Review

Radiopharmaceuticals in the elderly cancer patient: practical considerations, with a focus on prostate cancer therapy

A position paper from a SIOG Task Force

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Abstract (248 words)

Molecular imaging using radiopharmaceuticals has a clear role in visualizing the presence and extent of tumour at diagnosis and monitoring response to therapy. Such imaging provides prognostic and predictive information relevant to management, e.g. by quantifying active tumour mass using PET/CT. As these techniques require only pharmacologically inactive doses, age and potential frailty are generally not important. This may be different for therapy involving radionuclides because the radiation can impact normal bodily function (e.g. myelosuppression). Since the introduction of Iodine-131 as a targeted therapy in thyroid cancer, several radiopharmaceuticals have been widely used. These include antibodies and peptides targeting specific epitopes on cancer cells. Among therapeutic bone seeking agents, radium-223 (^{223}Ra) stands out since it results in survival gains in patients with castration-resistant prostate cancer and symptomatic bone metastases. The therapeutic use of radiopharmaceuticals in older cancer patients specifically has received little attention. In elderly prostate cancer patients, there may be advantages in radionuclides' ease of use and relative lack of toxicity compared with cytotoxic and cytostatic drugs. When using radionuclide therapies, close co-ordination between oncology and nuclear medicine is needed to ensure safe and effective use. Bone marrow reserve has to be considered. Since most radiopharmaceuticals are cleared renally, dose adjustment may be required in the elderly. However, compared with younger patients there is less, if any, concern about adverse long-term radiation effects such as radiation-induced second cancers. Issues regarding the safety of medical staff, care givers and the wider environment can be managed by current precautions.

Keywords: radionuclide imaging, radionuclide therapy, elderly, comorbidities, prostate cancer, molecular imaging, radium-223

Conflict of interest statement

John Prior, William Dale and Manfred Wirth have nothing to disclose. Wim Oyen has served on advisory boards and the speakers' bureau for Bayer. Matti Aapro is or has been a consultant for Amgen, BMS, Celgene, Clinigen, Eisai, Genomic Health, GSK, Helsinn, Hospira, JnJ, Novartis, Merck, Merck Serono, Mundipharma, Pfizer, Pierre Fabre, Roche, Sandoz, Tesaro,Teva, Vifor; he has received honoraria for lectures at symposia organized by Amgen, Bayer Schering, Cephalon, Chugai, Eisai, Genomic Health, GSK, Helsinn, Hospira, Ipsen, JnJ OrthoBiotech, Kyowa Hakko Kirin, Merck, Merck Serono, Mundipharma, Novartis, Pfizer, Pierre Fabre, Roche, Sandoz, Sanofi, Tesaro, Taiho, Teva, and Vifor. Silke Gillessen has served on advisory boards (compensated) for Astellas Pharma, Bayer, Curevac, Dendreon Corporation, Janssen, Millennium Pharmaceuticals, Novartis, Pfizer, Sanofi Aventis Group; and (uncompensated) on advisory boards for Astellas Pharma, ESSA Pharmaceuticals Corp, Nectar, Orion Corporation, ProteoMediX; on the speakers' bureau (compensated) for Astellas Pharma Europe, Bayer (Schweiz) AG; and on the speakers' bureau (uncompensated) for Amgen, Bayer, Janssen, Sanofi Aventis Group. She also declares a pending patent application for a method for biomarker WO 2009138392 A1.

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Introduction

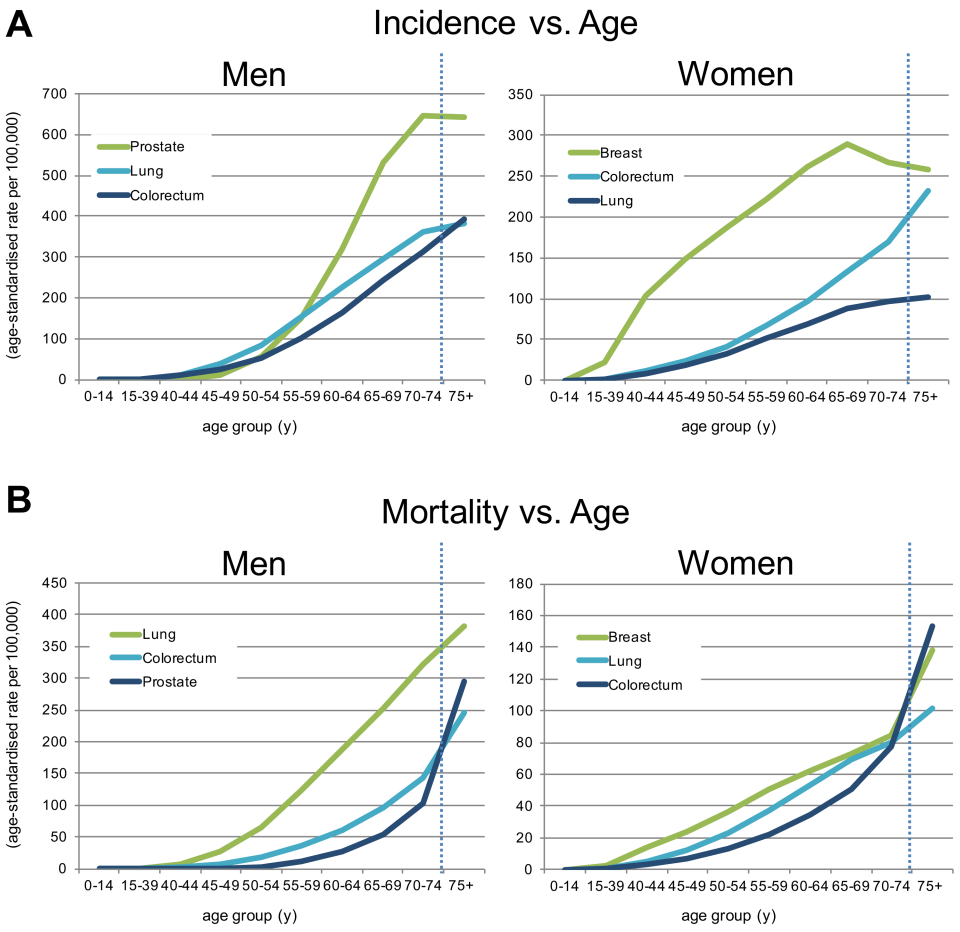
Diagnostic radiopharmaceuticals are generally pharmacologically inactive and given only in the relatively small doses needed for imaging. Such agents are considered to have no measurable pharmacodynamic impact.[1] For these reasons there is little concern about specific toxicity problems arising with age, although the practicalities of imaging older patients need to be considered. In contrast, with therapeutic radiopharmaceuticals, the desired clinical benefit arises from the effects of radiation on the tumour, and courses of treatment may involve frequent administration. In this context, both age-related changes in tissues, such as bone marrow, and questions of altered drug clearance arise.

