Review of current best practice and priorities for research in radiation oncology for elderly patients with cancer: the International Society of Geriatric Oncology (SIOG) task force


1Edinburgh Cancer Research Centre, University of Edinburgh, Edinburgh; 2Department of Surgical Oncology, University of Liverpool, St Helens, UK; 3Service de Radiothérapie, APHP-GH Henri Mondor, and UPEC (Université Paris Est Créteil), Créteil, France; 4Institut de Radio-oncologie, Hirslanden Lausanne, Lausanne, Switzerland; 5Department of Radiation Oncology, Medical College of Wisconsin, Milwaukee; 6Moffitt Cancer Center, Tampa, USA; 7Service D’Oncologie Radiothérapie, Institut Curie, Paris, France; 8Radiotherapy Center West (RCWest), The Hague, The Netherlands; 9Department of Radiation Oncology, Metaxa Cancer Hospital, Piraeus, Greece; 10Department of Radiation Oncology, Assuta Medical Center and Tel Aviv University, Tel Aviv, Israel; 11Department of Radiation Oncology, Catalan Institute of Oncology, Badalona, Catalonia, Spain

Received 27 September 2013; revised 5 February 2014; accepted 24 February 2014

Radiotherapy (RT) is a key component of the management of older cancer patients. Level 1 evidence in older patients is limited. The International Society of Geriatric Oncology (SIOG) established a task force to make recommendations for curative RT in older patients and to identify future research priorities. Evidence-based guidelines are provided for breast, lung, endometrial, prostate, rectal, pancreatic, oesophageal, head and neck, central nervous system malignancies and lymphomas. Patient selection should include comorbidity and geriatric evaluation. Advances in radiation planning and delivery improve target coverage, reduce toxicity and widen eligibility for treatment. Shorter courses of hypofractionated whole breast RT are safe and effective. Conformal RT and involved-field techniques without elective nodal irradiation have improved outcomes in non-small-cell lung cancer (NSCLC) without increasing toxicity. Where comorbidities preclude surgery, stereotactic body radiotherapy (SBRT) is an option for early-stage NSCLC and pancreatic cancer. Modern involved-field RT for lymphoma based on pre-treatment positron emission tomography data has reduced toxicity. Significant comorbidity is a relative contraindication to aggressive treatment in low-risk prostate cancer (PC). For intermediate-risk disease, 4–6 months of hormones are combined with external beam radiotherapy (EBRT). For high-risk PC, combined modality therapy (CMT) is advised. For high-intermediate risk, endometrial cancer vaginal brachytherapy is recommended. Short-course EBRT is an alternative to CMT in older patients with rectal cancer without significant comorbidities. Endorectal RT may be an option for early disease. For primary brain tumours, shorter courses of postoperative RT following maximal debulking provide equivalent survival to longer schedules. MGMT methylation status may help select older patients for temozolomide alone. Stereotactic RT provides an alternative to whole-brain RT in patients with limited brain metastases. Intensity-modulated radiation therapy provides an excellent technique to reduce dose to the carotids in head and neck cancer and improves locoregional control in oesophageal cancer. Best practice and research priorities are summarised.

Key words: radiotherapy, elderly, adjuvant

introduction

Cancer in older patients, particularly >70 years, represents a global health challenge [1]. Radiotherapy (RT) remains a cornerstone of the multidisciplinary management of solid tumours [2] and is an attractive curative option (alone or with systemic therapy) for older patients where frailty precludes surgery. Advances in radiation planning and delivery have improved the efficacy of RT, while reducing toxicity. However, the elderly are under-represented in clinical trials and extrapolation of randomised controlled trial (RCT) results to older patients is not straightforward [3]. More elderly specific trials are needed, given large variations in the management of older cancer patients [4, 5]. In this review, we examine the evidence base and make recommendations for curative RT for the principal tumours encountered in the elderly (Table 1), and identify future research priorities (Table 2).
Table 1. SIOG recommendations for standard radiotherapy in the elderly

