A Comment on the International Society of Geriatric Oncology Guidelines: Evidence-Based Advice for the Clinical Setting

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ABSTRACT

Largely a disease of older men, prostate cancer is likely to become a growing burden in the developed world as the population ages and overall life expectancy increases. Furthermore, prostate cancer management in older men is not optimal, reflecting the lack of training dedicated to senior adults in fellowship programs and the lack of specific guidelines to manage senior adults. The International Society of Geriatric Oncology (SIOG) convened a multidisciplinary Prostate Cancer Working Group to review the evidence base and provide advice on the management of the disease in senior age groups. The Working Group reported that advancing age, by itself, is not a reliable guide to treatment decision making for men with either localized or advanced prostate cancer. Instead, the SIOG guidelines

advise health care teams to assess the patient's underlying health status, which is largely dictated by associated comorbid conditions, but also by dependency in activities of daily living and nutritional status, and to use the findings to categorize the individual into one of four groups: healthy, vulnerable, frail, or terminally ill. The guidelines recommend that a patient categorized as healthy or vulnerable (i.e., with reversible problems following geriatric intervention) should receive the same approach to treatment as a younger patient. Frail patients should be managed using adapted treatment strategies, and the terminally ill should receive symptomatic/palliative care only. The guidelines may have ongoing relevance as the treatment options for prostate cancer expand. *The Oncologist* 2012;17(suppl 1):31–35

INTRODUCTION

Prostate cancer is largely a disease of older men. Data from the Surveillance, Epidemiology and End Results Medicare database for the years 2005–2009 indicate a median age at diagnosis of 67 years, with 70.6% of prostate cancer deaths occurring in men aged 75 years or over [1]. There is also growing evi-

dence that older men have more aggressive tumors [2], but only a minority receive curative therapy for localized high-risk disease [3]. Similarly, at an advanced stage where disease is incurable, many older patients are denied chemotherapy despite its proven benefits on survival, quality of life, and symptom relief [4].

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In the context of the aging demographic and increasing life expectancy in the developed world, prostate cancer is likely to be a growing burden for individuals, society, and for health care provision [5, 6]. It is perhaps surprising, therefore, that major clinical guidelines on prostate cancer have not specifically considered the essential parameters inherent in making treatment decisions in the management of older men with the disease [7–9]. To address this gap, and to provide practical advice for prostate cancer multidisciplinary teams, the International Society of Geriatric Oncology (SIOG) convened a Prostate Cancer Working Group comprised of urologists, radiation oncologists, medical oncologists and geriatricians from centers of expertise across Europe and North America. The panel's remit was to develop guidelines for the management of prostate cancer in senior men, based on a review of evidence obtained by a systematic search of the literature on the disease, including aspects relating to care of the elderly (e.g., evaluation of underlying health status, vulnerability, frailty of older patients).

The Working Group's recommendations were published in full in 2010 [5], followed by the separate publication of an abbreviated version, focusing on the practical aspects of patient assessment and the management of localized and advanced disease, designed to provide a convenient reference for use in the clinical setting [10]. Central to the recommendations is advice that a patient's health/fitness rather than his chronological age *per se* should be the guide to treatment decision making.

INDIVIDUAL PATIENT ASSESSMENT

Recent years have seen growth in the treatment options offering a survival benefit for men with prostate cancer, including advanced forms of the disease, with further novel approaches currently in development [11, 12]. However, when considering the management approach for an individual patient, it is imperative to assess whether he is likely to derive the treatment-related survival benefit (i.e., whether or not he is predicted to die of another cause before his prostate cancer is liable to become fatal) and whether he will be able to tolerate the toxicities of the proposed treatment. This assessment will serve not only to identify patients who are unsuitable for particular lines of treatment, but will also select individuals who are likely to obtain benefit from active treatment, despite being of advanced age.

