution, non-randomised study evaluated the risk of biochemical recurrence in 1682 patients treated either by radical prostatectomy (63%) or EBRT (37%) for localised prostate cancer [113]. Eight-year biochemical relapse-free survival rates were comparable for radical prostatectomy and EBRT (72 and 70%, respectively, p = 0.010). The slightly higher rate of relapse with EBRT was attributed to an increased number of ‘high-risk’ patients in this group and the known worse outcome of the standard dose radiation therapy (<72 Gy) compared with higher doses. Age (<65 versus ≥65 years) was not an independent predictor of treatment relapse (p = 0.78) [113]. The 5-year follow-up of 1591 newly diagnosed men with localised prostate cancer enrolled in the Prostate Cancer Outcome Study and treated either with either radical prostatectomy or EBRT demonstrated that urinary incontinence was significantly more common with surgery (14–16%) than with EBRT (4%), while bowel urgency and painful haemorrhoids were significantly worse with EBRT (29 and 20%, respectively) than with surgery (19 and 10%, respectively) [114]. Several studies have reported that senior adult patients undergoing radiation therapy for prostate cancer can achieve similar outcomes in terms of cancer control and treatment-related late morbidity to that achieved in younger patients [115–118]. Analysis of medical records from 527 patients with non-metastatic prostate cancer effectively showed no relationship between age (<60, 60–69, 70–74, and ≥75 years) and risk of acute or late genitourinary or gastrointestinal toxicity after EBRT [119]. However, a multivariate analysis of data from 381 patients who underwent EBRT for localised prostate cancer showed that age at diagnosis was an independent predictor of time to death from prostate cancer (p = 0.04) [120]. In those patients with ‘high-risk’ prostate cancer, age ≥75 years at diagnosis predicted for a shorter median time to death from prostate cancer (6.3 years versus 9.7 years; p = 0.002). A population-based study of 31,643 patients aged 65–85 years with non-metastatic prostate cancer who were treated with EBRT and/or brachytherapy, showed improved 5-year and 8-year survival rates for patients with stage T3/T4 disease who received adjuvant androgen deprivation therapy, but no survival advantage for men with T1/T2 disease [121]. These findings are consistent with practice guidelines. However, the survival advantage achieved by combining EBRT and androgen deprivation therapy in high-risk prostate cancer patients may apply only to those with no or minimal comorbidities (i.e., fit patients) as suggested by a recent publication by D’Amico et al. [34].

### 4.3.4. Brachytherapy

Brachytherapy is indicated in patients with clinical stage T1b–T2a–b tumours, N0, M0, Gleason ≤6 and PSA level ≤10 ng/mL with a prostate volume <60 cm³, and a good IPSS score [63]. This technique appears to be a suitable choice of therapy for older prostate cancer patients. Nevertheless, the benefit of brachytherapy in terms of survival in senior adult patients with low-risk localised prostate cancer is not established. Moreover, even though complications arising from the use of brachytherapy appear to be slightly less severe than those associated with EBRT or radical prostatectomy, evidence from the SEER database suggests that urinary, bowel and erectile complications increase significantly with both age and severity of comorbidities [122]. In multivariate analysis, Charlson comorbidity index was a stronger predictor of brachytherapy complications than chronological age [122]. However, the place of brachytherapy in senior adults is questionable as indications for brachytherapy are almost similar to those of a watch and wait policy.

### 4.3.5. High-intensity-focused ultrasound

High-intensity-focused ultrasound of the prostate is a minimally invasive procedure and has emerged as alternative therapeutic option in patients with clinically localised prostate cancer [123,124], but remains an experimental treatment [63]. Longer follow-up and comparison with established therapies are required before HIFU can be recommended as a standard treatment option. Should the efficacy...
of this treatment approach be confirmed, it could be an option for senior adult patients who are unable to undergo surgery or radiation therapy as curative treatment for localised prostate cancer. HIFU may be an option for salvage treatment of local relapse in older patients who have received prior radiation therapy before and who continue to be N0M0.

