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REVIEW

Geriatric Radiation Oncology: What We Know and What Can We Do Better?

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Abstract: Elderly patients represent a growing subgroup of cancer patients for whom the role of radiation therapy is poorly defined. Older patients are still clearly underrepresented in clinical trials, resulting in very limited high-level evidence. Moreover, elderly patients are less likely to receive radiation therapy in similar clinical scenarios compared to younger patients. However, there is no clear evidence for a generally reduced radiation tolerance with increasing age. Modern radiation techniques have clearly reduced acute and late side effects, thus extending the boundaries of the possible regarding treatment intensity in elderly or frail patients. Hypofractionated regimens have further decreased the socioeconomic burden of radiation treatments by reducing the overall treatment time. The current review aims at summarizing the existing data for the use of radiation therapy or chemoradiation in elderly patients focusing on the main cancer types. It provides an overview of treatment tolerability and outcomes with current standard radiation therapy regimens, including possible predictive factors in the elderly population. Strategies for patient selection for standard or tailored radiation therapy approaches based on age, performance score or comorbidity, including the use of prediction tests or geriatric assessments, are discussed. Current and future possibilities for improvements of routine care and creation of high-level evidence in elderly patients receiving radiation therapy are highlighted.

Keywords: radiation therapy, elderly, geriatric assessment

Introduction

Due to demographic changes, radiation oncologists are facing an increasing number of elderly patients in their daily practice at least in developed countries.[1] There is no clear preclinical, radiobiological or clinical evidence for a generally reduced radiation tolerance with increasing age.[2] Nevertheless, an emerging body of evidence shows that older patients are still less likely to receive radiation therapy (RT) in similar clinical scenarios compared to younger patients, especially with regard to adjuvant treatment settings.[3]

A variety of factors may play a role in the clinical decision-making process: Elderly patients are clearly underrepresented or even excluded from most randomized trials creating the evidence for certain treatment decisions.[4] Thus, for many physicians, it seems at least questionable if results commonly used for patient guidance can be simply transferred to the elderly population. Elderly patients are also more likely to have either distinct serious comorbidities or at least an accumulation of several minor limitations of organ functions. This may lead to a (anticipated) decreased treatment tolerance.[5] Moreover, socioeconomic factors such as limited mobility or inadequate resources for general care and/or management of common side effects at home may further impair their (anticipated) ability for outpatient RT treatments.[3] This seems especially true if long travel distances to the next RT facility are present. Different views on treatment aims focusing on the preservation on quality of life (Qol) and personal independence rather than pure survival may further prompt elderly patients more likely to refuse (anticipated) intense treatment approaches or long-lasting inpatient therapies.[6]

From a scientific point of view, addressing the question of an optimal RT approach in elderly patients is even more difficult. First of all, there is no generally agreed definition of the term "elderly", which seems to be even disease- and/or

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treatment specific. While most physicians would agree to designate a 70-year-old person with glioblastoma as "elderly", this would probably not been the case for prostate cancer. Moreover, there is no clear demarcation to patients with comorbidities and/or limited performance status. Many studies reporting outcomes of "elderly" patients include also "frail" patients without reporting subgroup analyses.[3] Severe comorbidities of organs within the radiation volumes obviously can limit RT tolerance, but this does not represent a specific difference compared to younger patients. While limitations in organ functions outside the treated area usually do not compromise the ability to tolerate RT, this might be true for combination approaches.

Radiation techniques as well as supportive care have constantly evolved over time, resulting in less severe toxicities and/or improved capabilities to reduce side effects.[7] The widespread adoption of intensity-modulated or stereotactic RT constantly reduced doses to adjacent organs at risk. Combined with the use of daily image-guidance, those advances resulted in improved tolerability of RT. Therefore, reports with outdated radiation techniques often describing increased toxicity in elderly patients should not be used anymore to draw conclusions on treatment tolerability.[3] In contrast, non-randomized analyses reporting equal toxicity inherit always some risk of selection bias.[3] Randomized comparisons specifically addressing elderly patients are desirable, however they likely face difficulties regarding the definitions of inclusion criteria: Because elderly patients show a greater variety in performance status and comorbidities, wide inclusion criteria would result in inhomogeneous cohorts. In contrast, strict inclusion criteria and/or stratification rules would compromise recruitment.