A Task Force of the International Society of Geriatric Oncology (SIOG) considered practical recommendations on the use of radiopharmaceuticals, both diagnostic and therapeutic, in older cancer patients. This increasingly important topic has not previously been reviewed from the perspective of older patients. Such a perspective is important since physiological reserves typically decline with age, many older patients have significant comorbidities, and there is increased risk of interactions with drugs taken for concomitant disease. [2,3]

Systemically administered therapeutic radiopharmaceuticals are used in thyroid cancer (an area in which there is more than fifty years of experience), in neuroendocrine tumours, in non-Hodgkin's lymphoma and in myeloproliferative diseases. However, these tumours are relatively infrequent, even in the elderly.

The most common tumours (lung, colorectal, breast and prostate), show a steeply rising incidence and mortality with increasing age (Figure 1).[4] Among these four tumours, the risk of skeletal involvement is high in three: in advanced stages of the disease, bone metastases are present in 47-85% of breast cancer patients, 32-60% of those with lung cancer, and 33-85% of prostate cancer patients.[5] Given recent increased interest in radionuclides in patients with bone metastases from castration resistant prostate cancer (CRPC), and since more than 90% of them have skeletal metastases,[6] discussion of the therapeutic use of radiopharmaceuticals focused on this area.

Figure 1 (A) Incidence and (B) mortality of the three most frequent cancers in Europe in men and women according to age (Data from [http://globocan.iarc.fr GLOBOCAN 2012, last accessed on September 2014, 21], IARC®)



The general principles underlying radionuclide use in the elderly are likely to be similar to those in younger patients. However, elderly patients have been under-represented in clinical trials, despite the fact that the majority of cancers – and hence of treatment – is in precisely these patients. Hence, as in most areas of oncology, specific data on the efficacy and toxicity of radionuclides in these populations are limited.

Task Force members conducted literature searches in their areas of expertise. We make no attempt to formally assign levels of evidence to recommendations. They should be considered those of an expert group, and the basis for further discussion. The recommendation that more elderly patients should be included in trials is an obvious starting point.

Age and frailty: general considerations

While chronological aging is uniform and relentless, biological aging is not. The main relevant factors are: i) functional losses, including those relating to cognition; ii) the effects of declining physiological reserves on resistance to toxicity and on drug handling; and iii) the implications of comorbidities and associated polypharmacy.

The broad concept of frailty, defined as vulnerability in the face of a stressor, is of interest to clinicians assessing the likely side effects of therapy.[7] Functional status and the presence of comorbidities are the most readily available guides to patients who are especially vulnerable to adverse effects of treatment.

Means of assessing the overall fitness of elderly patients and the likely toxicity of chemotherapy have been developed.[2,8,9] Although they have not been assessed in the context of radiopharmaceuticals, such tools may help predict any toxicity in elderly patients.

In the setting of prostate cancer specifically, a recent SIOG Task Force [3] has advocated initial screening for cognitive impairment, to establish patient competence in making decisions, followed by brief evaluation of health status using the validated G8 screening tool. Abnormal scores on the G8 should lead to a simplified geriatric assessment that evaluates comorbid conditions, dependence, and nutritional status (by estimation of weight loss).

Also in the prostate cancer setting, the potential importance of comorbidities is illustrated by the trial in which D'Amico et al randomized 206 men to radiotherapy (RT) alone or RT plus androgen suppression. [10] For the group as a whole, combined treatment was associated with significantly reduced all-cause mortality (30 vs. 44 deaths, p=0.01). However, among men with moderate or severe comorbidity, there was a trend in the opposite direction with more deaths in the RT plus androgen suppression group than in those treated with RT alone (19 vs. 13 deaths, p=0.08). While acknowledging that they derive from a subgroup analysis, such data make a strong case for distinct trials to be conducted in patients with comorbidities.

Most radiopharmaceutical studies do not include specific measures of comorbidity, frailty or functional loss. In their absence, the potential impact of such agents on less fit patients must be extrapolated from the healthier patients who were enrolled, or from studies of other agents which did include less fit patients.

Radiopharmaceuticals in imaging

Diagnosis and staging

The availability of information from radionuclide imaging contributes greatly to personalized cancer treatment. Here, we do not seek to compare the merits of different imaging techniques, but consider them from the perspective of the elderly.