4.3.6. Cryosurgery of the prostate

Freezing of the prostate is performed by the placement of cryoneedles under transrectal ultrasound guidance. Patients who are ideal candidates for cryosurgery are those who have organ-confined prostate cancer and those with disease with minimal extension beyond the prostate [125]. The prostate should be ≤40 mL in size, PSA serum levels should be <20 ng/mL and the biopsy Gleason score should be ≤7. In a recent meta-analysis of publications related to cryosurgery, it was demonstrated that no controlled trial was available for analysis, no survival data were presented, and no validated biochemical surrogate endpoints were available. Cryosurgery showed a progression-free survival (PFS) of 36–92% (projected 1- to 7-year data), depending on risk groups and the definition of failure. Negative biopsies were seen in 72–87% of patients [126]. However, the available data are still insufficient to recommend this technique as standard treatment.

4.3.7. Androgen deprivation therapy

Androgen deprivation therapy is widely used in localised prostate cancer, especially in senior adult patients. Analysis of the SEER data base showed that between 1991 and 1999, among men aged ≥80 years with localised, low-to-moderate grade tumours, primary luteinising hormone–releasing hormone (LH–RH) agonist use increased from 3.7 to 30.9% (p < 0.001) [127]. However, primary androgen deprivation therapy is not a standard in localised prostate cancer [63]; it may be employed for patients who need symptom palliation and who are unfit for curative therapy, but early use of androgen deprivation therapy remains controversial. A prospective study performed by the European Organisation on Research and Treatment of Cancer compared immediate versus delayed androgen deprivation therapy (i.e., use on symptomatic disease progression versus use on occurrence of serious complications) in patients with non-metastatic prostate cancer who were not suitable for curative treatment [128]. The results revealed that immediate androgen deprivation therapy had a modest overall survival (OS), but no impact on cancer-specific death rate and overall symptom-free survival. Nevertheless, a recent subanalysis of this trial suggested a survival advantage for early androgen deprivation therapy in patients at high-risk (PSA >50 ng/mL and PSA DT <12 months) of dying from their prostate cancer [129].

Moreover, androgen deprivation therapy is associated with a significant number of side effects [130], including osteopenia with an increased risk of fractures [131–134] and metabolic alterations with an increased risk of cardiovascular events [135–137]. Bone mass decreases with age and men ≥75 years of age are at particularly high-risk of developing fractures [138]. A high prevalence of osteopenia and osteoporosis has been reported in men with prostate cancer, including those not undergoing ADT [131,139]. Periodic measurement of bone mineral density among men undergoing androgen deprivation therapy would facilitate the early detection of osteoporosis [131]. Targeting potentially modifiable risk factors such as low body mass, weight loss, smoking, alcohol intake and low physical activity could help to reduce the risk of osteoporosis [131,138]. Senior adult patients with a low baseline bone mineral density or a high rate of bone loss during hormone therapy could be considered candidates for bisphosphonate therapy, the use of which has been shown to prevent bone loss during androgen deprivation therapy [140]. The results of a Medicare population-based cohort study of 73,196 senior adults (mean age at diagnosis 74.2 years) who were diagnosed with locoregional prostate cancer (from 1992 to 1999) also suggest that LHRH agonist treatment may be associated with a significantly increased risk of incident diabetes (adjusted HR = 1.44; p < 0.001), coronary heart disease (adjusted HR = 1.11; p = 0.03), acute myocardial infarction (adjusted HR = 1.11; p = 0.03) and sudden cardiac death (adjusted HR = 1.16; p = 0.004) [135]. The increased risk of diabetes and coronary heart disease was evident in the short-term (1–4 months after treatment initiation) [141]. Cross-sectional studies of men undergoing long-term (≥1 year) androgen deprivation therapy also revealed a higher prevalence of diabetes and metabolic syndrome than controls [137]. Androgen deprivation therapy in men aged ≥65 years seems also associated with a shorter time to fatal myocardial infarction [136] and an increased risk of death from cardiovascular causes following radical prostatectomy [142].