However, evolvement of radiation techniques offers also a chance to improve the adherence to RT in elderly and/or frail patients. Hypofractionated regimes using less fractions with higher single doses resulting in shorter overall treatment time have been widely adopted. This will likely reduce the impact of socioeconomic factors on treatment decisions on both sides (physicians and patients).[8] Nevertheless, more research is warranted, specifically addressing the value and tolerability of RT and/or combination approaches in elderly patients. This should include investigations about the optimal study design for the evaluation of more personalized treatment approaches.

While clear evidence and consequently specific recommendations or guidelines are still rare, our review aims at summarizing the current evidence for RT in elderly patients to support radiation oncologists and other treating physicians in their decision-making process. We hereby focused on the most relevant disease types presented in daily practice of radiation oncology.

Central Nervous System Tumors

Approximately 310.000 new cases of central nervous system (CNS) tumours are diagnosed globally and 67.114 new cases in Europe each year corresponding to a crude incidence rate of 4.0/100.000 and 9.0/100.000.[9] Almost half of them are diagnosed in patients aged 65 and older.[9] Around 50–70% of those tumours are diagnosed as glioblastoma[10] with incidence rates peaking at ages 60–80 years.[11] Despite this fact, elderly patients are an underrepresented age group in clinical trials.

Outcome in patients diagnosed with glioblastoma is bleak: 5-year overall survival (OS) still ranges between 3% (patients >65 years) to 27% (patients between 20 and 39 years).[10] Combined chemoradiation with temozolomide following resection has been established as treatment standard in 2005.[12] Stupp et al[12] could show impressive OS improvement by combining simultaneous radiochemotherapy with temozolomide plus adjuvant temozolomide. They observed an increase median survival from 12.1 months (radiotherapy only) to 14.6 months (chemoradiation).[12] In their subgroup analysis of patients ≥60 years, chemoradiation still improved OS (11.8 months vs 10.9 months), but the observed effect was not as pronounced as in younger patients. The benefit also seemed to decrease with increasing RPA class corresponding to decreasing overall performance status.[13] Patients with MGMT promotor methylation were shown to benefit from combined treatment significantly more than patients without methylation.[14] However, age itself was not a significant prognostic factor in this post-hoc analysis.[14]

Treatment outcomes can be further improved by tumour-treating fields. Their addition after completion of a regular Stupp regimen resulted in improved OS without detrimental impact on Qol.[15,16] Intensification of chemotherapy by the addition of CCNU to temozolomide in patients with MGMT promotor methylation in the CeTeG trial also increased median OS (48.1 vs 31.8 months) in patients ≤65 years.[17] However, fewer elderly patients seem to exhibit favourable

prognostic markers such as MGMT promotor methylation.[18] Iwamoto et al analyzed patterns of care in 4137 glioblastoma patients aged >65 years and could show that age and comorbidities significantly influenced treatment choice (resection, chemotherapy, radiotherapy) in this cohort.[19] Defining adequate treatment paths in elderly patients is therefore an important issue.

The considerable time burden of a standard course of radiotherapy may play an important role specifically in the elderly. Nevertheless, the French group showed that patients aged 70-85 years benefited significantly from 50.4Gy in 28 fractions vs best supportive care (BSC) in terms of OS and symptom control.[20] In order to shorten overall treatment time, Roa et al[21] established hypofractionated radiotherapy with 15×2.67Gy in elderly patients. Their regimen was equally effective compared to standard radiotherapy with 30x2Gy in a cohort with a median age of 71–72 years. No difference in either OS or performance score was noted. However, median survival was only 5.1 months (60Gy) and 5.6 months (40.05Gy).[21]