In older Medicare patients (mean age 73 years), analysis of registry data from more than twenty thousand imaging studies demonstrated that having information from fluorine-18-FDG (^{18}F-FDG) positron emission tomography computed tomography (PET-CT) led to a major change in management in 30-40% of cases and a minor change in another 10-30%.[11] The report covered the role of imaging in diagnosis, staging, restaging, and investigation for suspected recurrence and monitoring response to therapy. It concluded that physicians frequently change their intended management of elderly cancer patients on the basis of PET scans, and that this applies across the range of its uses. However, it is notable that only 5% of patients in the study were aged 85 years or more.

Other important applications include guiding and selecting biopsy sites, identifying tumours in patients with rising markers, guiding radiation therapy, and distinguishing tumour recurrence or residual tumour from post therapy changes (such as fibrosis and necrosis) on CT.

In several tumours, imaging with a variety of radiopharmaceuticals is an integral part of diagnosis. Although extremely rare, adverse allergic reactions have been reported with ^{18}F-FDG.[12-14] Overall, however, diagnostic nuclear medicine is associated with an exceptionally low risk of toxicity since, at the dose administered, the agents are not pharmacodynamically active. In a prospective questionnaire study conducted over four years covering 80,000 radiopharmaceutical administrations for PET in 22 participating institutions, Silberstein found no reports of adverse reactions.[15] In an earlier five-year prospective study in 18 institutions, only 18 adverse reactions were recorded in more than 780,000 radiopharmaceutical administrations.[16] Of these reactions, ten were rashes. None of the patients involved required hospitalization or had significant sequelae.

Use of diagnostic radiopharmaceuticals does not require assessment of renal insufficiency; and although diabetic patients should have a glucose level that is well controlled on the day of the ^{18}FDG PET, co-medication with metformin is not a potential problem. In both cases, this situation is different from that with computed tomography involving contrast media.

In general, no clinically relevant issues arise relating to the particular vulnerability of elderly patients, nor to the increased risk of drug interaction or toxicities related to comorbidities. Furthermore, compared with children and young adults, the long-term risks for radiation-induced second cancers associated with radiation exposure due to diagnostic medical procedures are unlikely to be relevant in elderly patients with more limited life expectancy.

However, there are certain practical considerations relating, for example, to technetium-99m-bisphosphonate bone scintigraphy, which is still the standard method of staging in

advanced prostate cancer.[17,18] Although safe, the length of time that may be required for scanning can be difficult for older patients, especially for those with musculoskeletal problems who find prolonged immobility uncomfortable and even painful. In frail elderly patients, it is worth considering an increase in the dose of isotope administered to allow shortening of the scanning time, thereby minimizing patient discomfort.

Prognosis and treatment monitoring

Prognosis is of concern with all patients but is particularly relevant to the elderly in whom expected benefits and toxicity must be balanced in the light of concomitant disease and competing causes of death. Information from radionuclide scanning can contribute considerably to management decisions. If used appropriately, it may avoid the need for other investigations, as well as unnecessary treatment. Such an outcome is desirable for reasons of patient comfort, quality of life and cost.

The quantification of overall tumour load and, more importantly, of biologically aggressive tumour is relevant to a variety of cancers. However, whether or not it is a predictor of poor outcome depends on the tumour type and on the treatments available. In colorectal and squamous cell lung cancer, a high standardized uptake volume (SUVmax) suggests poor prognosis.[19] Quantitative analysis of FDG PET has value in predicting relapse-free and overall survival independently of TNM staging in non-small cell lung.[20]. Also, in lymphoma FDG-PET has become a standard imaging method for therapy monitoring, providing prognostic and predictive information. A computer programme to aid such quantification is being developed to calculate its predictive value. [21]

FDG PET can identify previously unknown second primary tumours (which are present in about 1-2% of patients) or distant metastases (Figure 2), as in head and neck cancer cancer.[22] Knowing their presence may influence the timing and aggressiveness with which the initial or primary cancer is treated.

FDG PET also allows identification of patients who fail to respond to initial cycles of neoadjuvant chemotherapy. Such techniques seem especially useful in cancers including those of the head and neck, oesophagus, bladder and lung.[23-27]

Other radiopharmaceuticals are relevant to a specific cancer-related process. Use of fluorine-18-FLT, a marker for tumour cell proliferation, can be valuable e.g. in monitoring the treatment of lymphoma or the effectiveness of radiotherapy and in adjusting the treated volume. [28,29]

Such adaptive radiation therapy allows treatment to be confined to a smaller area at increased dose when a tumour has been reduced in size, or stopped or changed in those who are clearly not responding.[30]

Figure 2 A 69-year old patient with biochemical relapse from prostate cancer (Gleason 7, PSA 3 ng/mL) showing a single site of bone metastasis on the right ischium with ^{18}F-choline PET not visible by bone scintigraphy. The patient received isolated radiation therapy and the PSA decreased to <0.05 ng/mL). He has been relapse-free for 24 months.