Anti-androgens have also been studied in the adjuvant setting of standard care. A large randomised trial compared bicalutamide (150 mg once daily) versus placebo, in addition to standard care versus standard care alone in patients with localised and locally advanced, non-metastatic prostate cancer [143]. At a median follow-up of 7.4 years, no benefit in PFS was achieved by the addition of bicalutamide to standard care. However, in locally advanced disease, bicalutamide significantly improved PFS irrespective of standard care. In the overall adjuvant therapy population with locally advanced disease, there was no significant difference in OS between the treatment groups (HR 0.95; 95% CI 0.77–1.16; p = 0.59), but bicalutamide significantly improved OS in patients with locally advanced disease who had received radiation therapy. Bicalutamide also produced a trend towards improved OS in patients with locally advanced disease otherwise undergoing watchful waiting. However, no difference in OS was observed in men undergoing prostatectomy.

4.3.8. Watch and wait policy

Patients who are not receiving immediate treatment may be managed in two ways: ‘watchful waiting’ – that is expectant management – or ‘active surveillance’—that is delayed intervention in case of progression. These strategies are very
Table 7
Distribution of outcomes (%) after 15 years follow-up for men with a putatively localised prostate cancer managed conservatively, by age and Gleason score at diagnosis (data selected from Table 3 from Albertsen et al. [145]).

<table>
<thead>
<tr>
<th>Gleason score</th>
<th>Age at diagnosis (years)</th>
<th>65–69</th>
<th>70–74</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Alive (%)</td>
<td>Deceased from other disease (%)</td>
<td>Deceased from prostate cancer (%)</td>
</tr>
<tr>
<td>2–4</td>
<td>38</td>
<td>56</td>
<td>6</td>
</tr>
<tr>
<td>5</td>
<td>35</td>
<td>55</td>
<td>10</td>
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<td>6</td>
<td>25</td>
<td>48</td>
<td>27</td>
</tr>
<tr>
<td>7</td>
<td>11</td>
<td>36</td>
<td>53</td>
</tr>
<tr>
<td>8–10</td>
<td>3</td>
<td>25</td>
<td>72</td>
</tr>
</tbody>
</table>

Different in their objectives. The rationale for ‘watch and wait’ policy management is based on the premise that many patients who die while having prostate cancer will not die as a result of this disease. Nevertheless, these patients should undergo careful clinical follow-up; those who have symptomatic disease are likely to benefit from ad-hoc treatment. Suitable candidates for active surveillance are patients who have ‘low-risk’ tumours (low Gleason score, PSA level and clinical stage), those who have a potential risk of disease progression for a short period of time (i.e., have a short life expectancy owing to advanced age and/or the presence of comorbidities), and/or those who express a personal preference to avoid or delay the side effects of definitive therapy. Nevertheless, caution is recommended in offering active surveillance to older patients as undergrading of biopsy Gleason is common in men of advanced age, especially in those who have high PSA levels [144].

Advantages of ‘watch and wait’ and ‘active surveillance’ include avoiding side effects of definitive therapy, maintenance of QoL and reduced risk of unnecessary treatment for small, indolent tumours. Disadvantages include risk of progression or development of metastases, increased anxiety, and frequent medical examinations. However, in the specific scope of treatment of the senior adult population, there is no reason to perform periodic biopsies for patients receiving “expectant management or active surveillance” [65].

The decision between ‘watch and wait’ or ‘active surveillance’ approach in senior adult patients should not be made based solely on chronological age and methods to estimate individual risk of dying of other causes and health status should be employed. Results of a retrospective cohort study of 767 men with localised prostate cancer who received conservative management showed that within a 15-year follow-up, the risk of death from prostate cancer increased with increasing Gleason score, regardless of age at diagnosis (Table 7) [145]. Men with Gleason scores of 7–10 who received conservative management were at high-risk of death from prostate cancer, even when cancer was diagnosed at 65–69 or 70–74 years of age [145]. These results define the group of patients with localised prostate cancer who are likely to benefit from the ‘watch and wait’ policy or ‘active surveillance’: those in the low-risk group defined by D’Amico et al. [69].