The EORTC-trial therefore investigated the use of combining hypofractionated radiotherapy with temozolomide in a trial randomizing 562 patients with a median age of 73 years. Hypofractionated chemoradiation improved OS from 7.6 months (RT alone) to 9.3 months (chemoradiation). Patients with MGMT-promotor methylation again benefited more from the addition of chemotherapy (13.5 months vs 7.7 months) than patients with unmethylated MGMT-promotor (10.0 months vs 7.9 months). Qol was not affected by treatment arm.[22]

With the aim to further reduce in-hospital treatment time, Wick et al[23] investigated temozolomide only as an alternative to standard radiotherapy in patients with a median age of 71/72 years within the NOA-08 trial. Overall and event-free survival were higher in the radiotherapy group. In their subgroup analysis, MGMT-promotor methylated patients receiving temozolomide showed superior overall and event-free survival than MGMTpromotor methylated patients receiving radiotherapy. Hence, temozolomide only may be an option for this subset of patients.[23]

The NORDIC-trial was designed to clarify this question further: Malmstrom et al[24] randomized patients aged 60–83 years to standard radiotherapy (60Gy), 10×3.4Gy or temozolomide. Protocol completion in the 60Gy and temozolomide groups were only 72% and 34% vs 95% in the hypofractionated group. OS in the temozolomide group was 8.3 months vs 7.5 months (hypofractionated) vs 6.0 months (standard RT).

As described above, patient performance score, comorbidities and age often influence treatment choice in clinical routine. Mirimanoff et al[25] could show the influence of those aspects through analysis of the Stupp trial according to RPA classes: patients with lower RPA classes showed significantly improved outcomes. Gerstein et al[26] and Combs et al[27] retrospectively showed significant differences in outcome based on overall performance state or RPA class in elderly glioblastoma patients. Unfortunately, comorbidities are not reported in either of those trials specifically including elderly patients. Median age as well as minimum age also varies substantially between the trials. While two trials report Karnofsky performance and mini-mental state exam scores,[22,23] Malmstrom et al[24] does not include this information. Neither of those trials include any form of specific geriatric or frailty assessment, hence interpretation of those trials has some limits regarding those aspects.

As opposed to many other malignancies though, treatment of glioblastoma in elderly patients can be guided by prospective evidence albeit more detailed information is still somewhat scarce.

Elderly patients well enough to undergo treatment should at least receive hypofractionated radiotherapy. Elderly patients with MGMT-promotor methylation and good performance status may receive either combined chemoradiation or temozolomide alone, whereas patients with poor performance status may receive hypofractionated radiotherapy, temozolomide or BSC.[28]

Head and Neck Cancer

Squamous cell carcinoma represents the most common malignancy in the head and neck (HNSCC). Approximately 745.000 new cases were diagnosed in 2020 worldwide corresponding to a crude incidence rate of 9.6/100.000.[29]

Combined chemoradiation has been well established as a potentially curative treatment approach resulting in improved organ preservation, locoregional control and OS of around 60-70% in locally advanced HNSCC.[30–37] A recent SEER database analysis could demonstrate that modern regimens have improved survival for HNSCC patients over the past decades for all age groups except for patients aged ≥75 years.[38]

Current cancer statistics in the UK show peak incidence rates of HNSCC in males at 70–74 years and in females at 85–89 years. Around 33% (male) to 36% (female) of all new HNSCC patients are ≥70 years,[39] so a significant number of patients appear not to share the benefit from recent advances. Elderly patients (≥70–75 years) are often excluded from participation in clinical trials which represents a relevant knowledge gap in the treatment of patients in this age group.

We will therefore address the following issues in the treatment of elderly head and neck patients based on available – albeit mostly retrospective – data:

1. Do elderly HNSCC patients routinely receive standard treatment?
2. Is standard treatment feasible for elderly patients?
3. Which factors adversely affect prognosis in elderly patients?
4. Are there any objective criteria to guide treatment selection in elderly patients?

Do Elderly HNSCC Patients Routinely Receive Standard Treatment and is It Feasible for Elderly Patients?