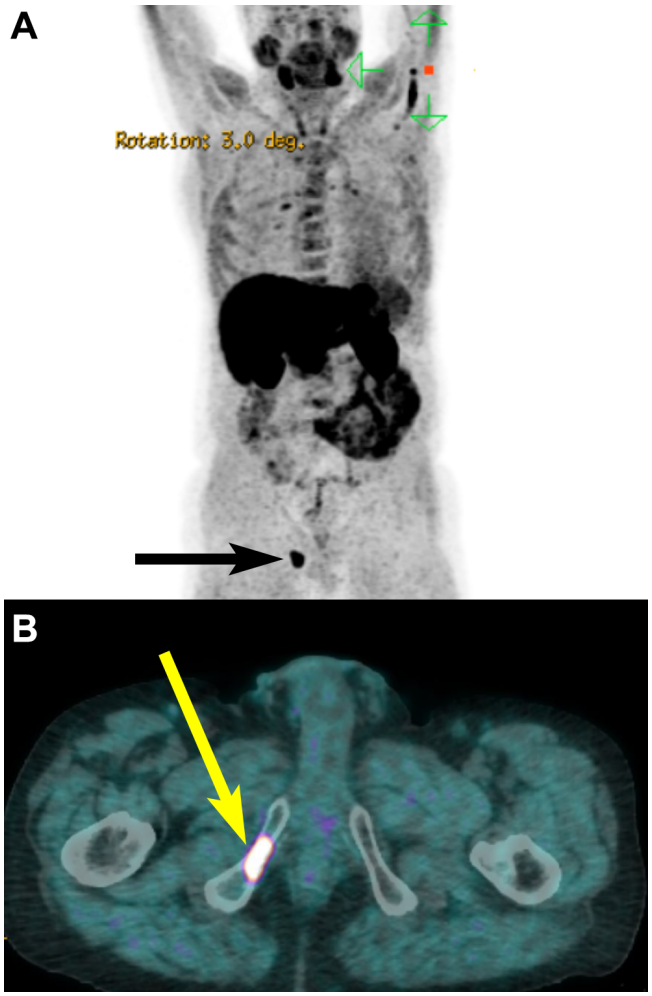


Table 1. Concerns about radiopharmaceuticals in diagnosis, monitoring and therapy and their potential relevance to the elderly cancer patient

	Diagnosis and monitoring, including for relapse	Therapy	
Age-related alterations in pharmacokinetics or pharmacodynamics resulting in reduced efficacy or increased toxicity	For FDG, check glucose levels	Minor for ^{223}Ra, which is excreted predominantly in faeces. But renal function is relevant for other therapeutic radionuclides	
Interaction with drugs being taken for comorbid conditions	None	Minor, though certain beta-blockers, for example, decrease MIBG targeting	
Effects on reproductive function, foetal toxicity and breast feeding	Not applicable	Not applicable	
Risk of long-term radiation toxicities such as induction of treatment-related solid and haematological cancers	None	Less concern in elderly populations than in younger patients	

In castration resistant prostate cancer (CRPC) patients on systemic treatment, current ESMO guidelines recommend regular imaging to monitor disease response or progression, although their recommendation is supported by a relatively low level of evidence (V).[31] At the time of writing, the latest EANM guidelines were still in preparation. FDG PET CT scan is not recommended for prostate cancer except for aggressive form of disease, while bone scan using ^{99m}Tc-labeled-diphosphonates is still standard.[18]

Techniques such as sodium ^{18}F PET-CT may prove valuable in relation to ^{223}Ra treatment.[32] At present, a standard bone scan is still routine to select eligible patients. In the individual patient, and in the absence of trial evidence, practice in relation to imaging should be guided by factors such as the goal of treatment, PSA increase and velocity, and clinical suspicion.

Newer agents targeting the prostate specific membrane antigen (PSMA) are being developed and used clinically based on ^{68}Ga and ^{18}F radioisotopes and have already been shown superior to choline-labelled tracers. These are likely to develop further and play a significant role in CRPC. [33,34]

In Europe, Ga-68-PSMA-11 PET/CT (PSMA PET/CT) is increasingly used and provides sensitivity and specificity superior to that of F-18-FCH, although it is not yet approved by the EMA. The technique has potential as a means of triaging patients to be treated by Ra-223 or Lu-177-PSMA. [35] ^{11}C- or ^{18}F-choline radiopharmaceuticals have proved useful in

detecting biochemical relapse in prostate cancer patients.[33] An example is shown in Figure 2.

Therapeutic radiopharmaceuticals

Age-related dose adjustment is generally not required. If necessary, anaemia should be corrected as part of general supportive care. There are no guidelines specific to the need for transfusions in the haematopoietic support of patients being treated with radiopharmaceuticals. Transfusion should therefore be used at the physician's discretion.

The use of phosphorous-32 (^{32}P) in refractory myeloproliferative diseases such as polycythemia vera and essential thrombocythemia should also be acknowledged. Although overshadowed by recent developments,^{32}P is well tolerated and can be particularly helpful in older patients in whom one or two doses provide adequate disease control. In short, established drugs may work well, and perhaps especially so in patients with limited life expectancy.

In solid tumour oncology, the archetypical targeted radiopharmaceutical is ^{131}I for the treatment of differentiated thyroid cancer following thyroidectomy. The safety and efficacy of this treatment in both adjuvant and metastatic settings, are well established and thoroughly discussed elsewhere.[36] In relation to the elderly, it is worth noting that it may be preferable to raise TSH levels by injection of recombinant TSH (rTSH) (Thyrogen®) pre-treatment rather than by thyroid hormone withdrawal. This avoids a prolonged period of hypothyroidism and the associated risks of depression and reduced metabolism and activity, which may be especially harmful in the elderly. However, this approach is not approved in all countries, and the number of rTSH administrations may be restricted to two in addition to the initial treatment.

Although this paper relates mostly to solid tumours, radioimmunotherapy contributes to the treatment of haematological malignancies. Most attention has focused on CD20-positive non-Hodgkin's lymphoma (NHL). Although effective in subgroups of patients, this treatment option is not widely used. In their 2005 review, [37] Rao et al. concluded that these agents are well tolerated in elderly NHL patients, even though marrow involvement is common. Caution is required if more than 25% marrow is involved, in case of prior marrow-ablative therapy or hypocellular bone marrow (< 15%).