Expert Panel recommendation for localised prostate cancer:
- Treatment decisions should be based on health status evaluation (which is mainly driven by the severity of associated comorbid conditions) rather than chronological age, and also on patient preference.
- ‘Fit’ and ‘vulnerable’ senior adults in the ‘high-risk’ group of the D’Amico risk classification with a chance of surviving >10 years are likely to benefit from curative treatment.
- Senior adults in the ‘low-risk’ and ‘intermediate-risk’ groups of the D’Amico risk classification are likely to benefit from an active surveillance approach.
- The benefits and harms of androgen deprivation therapy for localised prostate cancer should be carefully balanced in senior adults. Attention may be drawn to an increased risk of diabetes, cardiovascular complications and osteoporosis and bone fractures.

5. Advanced prostate cancer

This section concerns patients who are unlikely to benefit from curative treatment, i.e., patients with locally advanced disease (T4N0 and T1-4N1) or metastatic disease (M1).

5.1. Androgen deprivation

5.1.1. First-line hormonal treatment

Androgen deprivation therapy is the mainstay of treatment for patients with metastatic prostate cancer. It delays progression, prevents potentially catastrophic complications and effectively palliates symptoms. Surgical castration and castration by LH–RH agonists are the standard of care. In terms of efficacy, there is no established difference between these treatments. However, the use of LH–RH agonists is usually preferred because it avoids the physical and psychological discomfort of bilateral orchietomy [63]. There is no
evidence of a survival benefit with complete androgen blockade [146]. Finally, intermittent androgen deprivation therapy and anti-androgen monotherapy are not standard treatments. They may be discussed in a case-by-case setting, but cannot be recommended [146bis].

Analysis of a SEER-Medicare sample including more than 100,000 men (half of whom had prostate cancer and half of whom did not) showed that men receiving androgen deprivation therapy were more likely to have depressive, cognitive and constitutional disorders than men who did not [147]. This was in fact primarily attributed to the fact that men receiving androgen deprivation therapy were generally older, had more comorbid conditions and had more advanced prostate cancer [147].

The NCCN recommendations state that men receiving or starting androgen deprivation therapy should be evaluated for risk of osteoporosis [65]. This includes family history of osteoporosis, low body weight, prior fractures, excessive alcohol use, smoking, glucocorticoid use, low vitamin D levels and other medical comorbidities. All men receiving ADT should receive calcium and vitamin D supplementation and baseline bone mineral density should be determined. The routine use of bisphosphonates in patients undergoing ADT is not recommended unless there is documented evidence for the presence or a risk of osteoporosis [148] or androgen-independent prostate cancer with skeletal metastases.

5.1.2. Second-line hormonal treatment

The standard procedure for second-line hormonal treatment is cessation of anti-androgen therapy if given as first-line treatment in association with a LH–RH agonist. Thirty percent of patients derive a benefit from the anti-androgen withdrawal approach [149]. When the LH–RH agonist is used as monotherapy in the first-line setting, patients may benefit from the addition of an anti-androgen. However, it is important to note that no survival benefit of second- and subsequent lines hormone therapy has yet been established. When prostate cancer becomes castration-refractory it is recommended to continue LH–RH agonist therapy, but again, there are no available data supporting this approach specifically in senior adult patients.

5.2. Chemotherapy in castration-refractory prostate cancer

5.2.1. First-line chemotherapy

Docetaxel-based regimens are the unique palliative treatments that have demonstrated a survival benefit in patients with castration-refractory prostate cancer (CRPC) in two Phase III trials—SWOG 9916 and TAX 327 [150,151]. Docetaxel-based regimens are now the standard of care for patients with CRPC who are candidates for cytotoxic treatment [63,65]. Chemotherapy for patients with non-CRPC disease is being investigated in clinical trials, but its use currently remains experimental outside of the CRPC setting.