Other prostate cancer guidelines also refer to patient life expectancy. For example, the European Association of Urology (EAU) and the National Comprehensive Cancer Network (NCCN) both indicate that radical prostatectomy is appropriate for men expected to live for 10 or more years [7, 8]. However, they do not make clear that the patient's chronological age is not a reliable guide to life expectancy or to his likelihood of benefiting from treatment [10]. There are, of course, published values for median life expectancy according to current age [10, 11], which are useful for epidemiological purposes but not for individual assessment. These data reflect a wide range of likely survival according to the patient's underlying fitness, vulnerability, and frailty.

After examining the evidence base, the SIOG Working

Group identified three key patient factors that affect the survival of older individuals with prostate cancer: comorbidities (assessed using the Cumulative Illness Score Rating–Geriatrics), dependency (assessed using the Activities of Daily Living [ADL] and Instrumental Activities of Daily Living [IADL] scales) and nutritional status (indicated by the degree of weight loss in the previous 3 months). When a patient is deemed to be vulnerable or frail, a comprehensive geriatric assessment may be warranted. A detailed explanation of these key factors and their assessment is included in the full guidelines document [5].

The SIOG Working Group explains that these key assessment tools provide a rapid and simple evaluation, allowing the individual patient to be classified as follows [10]:

1. Healthy (controlled comorbidities, full independence in daily living and good nutritional status)
2. Vulnerable (reversible impairment)
3. Frail (irreversible impairment)
4. Terminally ill

For the purpose of this evaluation, vulnerable patients are those who are dependent in one or more IADL but not in ADL, who present with one comorbid uncontrolled condition, or who are at risk of malnutrition [10]. Geriatric impairments in vulnerable patients should be reversible through geriatric intervention. Patients who are dependent in one or more ADL, present with two or more uncontrolled comorbid conditions, or have severe malnutrition are classified as frail. Geriatric problems in frail patients cannot be reversed with geriatric intervention [10]. Although these criteria may not represent standardized nomenclature for geriatric oncology, they provide practical advice on which individualized assessment can be based.

The SIOG guidelines state that this four-group categorization, rather than chronological age, should be used to guide treatment decisions for men with prostate cancer, whether localized or metastatic [10]. Of note, the SIOG Working Group's recommendation for men in the healthy category is that they should receive the same treatment as younger patients. Vulnerable patients may be recategorized as healthy once underlying health impairments have been reversed. Frail patients should be managed using adapted treatment strategies, and the terminally ill should receive symptomatic/palliative care only.

TREATMENT DECISIONS IN LOCALIZED PROSTATE CANCER

The objective of therapy for localized prostate cancer is to be curative [10], either by performing a radical prostatectomy or external beam radiotherapy or brachytherapy [7–9, 13]. Other options include androgen-deprivation therapy (ADT) and watch and wait, but have no curative intent [7–9, 13]. The choice of intervention is based on risk stratification of the tumor as well as the individualized patient assessment described above. In its examination of the literature, the SIOG Working Group found that only a minority of older men in both Europe and the U.S. received curative treatment for localized prostate

Figure 1. Treatment decision algorithm for older men with localized prostate cancer, based on the International Society of Geriatric Oncology four-group categorization [5, 10].

Abbreviations: CISR-G, Cumulative Illness Score Rating–Geriatrics; IADL, instrumental activities of daily living. Adapted from Droz JP, Balducci L, Bolla M et al. Management of prostate cancer in older men: Recommendations of a Working Group of the International Society of Geriatric Oncology. *BJU Int* 2010;106:462–469, with permission.

cancer, despite being more likely than younger men to have large, high-grade tumors [10, 14, 15].

The SIOG Working Group strongly cautions against the simple assumption that older men are likely to die of causes other than prostate cancer, since those with a high Gleason score are more likely to die of prostate cancer than from another cause [16]. The SIOG Working Group's recommendations for the management of localized prostate cancer in older men are summarized in a treatment algorithm (Figure 1) [5, 10]. A risk-stratification tool developed by D'Amico et al. can be used to identify men with high-risk disease, according to the disease stage at presentation, Gleason score at tumor biopsy, and prostate-specific antigen level [17].