There is also evidence for the efficacy of ^{90}Y resin microspheres in the radioembolization of patients with advanced hepatocellular carcinoma.[38] This may have particular relevance in elderly patients needing to avoid chemotherapy. In a pan-European series of 325 patients treated by this method, the mean age was 65 years (range 22-87). However, the administration of ^{90}Y microspheres and of ^{131}I-lipiodol is invasive since it involves selective hepatic artery injection. Shunting to the lungs, normal liver and/or stomach may result in clinically significant short-term radiation burden (inducing pneumonitis, hepatitis or stomach ulceration). This may be particularly relevant in older patients with reduced

pulmonary or liver function and potential additional gastric toxicity arising from concomitant medication.

An interesting application of radioembolization is in the treatment of early-stage disease with a curative intent, given that 90% of ^{90}Y-treated tumours less than 3cm and two-thirds of tumours of 3-5cm show complete pathologic necrosis (so-called radiation segmentectomy).[39] Additionally, it has been observed that treatment of a lobe results in atrophy of that lobe and hypertrophy of the contralateral one, a characteristic that may aid in resection.[40]

When considering a patient for radioembolization, the tumor stage, liver function, renal function, performance status, α-fetoprotein level, coagulation parameters, and goals of treatment must be taken into consideration. This is most reliably achieved through a multidisciplinary board.

Patients with poor hepatic reserve are less likely to tolerate a whole liver treatment. Other patients at high risk include those with disease affecting >50% of the liver, albumin less than 30 g/L (3 mg/dL), or bilirubin greater than 34.2 µmol/L (2 mg/dL).[41] Patients with impaired pulmonary status should also be examined carefully, because a significant lung shunt fraction is more likely to cause life-threatening radiation pneumonitis. Prior external beam radiation therapy is also considered a contraindication.

Radiopharmaceuticals are also being used with good palliative effect in metastatic or unresectable neuroendocrine tumours. These agents target either the noradrenaline transporter (in the case of ^{131}I-MIBG) or somatostatin receptor subtypes overexpressed on tumour cells using ^{90}Y linked to the somatostatin analogues octreotide or octreotate (^{90}Y-DOTATOC and -DOTATATE). With the latter agents, which accumulate in the renal cortex, renal toxicity is a concern, as is thrombocytopenia due to bone marrow toxicity. However, a study of more than five hundred patients treated with DOTATATE found few adverse events.[42] A recent review concluded that, while mild haematological toxicity with the two agents was common, renal toxicity was rare.[43] However, the mean age of the patients was 57 years (range not given), so the impact on older, frailer patients has not been established.

Bone seeking agents

In relation to more prevalent cancers, the frequent occurrence of osseous metastases in advanced disease has focused attention on the potential of bone metastasis-seeking radiopharmaceuticals. Of these, ^{89}strontium, and ^{153}samarium-EDTMP emit β^- particles (electrons) with a few millimetre range and a relatively limited biological effect. (Table 3.) The alpha emitter ^{223}Ra, on the other hand, has effects that are confined to a few cell diameters (<0.1 mm) but are more powerful. Whereas a β^- (electron) emitter may require more than a thousand DNA hits to achieve cell kill, this effect is achieved with only 1-4 hits from an alpha emitter. The fact that radiation damage is confined to the 40-100µm area

immediately surrounding ^{223}Ra molecules, rather than up to 12 mm with β^- emitters, suggests a reduced likelihood of adverse effects on nearby bone marrow.

While ^{89}strontium and ^{153}samarium-EDTMP have proven valuable in the relief of pain due to bone metastases in mCRPC, ^{223}Ra has been shown in robust phase III studies to result in improved overall survival. Other radiopharmaceuticals have not been shown to have this effect.[44] Hence ^{223}Ra is a therapy to be considered alongside abiraterone or enzalutamide. In addition to its role in prolonging survival, the agent may provide effective pain relief.

Although important for all patients, patient preference is particularly relevant to the elderly in whom quality of life (QoL) is pre-eminent. In this context, it is worth noting that strontium-89 has been associated with well-maintained QoL in metastatic CRPC, and ^{223}Ra with improved QoL relative to placebo in the same setting. [45,46] There is a general reluctance to undergo chemotherapy if there are less toxic alternatives, and older patients may trade slightly reduced efficacy for higher quality of life or less risk of adverse events. In metastatic CRPC, the almost simultaneous advent of life-prolonging androgen receptor targeting agents, immunotherapy, a novel taxane and a new radiopharmaceutical poses acute questions about the optimal sequencing and potential combination of treatments.[31]

Use of therapeutic radiopharmaceuticals such as ^{223}Ra in the elderly, as in younger patients, is clearly feasible. Given patients' more limited life expectancy, long-term toxicities, notably the risk of inducing a second cancer, are of less (if any) concern. This raises the question of whether their use in elderly patients should be governed by regulations less stringent than those applicable to the treatment of younger adults.

Risk of short term toxicities arising from damage to the kidneys and bone marrow may be exacerbated by reduced renal and marrow reserves. However, since treatment is fractionated over six cycles one month apart, radiation exposure on each occasion is one sixth or less of the maximum tolerated dose. Even so, there is the possibility that prior treatment with radiopharmaceuticals may mean that subsequent chemotherapy is less well tolerated, raising issues of optimal sequencing. Age, especially in combination with poor PS, is considered a risk factor for febrile neutropenia.[47]

In the ALSYMPCA trial, 600 patients with CRPC were treated with ^{223}Ra and toxicities were generally mild.[48] The most frequent reported side effects, occurring in more than 10% of patients, were anemia, thrombocytopenia, constipation, nausea, diarrhoea, vomiting, fatigue, weight loss, anorexia, bone pain and peripheral oedema.