In the TAX 327 study, docetaxel-based therapy was associated with significant pain relief, reduction in analgesic consumption, and improved QoL [151]. Patients who received docetaxel 75 mg/m² every 3 weeks plus prednisone experienced a significant OS benefit compared with those who received either weekly docetaxel at 30 mg/m² plus prednisone or 3-weekly mitoxantrone plus prednisone. In subgroup analyses, the survival benefit with 3-weekly docetaxel was consistent between age classes (<65 years, ≥65 years and ≥75 years) [152]. Similar conclusions were drawn from updated results in March 2007 [153]; the HRs for OS in patients ≤68 years and >68 years were 0.81 and 0.77, respectively, for docetaxel 3-weekly schedule compared with mitoxantrone. Using a more extreme age cut-off of 75 years, the HR was of 0.80. A prospective study was performed comparing treatment toxicity and pharmacokinetic parameters in patients aged <65 years and ≥65 years receiving treatment with docetaxel 75 mg/m² every 3 weeks for solid malignancies [154]. The study results showed no difference in the pharmacokinetic profile of docetaxel between the two age groups. There was a similar incidence of non-haematological toxicities between the two groups although there was a non-significant increase in the incidence of grade 4 neutropenia and febrile neutropenia in the older group.

Although weekly docetaxel is not registered for the treatment of metastatic CRPC, it is often perceived by oncologists to have a better haematological toxicity profile compared with the 3-weekly regimen, especially in senior adults. An analysis of pooled data from two phase II trials of weekly docetaxel showed no difference between older (>70 years) and younger (<70 years of age) patients with metastatic CRPC in terms of PSA response rate (p = 0.54), measurable disease response rate (p = 0.84), median time to progression (p = 0.30) and median OS (p = 0.98) [155]. The incidence of grade 3–4 toxicities was similar in both groups. A randomised phase II study compared treatment with weekly docetaxel (35 mg/m²) plus prednisone with prednisone alone in 109 men (median age 70 years) with metastatic CRPC [156]. Patients were not permitted to cross over from one therapy to the other. The results demonstrated a significant increase in PSA response rate, pain relief and, more importantly, in median OS in patients who received weekly docetaxel plus prednisone compared with prednisone alone. The main AEs were non-haematological toxicities (nail changes, alopecia, conjunctivitis, asthenia, neuropathia); moreover no febrile neutropenia was reported. A survey of 175 patients aged ≥75 years who received, according to clinical judgment, either the standard 3-weekly regimen of docetaxel plus prednisone or an adapted regimen administered weekly, showed that senior adult patients with a good performance status responded to docetaxel therapy in similar fashion to younger patients and that the chemotherapy was generally well tolerated. Weekly docetaxel was associated with a significantly lower rate of febrile neutropenia than patients treated with the 3-weekly regimen (1% versus 9.5%, p = 0.02) [157]. However, the incidence of severe non-haematological AEs (mainly fatigue, 20%) was partic-
ularly high with the weekly regimen, resulting in a frequent early discontinuation (30%) [157]. A retrospective study of a cohort of CRPC patients who had some form of geriatric evaluation showed that patients who are likely to receive 3-weekly docetaxel had typically a good health status or a vulnerable status that could be reversed with geriatric intervention, while those who were likely to receive weekly docetaxel were usually frail patients [158]. Senior adult patients treated with docetaxel at a dose of 75 mg/m² every 3 weeks have been shown to experience grade 4 neutropenia and febrile neutropenia more commonly than younger patients. To date, there is no evidence to support the use of primary prophylactic G-CSF in this setting. Nevertheless, G-CSF may be given in selected cases, based on specific toxicity risk [50].

5.2.2. Second-line chemotherapy

There are generally two options for second-line chemotherapy in metastatic CRPC patients: the first is to switch to mitoxantrone plus prednisone, the benefits of which are minimal as demonstrated in the TAX 327 trial [159]. The second option is reserved for patients who experience a good response to docetaxel plus prednisone in the first-line setting, who may benefit from second-line treatment with docetaxel plus prednisone [160–162].