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Recommendations</th>
</tr>
</thead>
</table>
| **Breast cancer**   | • Fit older patients are candidates for postoperative WBRT after BCS for invasive cancer and for higher risk DCIS.  
                  | • WBRT with a boost to the site of excision is appropriate for all older patients with invasive breast cancer. There is no specific subgroup from whom WBRT can be systematically omitted.  
                  | • Patients ≥50 years of age are candidates for shortened treatment schedules when they do not need any lymph node irradiation.  
                  | • Partial breast irradiation should be considered investigational as there is insufficient evidence to support it in the elderly.  
                  | • Post-mastectomy irradiation should be considered for older patients with pT3–4 tumours or those with ≥4 axillary nodes.  
                  | • Axillary irradiation is recommended for macro-metastases on sentinel node biopsy or axillary node sampling.  
                  | • 3D CT-based planning is advised to minimise cardiac and lung irradiation, as are alternative techniques such as treatment in the prone or lateral position. |
| **Lung cancer**     | • While surgery remains the standard of care in early-stage NSCLC in the elderly, SBRT is a reasonable option in early-stage NSCLC when surgery is contraindicated.  
                  | • For inoperable locoregionally advanced NSCLC, concomitant chemoradiation is appropriate in fit elderly patients.  
                  | • For operable locoregionally advanced NSCLC, no elderly specific recommendations can be made concerning postoperative indications, where decisions should be individualised.  
                  | • In limited-disease SCLC, chemoradiation in the fit elderly is appropriate, with adapted regimens where necessary. |
| **Lymphoma**        | • For early-stage Hodgkin’s lymphoma (HD), involved-field radiotherapy (IFRT) after short-course chemotherapy is appropriate for elderly patients.  
                  | • For elderly patients with more advanced HD and stage I–II non-Hodgkin’s lymphoma, IFRT is an option in cases of symptomatic recurrence and in all patients with low-grade lymphoma.  
                  | • In some cases of localised disease, involved-node radiotherapy (INRT) can be considered, using new techniques as IMRT or 3D to decrease the toxicity. |
| **Prostate cancer** | • Patients with low-risk PC  
                  | • Management selection (HT, watchful waiting, EBRT, BCT or surgery) should be based on geriatric assessment.  
                  | • Significant comorbidity should be a strong relative contraindication to aggressive treatment.  
                  | • Patients with intermediate or high-risk PC  
                  | • Patients with no or mild comorbidity have a significant OS benefit from short-course ADT added to EBRT. In men without moderate or severe comorbidity, 6 months of hormones added to EBRT should be proposed.  
                  | • For high-risk PC, CMT with EBRT and long-term ADT is indicated after selection based on geriatric evaluation and treatment tolerance.  
                  | • EBRT technique in elderly  
                  | • 3D EBRT is recommended for all patients. IMRT is generally associated with less grade-3 proctitis, compared with 3D-EBRT.  
                  | • Shortened, hypofractionated RT may be a more convenient alternative in elderly patients.  
                  | • The role of BCT in elderly patients with low-risk PC is defined in prospective studies taking into account life expectancy and geriatric evaluation.  
                  | • Endometrial cancer  
                  | • ‘Low-risk patients’: no adjuvant treatment is required.  
                  | • ‘High-intermediate risk patients’: VB alone is the adjuvant treatment of choice.  
                  | • ‘High-risk patients’: no optimal treatment is defined for the elderly. EBRT ± VB is a reasonable option for this group.  
                  | • Combined modality treatment is commonly used for extra-uterine disease. |
| **Pancreatic cancer**| • Patients who cannot undergo resection can safely undergo SBRT with the expectation of local control at low toxicity.  
                  | • The role of adjuvant radiation is unclear, with available data in patients aged ≥75 showing a 2-year but not 5-year survival benefit, so patient selection is key. |
| **Oesophageal cancer**| • Early data suggest oesophageal cancer IMRT may have better outcomes compared with 3D CRT.  
                  | • Consider IMRT for elderly patients, possibly with tumour dose escalation if medically inoperable. |
| **Rectal cancer**   | • Elderly patients with locally advanced rectal cancer can safely receive preoperative long-course chemoradiation with 5-fluourouracil chemotherapy or a 1-week short course of pelvic radiation alone.  
                  | • For elderly patients with early rectal cancer who are medically inoperable, endorectal contact X-ray treatment offers the potential for local control without significant toxicity.  
                  | • Tailored strategies for those elderly patients who receive preoperative treatment with a complete clinical response, such as surveillance or transanal endoscopic microsurgery, may be appropriate if there are contraindications to radical surgery, which remains the standard of care.  
                  | • Colorectal cancer oligometastases to the lung and liver can be treated with stereotactic ablative radiotherapy in elderly patients not eligible for surgery, with minimal morbidity and a high likelihood of local control.  
                  | • Conformal short-course RT with or without concomitant temozolomide can be advised for elderly patients with malignant glioma. For elderly patients whose tumour shows MGMT methylation, it is reasonable to treat initially with temozolomide alone, reserving RT for patients with progressive disease.  
                  | • For elderly patients with limited brain metastases, focal stereotactic radiation (radiosurgery) can be recommended due to similar results in terms of survival and less neurotoxicity than whole-brain radiotherapy.  