Grade 3-4 anemia was reported in 13% of ^{223}Ra-treated patients, but this rate was not significantly different from that with placebo. Anemia seemed related to extensive disease rather than treatment; and patients experiencing anemia did not suffer more than others from side effects. Grade 3 or 4 thrombocytopenia occurred in 6% of ^{223}Ra-treated patients. One death from thrombocytopenia was reported. The fall in platelets seemed related to treatment, since it was less frequent with placebo, occurring in only 2% of

patients. However, the 6% rate seen in patients receiving ^{223}Ra was still low. Grade 3-4 neutropenia occurred in 3% of treated patients.

It should be noted that certain toxicities associated with ^{223}Ra are of particular concern in the elderly. They are at greater risk in the case of diarrhoea, a known side effect, leading to dehydration and possible kidney damage and other sequelae such as confusion and electrolyte disturbance; anaemia is less well-tolerated; and thrombopenia may be a particular problem in patients on anticoagulants.

The EMA-approved label for ^{223}Ra indicates that there are limited data on patients with moderate renal impairment, and no data on severe impairment or end-stage renal disease; and safety has not been studied in patients with hepatic impairment. However, since ^{223}Ra is not cleared through the kidneys, nor metabolised by the liver or eliminated via the bile, renal or hepatic impairment are not expected to affect its pharmacokinetics.

Radiopharmaceuticals in prostate cancer

Prospective phase III data in metastatic CRPC support the first-line use of docetaxel, enzalutamide and abiraterone (all of which significantly extend OS) and of sipuleucel-T and ^{223}Ra. These latter agents also extend OS but their pivotal trials also included patients who had had prior chemotherapy (though in the case of the sipuleucel-T trial, they amounted only to 15%).[49-53] Second line, there are prospective data only for patients who had had prior docetaxel.

With regard to ^{223}Ra, the ALYSMPCA trial included patients with CRPC metastatic to bone.[48] Fifty-seven percent had received prior docetaxel. The chemo-naïve subgroup was not clearly defined and included patients unfit for chemotherapy, those unwilling to undergo it, and those without access to it. Patients with visceral metastases and bulky lymph node disease were excluded.

Table 2 summarises current recommendations relevant to use of radiopharmaceuticals in mCRPC.

Of note, the 2016 European Association of Urology (EAU) guidelines on prostate cancer contain a section specific to management of the disease in elderly men, which should be undertaken by a multidisciplinary team.[54]. In accord with the SIOG working group on prostate cancer,[55] the EAU recommends use of the G8 screening tool for initial assessment of health status, followed when appropriate by full, specialist geriatric assessment to determine the reversibility of any impairments. Subsequent management should be based on an elderly patient's individual health status.

The role of newly developed agents for mCRPC has not been well defined in elderly men specifically. However, the relative ease of administering ^{223}Ra (i.v. every four weeks) and the fact that it seems generally well tolerated and does not interact with co-medication may make it a good option in elderly patients, especially those with multiple co-morbidities (Figure 3). It would be of great help to randomize the new CRPC agents against each other

in a trial specifically designed to include elderly patients and with a focus on quality of life and patient-reported outcomes.

Figure 3 Example of bone scintigraphic response in a 72-year old patient with metastatic castration-resistant prostate cancer and multiple bone metastases (A) in the skull, right hemi-jaw, left shoulder, ribs, thoracic and lumbar spine and (B) after 6-courses of ^{223}Ra over 6 months.

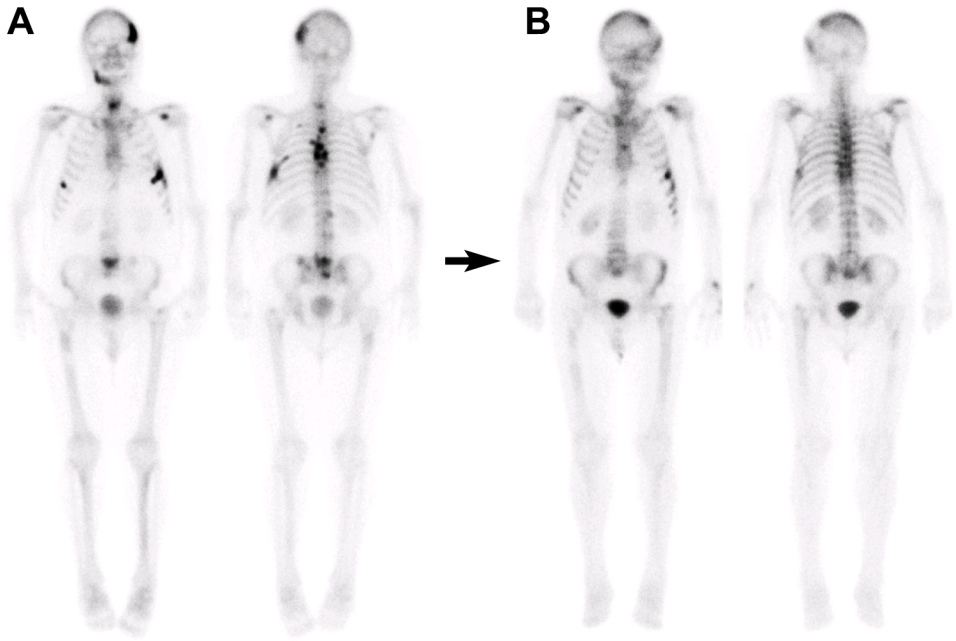


Table 2 Summary of current recommendations relevant to use of radiopharmaceuticals in metastatic castration-resistant prostate cancer (mCRPC)