For older men, the choice of intervention requires balancing the individual patient's risk of dying from his prostate cancer (i.e., the tumor grade/stage), his likelihood of dying from another cause (i.e., the findings of his health assessment, as described above), and the preferences of the patient himself. Hence at one extreme, a fit/healthy older man with high-risk disease is likely to benefit from curative treatment, whereas an individual with low-risk disease may be suitable for active surveillance; a low-risk patient with severe comorbidities or a preference to avoid experiencing treatment toxicity is a candidate for watch and wait. The SIOG Working Group also warns that the potential benefits of ADT for localized prostate cancer should be balanced against the risk of diabetes, cardiovascular complications, and osteoporosis in the older age group [10].

TREATMENT DECISIONS IN ADVANCED PROSTATE CANCER

The standard of care for metastatic prostate cancer is ADT, initially using a luteinizing hormone-releasing hormone (LHRH) agonist [7, 8, 10]. When treating older men, the SIOG guide-

lines recommend assessment of bone mineral status with the aim of preventing osteoporosis and fractures [10].

When the disease becomes castrate resistant, docetaxel-based chemotherapy is presently the mainstay of regulatory approved treatment [18]. Again, chronological age is not regarded as a reason to withhold chemotherapy, which can improve survival, pain control, and quality of life, and has been shown to be effective and tolerable in older as well as younger patients [19, 20]. A 3-weekly docetaxel regimen is the standard of care for metastatic castrate-resistant prostate cancer (mCRPC) [18] and is recommended by the SIOG guidelines for healthy older men and the vulnerable group [10]. The tolerability of the docetaxel 3-weekly regimen has not been specifically studied in frail senior patients with poor performance status and severe comorbidities. In practice, weekly docetaxel is often perceived by physicians as having less hematologic toxicity than the 3-weekly regimen in such patients [21], but further research into the efficacy of this approach is needed. The SIOG Working Group's recommendations for the management of advanced prostate cancer in older men are summarized in a treatment algorithm (Figure 2) [5, 10].

Since the SIOG Working Group met to consider the treatment of older men with prostate cancer, further advances have been made in the management of advanced disease. Two treatments—cabazitaxel and abiraterone—have been approved by the U.S. Food and Drug Administration and the European Medicines Agency, based on survival benefit (versus mitoxantrone for cabazitaxel [22] and versus placebo for abiraterone [23]) in patients with mCRPC that progresses during or after docetaxel-based chemotherapy. There are also promising data emerging on a variety of novel interventions. Among these are MDV3100, a first-in-class androgen-receptor signaling inhibitor [24], and Alpharadin, a new radioisotope that induces

Figure 2. Treatment decision algorithm for older men with advanced prostate cancer, based on the International Society of Geriatric Oncology four-group categorization [5, 10].

Abbreviations: CISR-G, Cumulative Illness Score Rating–Geriatrics; IADL, instrumental activities of daily living. Adapted from Droz JP, Balducci L, Bolla M et al. Management of prostate cancer in older men: Recommendations of a Working Group of the International Society of Geriatric Oncology. *BJU Int* 2010;106:462–469, with permission.

double-strand DNA breaks in adjacent tumor cells [25]. Regulatory approval for these new approaches is anticipated in the near future. The survival advantages reported in prostate cancer trials are not influenced by age [22, 23], and we suggest that the SIOG recommendation to treat healthy and vulnerable older men in the same way as younger men may remain valid in the new and emerging post-docetaxel setting.

CONCLUSION

The SIOG guidelines set out a comprehensive, evidence-based rationale for the management of localized and advanced prostate cancer in older men, based on a rapid and simple assessment of the patient's underlying health status and an objective assessment of the risk status of the disease [5, 10]. The advice specifically challenges the notion that chronological age is an appropriate guide to effective management, and instead proposes four health categories—healthy, vulnerable, frail, and terminally ill. It is recommended that patients in the healthy category receive the same treatment as younger men, and that the vulnerable group may be able to be recategorized as

healthy once reversible health impairments have been addressed. Frail patients may benefit from adapted treatment strategies, and terminally ill individuals should receive symptomatic/palliative care.

As well as the full guidelines document [5], the advice from the SIOG Working Group is available in a shorter form, with a practical focus, for use in the clinical setting [10].

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