Continued
**Table 1.** Continued

| Head and neck cancer | • Radical RT using IMRT or other highly conformal techniques to reduce acute and late toxicity is appropriate in elderly patients without severe comorbidities.  
| | • Aggressive combined modality treatment is appropriate where comorbidities permit. |

**Table 2.** Priorities for future radiotherapy research in the elderly

| Breast cancer | • Identification of ‘low-risk’ population for omission of radiotherapy after breast-conserving surgery  
| | • Role of partial breast irradiation  
| | • Alternative new techniques which reduce morbidity |
| Lung cancer | • Prospective studies comparing SBRT to surgery (both standard and limited, e.g. wedge resection) in the elderly  
| | • For both locoregionally advanced NSCLC and limited-disease SCLC, investigation of concomitant treatment strategies incorporating newer chemotherapy and targeted agents, potentially less toxic than current cisplatin-based standards  
| | • Refine gating techniques and investigate adaptive RT to further limit the toxicity of curative thoracic RT  
| | • Role of supportive care |
| Lymphoma | • PET-CT-based conformal radiotherapy in patients with comorbidities  
| | • Duration of effect of low-dose radiotherapy (2 Gy x 2) for low-grade lymphoma |
| Prostate cancer | • Systematic geriatric assessment in (i) the decision tree of treatment policies and (ii) patient selection for brachytherapy  
| | • Trials to assess the role of radiotherapy versus hormone therapy, watchful waiting and surgery  
| | • Hypofractionated EBRT- and IMRT-specific studies for elderly patients |
| Endometrial cancer | • In patients unsuitable for brachytherapy because of technical or medical reasons, can IMRT be considered in terms of a daily adaptive modality image-guided IMRT? |
| Pancreatic cancer | • Integration of novel systemic and potentially radio-sensitising targeted agents along with SBRT to improve outcomes  
| | • Clarification of the benefit of adjuvant RT in the elderly node positive and node negative patient populations compared with chemotherapy alone |
| Oesophageal cancer | • Prospective validation of IMRT for patients with locally advanced disease to determine potential superiority of outcomes compared with 3D CRT  
| | • Investigation of dose escalation strategies as definitive therapy in elderly patients with contraindications to resection |
| Rectal cancer | • Identification of a pre-treatment molecular signature to indicate those patients likely to be complete responders  
| | • Identification of additional agents that can be given concurrently with radiation using advanced technologies to improve the response rate while not increasing morbidity  
| | • Identification of subsets of patients who are candidates for radiation to a smaller volume in order to avoid the morbidity of whole pelvic RT |
| Central nervous system | • Improved imaging (co-registration using MRI scan with sequences including GD-T1 and diffusion, and PET scan with methionine) of brain metastases to exclude multiple metastases and allow treatment with focal radiotherapy  
| | • Identification of subsets of glioblastomas to be treated with temozolomide alone (positive MGMT methylation or large radiation volume) or radiotherapy alone (negative MGMT methylation) |
| Head and neck cancer | • Further refinement of IMRT organ-sparing techniques, with prospective studies comparing novel strategies (e.g. carotid-sparing IMRT) and standard RT  
| | • Investigation of other potential concomitant targeted therapies with less toxicity than cisplatin-based regimens and potentially better tolerance than cetuximab |

**search strategy and selection criteria**

Medline was searched for English language publications, using a lower age limit of 70 years (but series are included with <70 years). Mesh terms used were: ‘aged’, ‘frail’, ‘elderly’, ‘breast/ lung/prostate/rectal/pancreatic/oesophageal/endometrial/head and neck/central nervous system neoplasms’ and ‘lymphomas’, ‘Hodgkin disease’ and ‘non Hodgkin lymphoma’. RCTs (including subgroup analyses), meta-analyses, reviews, retrospective studies and cohort studies but not abstracts from January 1990 to October 2013 were included, as were meeting abstracts from...
international conferences. Consensus was reached by group discussion.

**advances in radiation planning and delivery**

Conventional RT is a preferred treatment of many elderly patients, often with less toxicity than systemic therapy or surgery. Technological advances have improved radiation effectiveness while reducing morbidity, sometimes providing new curative treatment options for elderly patients.