Source	Setting	Recommendations	Evidence level Grade	Reference
ESMO	First line in mCRPC	Docetaxel	I A	Parker et al 2015 [31]
		For asymptomatic or mildly symptomatic disease: abiraterone, enzalutamide	I A	
		or sipuleucel-T	II B	
		For bone predominant, symptomatic disease without visceral metastases: ^{223}Ra	I A	
	Second line (post docetaxel)	Abiraterone, cabazitaxel, enzalutamide, and ^{223}Ra (in those without visceral disease)	I A	
European Association of Urology		No clear-cut recommendation can be made for the most effective drug for secondary treatment (ie hormone therapy or chemotherapy)	3 A	Mottet et al, 2016 [54]
	Candidates for cytotoxic therapy	Offer docetaxel 75 mg/m2 every 3 weeks.	1a A	
	Relapse following docetaxel	Offer further life prolonging treatment options, which include cabazitaxel, abiraterone, enzalutamide and radium-223.	1a A	
		Base second-line treatment decisions on pre-treatment performance status, comorbidities and extent of disease.	B	
	Non-specific management	In painful bone metastases, palliate early using radionuclides, external beam radiotherapy and analgesics	1a B	
NCCN	Initial therapy:			NCCN.org v2.2016 [56]
	no visceral metastases	Abiraterone, docetaxel, enzalutamide, or ^{223}Ra (for symptomatic bone mets); or clinical trial; or secondary hormone therapy	Cat. 1	
	visceral metastases	Docetaxel, enzalutamide;	Cat. 1	
		or abiraterone, or mitoxantrone (if not candidate for docetaxel); clinical trial; or secondary hormone therapy		
	Subsequent systemic therapy:		Cat. 1	
		For patients with prior exposure to		

	no visceral metastases visceral metastases	docetaxel, ^{223}Ra is among the 10 options (including docetaxel re-challenge and best supportive care); for patients with prior enzalutamide or abiraterone, ^{223}Ra is among 8 options ^{223}Ra not among the options		
American Urological Association	Symptoms related to bony metastases; no known visceral disease no prior docetaxel prior docetaxel	^{223}Ra an option in patients with good PS; also an option in selected poor PS patients when PS is directly related to symptoms related to bone mets. ^{223}Ra an option in good PS patients	STANDARD EXPERT OPINION STANDARD	AUA 2015[57]
American Society of Clinical Oncology	No prior docetaxel Prior docetaxel	Continue androgen deprivation indefinitely Offer abiraterone, enzalutamide or ^{223}Ra; may also offer docetaxel/prednisone accompanied by discussion of toxicity risk; and sipuleucel-T if no or minimal symptoms. May offer cabazitaxel with toxicity discussion; or mitoxantrone with discussion of limited benefit and toxicity risk.	Benefit of ^{223}Ra moderate; harm low; evidence strong; recommend-ation strong	Basch E et al 2014 [58]

PS: performance status NCCN: National Comprehensive Cancer Network

When any of these recommendations go beyond existing data, they are phrased with caution, as is appropriate given the absence of comparative studies. Use of radiopharmaceuticals is cited as one of several options, but ^{223}Ra is linked to the presence of symptomatic bone metastases and the absence of visceral involvement – which implies that clinicians must look for such disease. Although PS is a factor in the AUA management plan, none of the recommendations is age-specific or accounts for age-associated factors such as comorbidities and frailty.

The NCCN suggests that estimation of remaining life expectancy is critical to informed decision making about disease management and recommends that clinicians consult the actuarial life tables. For patients judged to be in the best quartile of overall health, 50% should be added to the given life expectancy for age; and for patients in the poorest quartile, 50% should be deducted.

Guidance from trial data related to age

The pivotal trials mentioned above differ in their inclusion and exclusion criteria with respect to factors such as PS, the presence of visceral metastases and whether or not patients had received prior docetaxel. Within the recommendations, there is a certain amount of age-related evidence to guide choice of an agent for older patients. With docetaxel, the OS benefit in patients aged 75 years and in patients aged 65 years and above is similar to that in the wider population studied.[59] Forty percent of elderly patients had grade 3-4 AEs, and there was a greater need for dose reduction.

In the pivotal, placebo-controlled enzalutamide trial, 35% of enrolled patients were aged 75 or more.[60] The PFS and OS benefits of treatment were significant both in this age group and in younger patients. Similarly, in the pivotal trial versus mitoxantrone, the OS benefit of cabazitaxel was similar across prespecified subgroups, including patients aged 65 and above.

Table 3 shows the physical characteristics and clinical outcomes of currently available radiopharmaceuticals.