In conclusion, docetaxel is the standard treatment in senior adult patients with CRPC. The chemotherapy schedule to be used for each patient should be determined according to the patient’s health status and could be given together with specific geriatric interventions.

5.3. Radiation therapy/radiopharmaceuticals

Radiation therapy and radio pharmaceuticals are useful tools for the treatment of painful lesions in senior adult patients with CRPC. Radiation therapy is the first choice for localised painful metastasis and two radiopharmaceuticals – strontium [163,164] and samarium [165] – have demonstrated a significant improvement in pain control in randomised trials when compared to localised radiation therapy. It is possible to repeat samarium administration [166] and it has been shown that this approach does not result in clinically significant platelet toxicity [167]. As yet, no study has been conducted specifically in senior adult patients, but the toxicity profile of radiopharmaceuticals appears appropriate for administration in this patient population. There are no published data on the effect of radiopharmaceuticals in patients who have previously received chemotherapy, although such an approach may be offered to frail patients who have pain and are unable to receive adapted chemotherapy.

5.4. Bisphosphonates

The use of bisphosphonates for the treatment or prevention of androgen deprivation-induced osteoporosis has been discussed earlier (see Section 5.1). In a randomised phase III study of men (mean age 71–72 years) with CRPC and history of bone metastases, administration of zoledronic acid resulted in a 25% reduction in the risk of ≥1 skeletal-related event(s) (pathological fracture, spinal cord compression, surgery or RT to bone, or a change in antineoplastic therapy to treat bone pain) compared with placebo [168]. The increase in pain and analgesic scores was greater in patients who received placebo compared with those who received zoledronic acid, but there were no differences between the two groups in terms of disease progression, performance status, or QoL scores [168]. There is no specific information on the effects of bisphosphonates use in senior adult patients. The NCCN and the EAU guidelines recommend the use of bisphosphonates in patients with painful metastases, stating that evaluation of renal function and the potential risk for jaw osteonecrosis should be performed [169].

Expert Panel recommendation for advanced prostate cancer:

• Androgen deprivation therapy is the first-line treatment in hormone-sensitive metastatic prostate cancer. Evaluation of mineral bone status and prevention of osteoporosis are recommended.
• In metastatic CRPC, chemotherapy with docetaxel (75 mg/m² every 3 weeks) is the standard for fit and vulnerable senior adults.
• The tolerability of the docetaxel 3-weekly regimen has not been specifically studied in frail senior adults. The place of weekly docetaxel in metastatic CRPC should be further evaluated.
• Palliative treatments include palliative surgery, radiopharmaceuticals, RT, medical treatments for pain and symptoms.

6. Conclusions

Senior adult patients with prostate cancer should be managed according to their individual health status, which is mainly driven by the severity of associated comorbid conditions and not according to chronological age.

Evidence-based medicine established guidelines must be applied in senior adult patients with prostate cancer in addition to that used for younger patients. Therefore, the standard and universally accepted NCCN and EAU guidelines should be adhered to, but nevertheless, their application must be modified according to the evaluation of health status of each individual patient.