Modern computed tomography (CT)-based RT planning relies on improved conformity of treatment portals and use of multiple treatment angles (Figure 1A). Toxicity can be better predicted and minimised through volumetric calculation of normal tissue doses.

Intensity-modulated radiation therapy (IMRT) improves treatment precision and normal tissue sparing by modulating dose across each field (Figure 1B), reducing toxicity with standard doses and in some settings permitting 'dose escalation' without increased toxicity.

The precision of IMRT has fostered tumour- and organ-motion tracking techniques as well as innovations in target positioning [6], as advanced treatment delivery hinges on consistent daily patient set-up and immobilisation. While these can be hampered in the elderly by comorbidities, poor respiratory control and unintentional movements, there are tools to assist adaptive and reproducible daily set-up and immobilisation. Image-guided radiation therapy (IGRT) (Figure 2) uses imaging carried out at each treatment session to allow millimetric adjustments in patient positioning [7].

Techniques limiting respiratory motion include controlled breath-hold and abdominal compression, which, while effective, are frequently not tolerated by the elderly. Incorporation of 4D planning CT scans permits better integration of tumour and normal tissue respiratory motion as well as other predictable motion captured during scanning into treatment planning. Strategies to compensate for motion include respiratory gating [8], adjustment of field sizes and tumour tracking.

Precise target definition allows better normal tissue sparing and facilitates the safe delivery of higher doses/fraction, sometimes permitting shorter treatment courses in the elderly. Stereotactic body radiation therapy (SBRT), which delivers higher than conventional doses to small target volumes in <5 fractions [9] is transforming the management of early-stage non-small-cell lung cancer (NSCLC) (Figure 3).

Adaptive radiation therapy (ART) uses a feedback process for dynamic treatment planning with each fraction. Treatment plans are re-optimized to account for daily variations in physical set-up and in internal tumour and normal tissue location and biological changes [10]. This highly individualises daily radiation therapy. ART has been applied primarily in prostate and head and neck cancer and is being studied for other sites [10–13]. ART may be particularly useful for patients whose treatment set-up varies due to impaired mobility or unpredictable internal organ motion.

The ability to estimate normal tissue doses more precisely has improved understanding of radiation tolerance and provided tools to study it specifically in elderly patients, potentially leading to better appreciation of the complex interactions between advanced age, comorbidity and radiation and the development of objective tools to individualise therapy.

**geriatric assessment**

Validated assessment tools such as the Comprehensive Geriatric Assessment (CGA) can add substantially to the functional assessment of elderly cancer patients, in whom Performance Status alone is an unreliable indicator of functional status. Quickly administered tools (i.e. Groningen Frailty Index, Vulnerable Elders Survey or timed ‘up and go’) are being tested against the more time consuming CGA. These tools are potentially applicable in the assessment of elderly patients being considered for curative RT.

**breast cancer**

Postoperative whole breast radiotherapy (WBRT) is the standard of care for all fit patients following breast-conserving surgery (BCS) for early invasive breast cancer (IBC). The Oxford overview of trials of BCS ± WBRT shows a twofold reduction in first relapse even in ‘low-risk’ older patients, although the absolute reduction in 10-year risk of any locoregional or distant recurrence is lower in women ≥70 years compared with younger women (8.8% versus 17.7%) [14]. The CALGB 9343 trial randomised 636 women with IBC aged 70 years or older (55% >75 years) after BCS and adjuvant tamoxifen to WBRT or no

---

**Figure 1.** (A) Three-field rectal cancer radiotherapy plan (courtesy of EG). (B) Typical IMRT dose distribution sparing a parotid gland (in orange), here in the case of a T2 N2b hypopharyngeal squamous-cell carcinoma treated to a cumulative dose of 70 Gy (courtesy of MB).
WBRT. It showed an absolute decrease in the ipsilateral breast tumour recurrence rate (IBTR) of 3% (1% versus 4%) at a median follow-up of 5 years and of 7% (2% versus 9%) at a median follow-up of 10.5 years in the RT group [15, 16].

Among the attractive alternatives to standard WBRT in older patients are shorter courses using higher doses per fraction [hypofractionation (HF)]. RCTs evaluating different HF-RT regimens after BCS have shown that HF schedules offer similar rates of local control and late cosmetic outcome [17–19].