A recent pattern-of-care survey in Germany, Austria and Switzerland reported that the majority of respondents apparently treat elderly patients within standard regimens.[40] Several groups also report outcomes of elderly patients undergoing chemoradiation. Maggiore et al[41] share their experience in 89 patients ≥70 years treated with a 5-FU/hydroxyurea-based regimen between 1997 and 2009. At a median follow-up of approx. 40 months, OS was 32%. Most patients (86.5%) completed their treatment; toxicity, however, was considerable: grade 3–4 neutropenia occurred in 34%, 44% of patients experienced aspiration, 62% required feeding tubes. The treatment was still deemed feasible in selected patients.[41] Treatment toxicity in 246 elderly patients (65 years) mainly treated by chemoradiation was found to be high also in the Freiburg analyses: incidence of at least one grade 3/4 toxicity was 56%. While treatment adherence was high (87%), OS only reached 57% at 2 years.[42] Brown et al[43] reported the outcome of patients ≥80 years treated with intensity-modulated techniques from 2003 to 2015. Only 7% of those patients received chemoradiation. Twenty-six percent required in-patient treatment during radiotherapy. However, overall grade 3/4 late toxicity at a median follow-up of 25 months was only 2%. The authors concluded that treatment tolerance was high even in this age group.[43] Considering low overall patient numbers and also low rates of patients treated with concomitant chemoradiation, it is doubtful whether elderly patients routinely receive standard treatment. As reported, standard treatment may be feasible for some patients, though selection is still largely subjective. Potentially, an evaluation of larger databases and registries regarding treatment specifics – which to our knowledge is currently lacking – may help to answer these questions.

Which Factors Adversely Affect Prognosis and are There Any Objective Criteria to Guide Treatment Selection in Elderly Patients?

As mentioned, chemoradiation is associated with considerable treatment-related toxicity. In cumulative analysis of RTOG studies, approximately 43% of patients developed late toxicities grade 3+.[44] Patient age was one of the most important predictors for development of severe side effects.[44] Age was also found to predict for higher rates of treatment modifications, interruptions or discontinuation in two retrospective cohorts of 272 and 40 elderly patients receiving chemoradiation.[45,46] Moreover, age adversely affected outcomes in elderly patients receiving chemoradiation according to a SEER analysis.[47] Comorbidity has also been shown to adversely impact survival[48,49] and toxicity,[50,51] while prevalence of comorbidity in HNSCC patients increases with age.[51,52] Paleri et al[53] analyzed 180 patients with larynx carcinomas: 64% of patients had comorbidities, 26% more than one comorbid condition. OS in patients without comorbidities was significantly higher than in patients with one or more comorbidities. Patients with independent neurological disorders as part of their comorbidities showed the highest mortality rate of 70% in this analysis.[53] No reliable statement can be made regarding the frequency of treatment modifications in elderly patients (see above). However, Derks et al[53] could show in their analyses that both age and comorbidities independently influenced treatment choice in HNSCC patients. Frailty is a relatively new term summarizing age-related physiological decline and

functioning leading to increased vulnerability. De Vries and collaborators[54] analyzed 160 patients undergoing radiotherapy for head and neck cancer from 2014 to 2016. Type of treatment and neither frailty or geriatric assessment were predictive of treatment toxicity in their cohort.[54] In contrast, Morse et al[45] found that patients showing sarcopenia as a surrogate for frailty were more prone to developing treatment toxicities during chemoradiation. This finding is supported by Chou et al[55] and Karavolia et al,[56] who showed associations between increased vulnerability and OS and toxicity. The most concordant parameter to predict for adverse outcome in the elderly seems to be overall performance state. Despite several attempts to identify other predictors, performance state was found to be an independent predictor for OS in several analyses.[52,57–59] However, Nicolay et al[59] recently proposed a novel prognostic score. Based on their initial cohort of 284 patients, they found performance state, comorbidity index, CRP level and tumour and nodal stage as independent prognostic factors. Their nomogram based on CRP, Charlson comorbidity index and Karnofsky performance state could predict for outcomes in their validation cohort (217 elderly patients) reasonably well and may be used to select treatment in the elderly population.[59] Further prospective data are, however, pending.