One recommendation raised at the end of this review is that screening to detect asymptomatic prostate cancer in senior
adult patients should be more precisely defined. The question was not addressed earlier, because the answer requires the understanding of the importance of health status evaluation and depends on the results of treatment modalities in senior adult patients. PSA testing and DRE can detect prostate cancer before it becomes clinically evident (i.e., at an earlier stage), however, screening policy remains highly controversial and there is no clear evidence that screening for prostate cancer produces more benefit than harm for patients. The European Randomized Study of Screening for Prostate Cancer which included 162,243 men with a median follow-up of 9 years, demonstrated a reduced mortality from prostate cancer by 20% in the screening group, but this was associated with a high-risk of over diagnosis [170]. Conversely, the first report from the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial which included 76,693 US men followed for 7 years, revealed that the rate of death due to prostate cancer was very low and did not differ significantly between screened and non-screened groups [171]. Although prostate cancer incidence and related mortality increase with age, there is a similar trend for non-prostate cancer-related mortality. Hence, the probability that an individual could experience a survival benefit from prostate cancer screening, even with state of the art treatment, is likely to decrease with increasing age. In asymptomatic senior adults, screening may lead to the detection and treatment of prostate cancer that will not progress to clinically symptomatic disease during the patient’s life time. In addition, screening may be associated with psychological distress owing to the screening process itself, the diagnosis of cancer, or both. It is generally advised that screening (PSA blood test and DRE) should be offered annually to men ≥50 years of age with a life expectancy ≥10 years [172,173]. The US Preventative Services Task Force guidelines suggest that “if early detection improves health outcomes, the population most likely to benefit from screening will be men aged 50–70 years who are at average risk, and men over the age of 45 years who are at increased risk. Older men and men with other significant medical problems who have a probability of living fewer than 10 years are unlikely to benefit from screening [174].” It also advises that “men aged older than 70–75 years are unlikely to benefit substantially from screening because of their shorter life expectancy and higher false-positive rates” [175]. However, there is substantial variation in the chance that senior adult individual will be alive at 5 or 10 years after diagnosis. The probability largely depends on the number and severity of comorbid conditions and the patient’s functional status [176]. Hence, individualised cancer screening decisions would seem more appropriate than those based on strict chronological age criteria alone [43,177]. Surveys of PSA screening in the US community have shown that up to a third of men older than 75 years undergo PSA testing despite an average life expectancy of less than 10 years [178]. A framework for individualised decision-making has been proposed for cancer screening on senior adult patients. This involves assessing the balance of quantitative information such as risk of cancer death and likelihood of beneficial and adverse screening outcomes, and qualitative factors such as individual patients’ values and preferences [43,179]. The ‘pros’ and ‘cons’ of having a PSA test should also be discussed in light of the patient’s unique assessment. The NCCN has published guidelines on Prostate Cancer Early Detection to aid decision-making [180].

Conflict of interest

Dr. Droz has received conference honoraria from Sanofi-Aventis and has acted as consultant for Sanofi-Aventis and Pharmion.

Dr. Fitzpatrick has received conference honoraria from Sanofi-Aventis, GSK, and Pfizer.

Dr. Moul has received consultancies from Ferring, Astra-Zeneca, Sanofi-Aventis. Honoraria from Sanofi-Aventis, Astra-Zeneca, grants from GSK and other funding from Theralogix LLC.

Prof. Van Poppel is member of the advisory board of Astra-Zeneca, Gen Probe, Pfizer, Ferring, Sanofi-Aventis, Bayer, Antigenics and Wyeth.

Dr. Sternberg has to disclose honoraria from Sanofi-Aventis, Novartis and Pfizer.

Lodovico Balducci; Michel Bolla; Michael Kattan; Silvio Monfardini: No conflict of interest.

Mark Emberton, Steven Joniau, Arash Naeim, Fred Saad have not declared conflict of interest.

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Biography

Jean-Pierre Droz obtained his M.D. degree in 1975 at the Paris-VI University School of Medicine, followed by his Ph.D. at the Lyon-I Claude-Bernard University. He was formerly Chairman of the Department of Medicine at the Institut Gustave-Roussy in Villejuif and thereafter, was Chairman of the Department of Medical Oncology and Director of Teaching Program at the Centre Léon-Bérard in Lyon. He is Emeritus Professor of Medical Oncology at the Lyon-RTH Laennec School of Medicine and Scientific Consultant at the Centre Léon-Bérard. His major subjects of clinical research are genitorinary tumours, mainly germ-cell tumours and prostate cancer, geriatric oncology and endocrine tumours medical treatment. He was the chairman of the Genito-Urinary Tumour Group (GETUG) of the French Comprehensive Cancer Center Network (1994–1999). He is past-president of the SIOG (International Society of Geriatric Oncology) and serves as President of the Geriatric Oncology Board of the French National Cancer Institute. He has managed and/or participated to more than 80 clinical trials and has published more than 200 manuscripts in international peer-reviewed journals.