Accelerated partial breast irradiation (APBI) combines increased dose per fraction, short duration of treatment and small target volume confined to the tumour bed. Intraoperative RT (IORT), one form of APBI, is attractive in older patients since it can be delivered in one session. There are two published randomised trials of APBI (TARGET and ELIOT). TARGET randomised >2000 patients to standard WBRT or to a single intraoperative dose of 20 Gy to the operative bed [20]. Of the 3451 patients in the TARGET-A trial, minimum follow-up was 4 years for 1010 patients and 5 years for 611 patients. The absolute difference in local recurrence at 5 years was 2% higher for the IORT group (3.3%) compared with the WBRT group (1.3%) which was statistically significant ($P = 0.042$) [21].

In the ELIOT trial, 1305 patients up to the age of 75 years with T1–T2 (up to 2.5 cm) breast cancer treated by quadrantectomy were randomised to postoperative whole breast irradiation or to a single dose (21 Gy) of intraoperative electrons. The IBTR rate was 4.4% in the IORT group and 0.4% in the external RT group at a median follow-up of 5.8 years [22]. APBI is not currently advised in elderly patients outside clinical trials.

For post-mastectomy radiotherapy (PMRT), there are non-randomised but no level 1 data suggesting that the survival advantage of PMRT may extend to women >70 years (see web version) [23]. For ‘intermediate-risk’ IBC with 1–3 involved axillary nodes, the role of PMRT is controversial and is currently being studied in the MRC SUPREMO trial [24].

Potentially advantageous technical strategies in older patients include breast irradiation in lateral or prone position to spare the lung and heart [25, 26]. Three-dimensional CT-based planning helps limit cardiac doses, an important consideration in older patients at higher risk of ischaemic heart disease.

**lung cancer**

Lung cancer is common in the elderly who may be denied effective multimodal therapy [27]. In this subgroup of patients whose
comorbidities may preclude surgery, RT plays a critical role, particularly with recent advances in the development of highly conformal techniques. In NSCLC, involved-field strategies without elective nodal irradiation and improved positron emission tomography (PET)-assisted staging have been adopted and are feasible without increased toxicity and with improved outcomes in the

Figure 3. An 81-year-old patient with stage Ib non-small-cell lung cancer treated with stereotactic body radiotherapy (SBRT). First panel: treatment plan showing isodose encompassing tumour volume. Second panel: chest CT 2 months after SBRT fused with treatment plan to show >90% shrinkage (courtesy of RP).
elderly subgroup [28]. IMRT, IGRT, gated treatment and SBRT are all techniques with the potential to improve the outlook for lung cancer in selected elderly patients.

Where comorbidities or patient preference preclude surgery, SBRT is a promising strategy. In a Dutch study of 193 patients aged >75 with stage I disease, SBRT was well tolerated with 1- and 3-year survival rates at 86% and 45%, respectively, comparable with surgical outcomes in the elderly [29]. While SBRT is not feasible for more advanced NSCLC, combined modality therapy (CMT) with RT to the primary and involved nodes and chemotherapy tailored to renal/other comorbidities is appropriate in selected inoperable patients [30]. For patients undergoing surgical resection, postoperative treatment for positive margins or pN2 disease should be individualised.

In limited-disease small-cell lung cancer (LD-SCLC), the standard approach combining four to six cycles of platinum-based multiagent chemotherapy and thoracic and cranial irradiation is derived from phase III trials in which the elderly were under-represented [31]. While a meta-analysis showed no clear survival benefit of thoracic irradiation in patients >70 (HR 1.07 for CMT versus chemotherapy alone), the pivotal trial establishing twice-daily RT to 45 Gy as a standard suggested a real but reduced benefit in the elderly [5-year overall survival (OS) 16% versus 22% in patients > versus <70], at the cost of increased toxicity [32]. Less intense strategies for the elderly have been explored through reductions in duration and intensity of both chemotherapy and RT with mixed results, and standard chemoradiation remains appropriate for fit patients in this age group [31]. The ongoing phase-III CONVERT trial comparing conventional (66 Gy) and accelerated (45 Gy b.i.d.) fractionation with standard cisplatin/etoposide in a population with no upper age limit will provide more information on treatment tolerance in the elderly [32]. For complete responders with LD-SCLC, a meta-analysis of prophylactic cranial irradiation (PCI) showed a benefit independent of age, but in a patient pool with a maximum age of 80, leaving the role of PCI unclear in many elderly patients although its cautious use may be justified in both limited and extensive disease [33].