Table 3. Physical and clinical characteristics of therapeutic radiopharmaceuticals in current use for prostate cancer

Agent	T ½ Days	Tissue penetration max (mean) mm	Standard dose	Efficacy	Toxicity
^{89}strontium	50.5	5.5 (2.4)	148 MBq	Pain reduction: 33% CR; time to response 4-28 days; no OS benefit	Leucopenia in 20-80% and thrombocytopenia in 30-80% (both reversible); minimal anaemia
^{153}samarium	1.9	2.5 (0.6)	37 MBq/kg	Pain relief in 83% of pts, complete in 31-38% no OS benefit	Reversible leucopenia in 40-50% of pts and thrombocytopenia in 20-42%
^{223}radium	11.4	<0.1	50kBq/kg	Significantly increased OS compared with control group (14.9 vs. 11. 3 months); significantly longer time to first skeletal event (15.6 vs. 9.8 months)	Grade 3-4 anemia in 13% of ^{223}Ra-treated patients was not significantly different from placebo. Gr 3-4 thrombocytopenia in 6% of treated patients versus 2% with placebo. Occasional cases of fatigue, nausea and loose stools; but toxicities in general are comparable with placebo.

In the ALSYMPCA trial in men with CRPC and symptomatic bone metastases, the median age of patients enrolled was 71, and 28% were aged over 75 years.[48] The mean haemoglobin level of patients included was 12.2g/dl, which seems higher than expected in routine practice for this patient population; and no data are given about comorbidities or geriatric functional assessment.

It is not clear how many of the patients who did not have prior docetaxel had refused chemotherapy, how many were judged unfit for chemotherapy, and how many had no access to it. It is therefore difficult to judge the efficacy and safety of this treatment in elderly patients. In the poorer PS group, the 0.73 HR for OS was in the same positive direction as for the population as a whole. However, the benefit of treatment did not achieve statistical significance; and, as with any subgroup analysis, this finding can be considered only as hypothesis generating.

Protection and safety when using therapeutic radiopharmaceuticals

Protecting hospital staff, the general public and the environment from unnecessary exposure to radiation is a major concern in radiopharmaceutical diagnostics and therapy. Relevant regulations differ considerably from one country to another. For example, there have been concerns in Germany about the possibility of exhaled radon. Swiss patients given ^{223}Ra have to accept that cremation must be postponed (or burial used instead) if they die within seven days of its administration. Nuclear medicine physicians and technicians need to check which are applicable to the place they practice.

Elderly patients are more likely than their younger counterparts to require urgent surgery for conditions unrelated to cancer. In any patient with bone metastases, there is the possibility that fracture or spinal cord compression will necessitate surgical intervention. More generally, a patient's overall functional status – especially possible incontinence – is an age-related factor that is clearly relevant to radioprotection.

Appropriate radioprotection advice should be available to hospital staff when required in managing a patient recently treated with a radiopharmaceutical (protective eyeware for operating theatre staff and double pairs of gloves, for example, would be appropriate).

Discussion and conclusions

The use of radiopharmaceuticals to accurately image the spread of disease is of proven value. They are also likely to be useful in quantifying the burden of metabolically active tumour, which will further aid in personalising treatment. In relation to the elderly patient with significant comorbidities and limited life expectancy, the prognostic information such imaging could provide would be particularly valuable in enabling them to avoid unnecessary treatment and preserve quality of life.

When attempting to make recommendations for the elderly, it is striking to find that so few older patients have been entered into pivotal clinical trials, even of targeted anti-cancer agents.[61] In an ideal world, the proportion of elderly patients included in a trial would match the proportion of those with the disease. In the real world, there may be a case for providing companies with incentives to enrol such patients in key studies, or with requiring them to conduct trials specifically in the elderly, those who have comorbidities and those who are frailer.[62]

The fifty-year history of ^{131}I in thyroid tumours should give us confidence that radiopharmaceuticals can safely be used in the treatment of cancer in a wide range of patients. However, with each new radioisotope and indication come unquantified risks. This applies both to the patients treated and to the staff treating them. In the elderly prostate cancer patient with symptomatic bone metastases and a life expectancy of under five years, it is very unlikely that long-term effects of radiation exposure will become apparent. In a young woman with breast cancer, this is not necessarily the case. However, both kinds of patient must be assessed for the risk of short-term toxic effects, for example to bone marrow or the kidney. And staff administering radiopharmaceuticals are understandably concerned about the potential long-term impact of radiation on their general health and wellbeing, including fertility. Both patients and staff should be fully informed and given written information about risks.

Bone-seeking radiopharmaceuticals have no role in preventing the development of visceral metastases. While the risk of such involvement is initially low in prostate cancer, almost 50% of patients develop them at later stages of disease, and, with the prolongation of survival following the introduction of new drugs, this proportion is likely to increase. [63] Studies to assess whether the use or radiopharmaceuticals in combination with chemo- and other systemic therapies will increase clinical benefit with acceptable additional toxicity are now being conducted.

Since the relative costs of individual agents vary greatly from one health system and country to another, it is difficult to include such factors in clinical recommendations. However, the availability and expense of different agents are clearly relevant to the making of therapeutic decisions in the everyday management of the elderly, as with all cancer patients.

Table 4 Take-home messages

- **Include more elderly patients in pivotal clinical trials; this applies also to targeted anti-cancer agents**
  The under-representation of elderly cancer patients in pivotal clinical trials restricts our ability to tailor management to their specific circumstances (comorbidities and fraility)
- **Diagnostic radiopharmaceuticals are not an issue of particular concern in elderly patients, even in the presence of vulnerability**
  Consider increasing isotope dose activity to decrease scan time and so minimize patient discomfort
- **Therapeutic radiopharmaceuticals in elderly patients with hormone-resistant prostate cancer and symptomatic metastases are safe but require**
  - **assessment of short-term toxic effects on bone marrow and**
  - **adequate information to be given to patients, family members and care staff**
- **More studies are needed on the combination of therapeutic radiopharmaceuticals with chemo- and/or other systemic therapies to determine if increased clinical benefit can be achieved with acceptable additional toxicity**

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