In early-stage NHL and HL, curative treatment includes chemotherapy followed by RT. A NHL study in which half the patients were aged ≥60 showed three courses of cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP) followed by IFRT to be superior to eight courses of CHOP in terms of outcome and toxicity [36]. In contrast, a French study in elderly patients (>60) with localised aggressive NHL comparing four cycles of CHOP ± IFRT showed no difference in 5-year event-free survival (64% for CHOP + RT, 61% for CHOP alone) although RT reduced isolated local recurrences (21% versus 47%) [37]. Systemic therapy of NHL in all age groups has improved with the addition of rituximab to the CHOP regimen. IFRT is recommended for patients not achieving a complete response to R-CHOP, especially elderly patients who are not candidates for salvage bone marrow transplantation.

Older HL patients are more likely to have Epstein-Barr virus positive disease and mixed cellularity subtype, both associated with poorer prognosis and more advanced disease [38]. The 5-year survival of HL patients >55 years is around 65% compared with 90%–94% for younger patients. A retrospective German study of patients aged >60 receiving RT for HD showed worse prognosis with increasing age. Stage I–II patients treated with CMT fared better than those receiving only RT or chemotherapy [39]. The HD8 study (early-stage unfavourable disease) comparing IFRT to extended-field RT in patients ≥60 showed improved freedom from treatment failure (FFTF) (70% versus 58%) and reduced grade 3–4 toxicity (8.6% versus 26.5%) in patients ≥60, while confirming the poorer prognosis in this age group (FFTF 64% overall, versus 87% in patients ≤60 years) [40]. Of interest for elderly patients, the HD10 study (early-stage favourable disease) shows that two cycles of adriamycin, bleomycin, vinblastine, dacarbazine (ABVD) followed by 20 Gy IFRT is as effective as four cycles of ABVD followed by 30 Gy IFRT in all age groups, with reduced grade 3–4 toxicity (2.9% versus 8.7%) in patients receiving 20 versus 30 Gy [41].

**prostate cancer**

Elderly patients with moderate to severe comorbidity are more likely to die from comorbidities than from prostate cancer (PC). Conversely, patients with no/mild comorbidity and intermediate/high-risk PC benefit from combined RT and short-course androgen deprivation therapy (ADT) [42, 43].

**External beam radiotherapy**

In low-risk patients, there are no published studies limited to the elderly. Management decisions should be based on life expectancy and geriatric assessment. In the SEER registry study comparing treatment (excluding hormones) versus watchful waiting for patients aged 65–80 years, there was a significant advantage in favour of treatment. However, recent data suggest that significant comorbidity in elderly patients ≥75 years should be a relative contraindication to aggressive treatment in low-risk PC [42]. When RT is selected, ADT benefit is still unproven. In the RTOG 94-08 trial, 10-year survival in the low-risk group was similar after EBRT ± ADT [44].

In intermediate-risk patients, large randomised trials showed that the addition of 4–6 months of hormones to EBRT resulted...
in an increased survival after 4.5–8 years of follow-up [43, 45, 64]. Similar results have been reported from subset analyses of the RTOG 94-08 [44] and EORTC trials [47]. However, no stratification according to co-morbidity was planned in these trials. Indeed, in an updated study, only men with low/no comorbidity benefited from 6 months of ADT + EBRT after 7.6 years of follow-up [48].

In high-risk PC patients, combined therapy is the gold standard established by the Early Prostate Cancer Program [49] and EORTC trials [47]. In addition, long-term ADT is supported by the latter trial [47]. Extrapolation specifically to elderly patients is not straightforward and management decisions should incorporate geriatric evaluation.

**IMRT and hypofractionation**

While one study has shown reduced toxicity with 3D EBRT compared with older techniques [50], several studies using historical controls suggest that IMRT is associated with less grade 3 proctitis compared with 3D EBRT. Recent data suggest that a 5-week schedule delivering 62 Gy is equivalent to a conventional fractionation schedule (80 Gy in 8 weeks) in terms of acute and late toxicities [51], although follow-up is short.

**Brachytherapy**

The role of brachytherapy (BCT) for elderly patients with low-risk PC and a life expectancy of <10 years is controversial. While selection criteria for prostate BCT should be strongly influenced by life expectancy and comorbidity [42], SEER data show that clinical factors play a limited role in treatment selection among elderly patients with localised PC [52]. International consensus based on biological and clinical geriatric criteria is needed to define a subset of elderly patients for prospective evaluation of BCT [53].

**Endometrial cancer**

Endometrial cancer (ECM) tends to be more aggressive in the elderly. While medically inoperable stage I/II patients or frail elderly may be treated by RT, surgery is the standard curative therapy. The need for postoperative RT is usually determined by pathological prognostic features [moderately to poorly differentiated tumours, lymph vessel invasion (LVI), outer third invasion] as well as patient age. There are no studies specific to elderly patients, but some elderly patients were included in studies of RT in general EMC populations.

The PORTEC-1 and GOG-99 trials [54, 55] demonstrated the value of postoperative RT in elderly stage-I EMC patients in the high-intermediate risk (HIR) group defined in Table 3. There was a reduction in local recurrence rate (LRR) with RT in the HIR group (from 26% to 6% at 2 years in the GOG-99 study and from 23.1% to 4.6% at 10 years in the PORTEC-1 trial). Furthermore, these trials demonstrated a prognostic significance of age ≥60 which correlated with an increased LRR \( (P = 0.002) \) and increased EMC-related deaths (ECRDs) \( (P = 0.01) \) [56]. While EBRT reduces the LRR, the associated decline in health-related quality of life (HRQL) of patients supports its avoidance in low-risk disease (elderly patients with stage IA* grade 1–2, no LVI) [57]. Concerns about gastrointestinal toxicity (mainly diarrhoea) due to pelvic RT led to the PORTEC-2 trial, comparing EBRT and vaginal brachytherapy (VB) in patients aged >60 with stage IB** G3 and stage IC G1-2, IIA (G1-2). There was no significant difference in vaginal, pelvic or distant recurrence at 5 years but also reduced toxicity and improved quality of life (QoL) in the VB arm. VB is thus the adjuvant treatment of choice for HIR ECM [58, 59]. A Cochrane systematic review and meta-analysis [60] comparing postoperative EBRT or VB, or both versus no further therapy in stage I ECM confirmed these findings. For the HIR group, VB alone appears to be adequate in ensuring vaginal control compared with EBRT.

The best management strategy for stage IC** grade 3 EC (high risk) remains uncertain, given the high rates of distant metastasis and ECRDs, even after pelvic RT. The PORTEC-3 trial [61] is comparing concurrent chemoradiation followed by adjuvant chemotherapy with pelvic radiation alone in this group with advanced stage disease.

*According to FIGO staging (2009).

**According to FIGO staging (1998).

**Gastrointestinal, pancreatic, oesophageal and rectal cancer**

Data reporting integration of advanced EBRT technologies in elderly patients with GI cancers is promising. Pancreatic SBRT (Figure 4) offers local control with the convenience of ≤5 fractions and low toxicity [62]. Patients ≥80 who are unable to undergo surgery can safely receive definitive SBRT [63]. However, for those elderly patients undergoing pancreatic resection, the role of RT is not clear. Analysis of Johns Hopkins data in patients ≥75 showed that adjuvant therapy is significantly associated with increased survival at 2 years but not at 5 [64].

Oesophageal IMRT (Figure 5) is associated with significantly better OS, locoregional control and non-cancer-related death compared with 3D conformal RT [65]. There are no prospective data yet, but retrospective series suggest treatment is well tolerated and may allow delivery of a higher tumour dose, of significant interest for the treatment of medically inoperable elderly patients [66, 67].

In rectal cancer, patients with locally advanced disease benefit from CMT [68], with prospective data showing that preoperative RT is associated with significantly better local control and less acute and late toxicity than postoperative RT [69]. RT options...
include preoperative long-course RT (LCRT) with concurrent chemotherapy [70] and short-course RT alone in the elderly with acceptable tolerance of therapy and associated lower rates of local recurrence [71]. However, since the overall rates of local failure in the total mesorectal excision era are low, the issue is patient selection, with possible omission in those elderly patients with an increased risk for complications or early death [72]. With early rectal cancer in medically inoperable patients, endorectal BCT has been associated with low rates of local failure for T1 and favourable T2 lesions [73]. There is interest in the potential for those elderly patients with a complete clinical response after LCRT to be observed, reserving surgery for salvage, but further data are needed to validate this approach [74]. For elderly patients who are not candidates for potentially curative resection of solitary liver or lung metastases, SBRT yields high local control rates with minimal toxicity [75].

central nervous system tumours

Irradiation of brain tumours in the elderly is particularly challenging given concerns about the potential exacerbation of declining mental function. The two major indications for central nervous system RT in the elderly are glioblastoma (GBM) and brain metastases. Almost half of patients with GBM are aged ≥65 years. The incidence of GBM and brain metastases is increasing in the elderly, in whom both age and performance status are major prognostic factors [76].

A large study showed that the poor prognosis of elderly patients with GBM or brain metastases is age-related and is not only due to less intensive work-up or access to therapy [77]. Older patients are more likely to have primary GBMs characterised by epidermal growth factor receptor gene amplification and lack of isocitrate dehydrogenase mutation with an aggressive clinical course [78].

Treatment options for GBM include surgery, RT and chemotherapy. An attempt at maximal safe debulking is usually recommended.

The value of RT in patients ≥70 years with GBM has been confirmed [79]. Median survival following RT (50 Gy in 5 weeks) was 29.1 versus 16.9 weeks for supportive care only. PFS was 14.9 versus 5.4 weeks. RT did not impair cognition or QoL. An RCT in patients aged ≥60 years showed that a 3-week course of RT...
(40 Gy) was equivalent to the conventional 60 Gy in 6 weeks with a median survival of 5–6 months in both arms [80].

The EORTC-NCIC study, which established RT combined with concomitant and adjuvant temozolomide (TMZ) as standard treatment of GBM, included good performance status patients ≤70 years. The 2-year survival in the 60- to 70-year age group receiving RT with TMZ was 21.8% versus 5.7% with RT only [81]. MGMT gene methylation predicts benefit from combination therapy and is the most important prognostic factor in patients in this age group treated with RT and TMZ. RT combined with TMZ is well tolerated in fit elderly GBM patients. However, in one study, 56% of patients suffered neurocognitive decline despite target volumes limited to the visible tumour and small field margins of around 2 cm [82]. Two recent phase III studies compared TMZ alone with RT alone in elderly GBM patients. The NOA study [83] showed that TMZ is non-inferior to RT, although RT achieved better survival as a whole. However, patients receiving RT had greater discomfort from communication deficits. The Nordic study [84] showed better survival with TMZ compared with standard RT but not compared with hypofractionated RT. For patients aged >70, both TMZ and hypofractionated RT yielded longer survival than conventional RT. In both studies, MGMT methylation predicted response to TMZ but not to RT, suggesting the MGMT status could be used to select elderly patients to receive initial therapy with TMZ alone.

Conventional treatment of brain metastases is whole-brain radiotherapy (WBRT) delivering 30 Gy over 2 weeks. An alternative for elderly patients with limited brain metastases is stereotactic radiosurgery (SRS) (Figure 6). A retrospective series of patients >65 years treated with SRS reported local control >90% and a median survival of 8 months [85]. WBRT added to local resection or SRS does not improve OS or function for limited brain metastases. SRS alone should probably be considered for elderly patients at increased risk of cognitive impairment [86].

**head and neck cancer**

While about 25% of patients with head and neck cancer are aged >70 [87], elderly patients continue to be offered suboptimal treatment [88]. RT plays a critical role in this population where surgery is often contraindicated. However, radical treatment is associated with increased toxicity, particularly when concomitant chemotherapy or altered fractionation strategies are used.

Meta-analyses of both combined chemoradiation and altered fractionation confirmed significant locoregional control and survival benefits overall, but were unable to demonstrate a survival benefit in the >70 age group [89]. Competing risks of mortality from non-cancer causes are more likely to explain this rather than either a reduced treatment efficacy per se or increased risk of death from toxicity. While elderly patients tolerate aggressive treatment less well [88], expert consensus has recommended that age alone should not be used as a criterion to exclude more effective radiation strategies [87].

Recent advances in both RT delivery and concomitant treatment modalities may improve outcomes for curative RT in the elderly. The introduction of IMRT offers the potential to reduce both acute and long-term treatment toxicity, confirmed in a

![Figure 6](https://example.com/figure6.png)
recent RCT comparing IMRT and conventional/3D techniques [90]. While early attention focused on parotid-sparing IMRT to decrease the risk and severity of late xerostomia, more recent studies include dysphagia- and carotid-sparing IMRT strategies aiming to reduce dose to swallowing structures and to the carotid arteries for early larynx cancer, where cure rates are traditionally high and late cerebrovascular events related to high-dose carotid exposure remain a concern [91].

acknowledgements
We thank Karen Wishart for the preparation of the manuscript.

disclosure
The authors have declared no conflicts of interest.

references