In summary, data regarding standard treatment in elderly HNSCC patients are scarce. In addition, consensus regarding absolute age-groups termed "elderly" seems to be lacking. Retrospective analyses frequently report on comparatively low patient numbers in view of the considerable incidence of HNSCC in the elderly, hence one may safely assume that treatment is frequently modified and adjusted. Several factors, including age, comorbidities, frailty and performance score impact treatment as well as treatment outcome in HNSCC. Prospective data to guide objective scores and hence treatment recommendations are still lacking.

Lung Cancer

RT is an important component of lung cancer therapy alone or in combination with systemic treatments. With a median age of about 70 years at diagnosis, lung cancer is clearly a disease of the elderly, often associated with comorbidities and limited performance status. Many patients cannot receive standard treatment and were excluded from randomized trials, leading to limited evidence in the treatment of this patient group.[60–62] Therefore, the decision-making process should aim at maximizing benefits and minimizing harms depending on patients' individual values and preferences.[63] Lung cancer can be generally divided into small-cell (SCLC) and non-small-cell lung cancer (NSCLC). In SCLC, systemic therapy is the dominant option for the vast majority of patients, while the role of RT is restricted to early stages or palliative treatments. Within these situations, the used RT regimens (and their general limitations) for SCLC are similar to those for locally advanced or metastatic NSCLC. Therefore, it will not be specifically addressed in the following:

NSCLC Stage I/II

Standard of care in patients with Stage I/II is resection, alternatively stereotactic ablative body radiotherapy (SABR) is well established. A pooled analysis of the prospective randomized STARS and ROSEL trials showed even improved survival with SABR compared to surgery for resectable patients, although not focusing on elderly patients.[64] In 2021, the updated propensity score matched results of the STARS trial confirmed that SABR is a comparable curative treatment with minimal toxicity, noninvasive character and possibility for an outpatient setting with a short treatment period (generally 1 week), which is often important for frail or elderly patients.[65] Brooks et al[66] retrospectively analysed 772 patients in Stage I/II NSCLC (n = 442 < 75 years, n = 330 >75 years) treated with SABR and found no difference in major endpoints (time to progression, lung-cancer-specific survival, 2yr-OS and toxicity) according to age. OS in the group >75 years deteriorated after 5 years, due to natural shorter life expectancy. Toxicity did also not differ, no grade 4/5 toxicity was observed in the elderly group.[66] A large retrospective database confirmed these results.[67] In conclusion, SABR should be offered preferably to elderly and frail patients.

NSCLC Stage IIIA/B (Resectable)

In potentially resectable Stage IIIA, multimodal treatment with neoadjuvant chemotherapy/chemoradiation followed by surgery is recommended. However, this seems feasible only in highly selected elderly patients without relevant comorbidities and high performance score.[61] Although beneficial in other endpoints, prospective data showed no difference in OS comparing chemoradiation alone vs chemoradiation followed by surgery[68,69] in well

selected Stage IIIA/B tumors. The number of patients ≥70 years was not reported in the study of Eberhardt et al[68] and very small (16%) in the study of Albain et al.[69] No relevant prospective trials are available comparing trimodal therapy vs definitive chemoradiation in the elderly group. Both treatments are generally valid therapeutic options, while chemoradiation alone is less invasive and toxic and therefore likely the preferable option in frail or elderly patients. Furthermore, no prospective data are available addressing the role of surgery specifically in the elderly. Retrospective reports also included only very small numbers of patients ≥75 years (17%) evaluated for surgery[70] due to the strict pulmonary/cardiac functional requirements for resections.[61,71]

One small prospective trial specifically assessed the role of RT in patients ≥75 years and reported a median survival of 19 months with very limited toxicity.[72] Pignon et al found no significant differences regarding OS and toxicity after curative intent RT according to age.[73] Although comorbidities and poor functional status may influence the tolerability of radiotherapy, modern radiation techniques have clearly increased the therapeutic index. Especially if conventional chemoradiation seems not tolerable, hypofractionated RT should be evaluated.[74]

NSCLC Stage IIIB/C (Unresectable)

Concurrent chemoradiation was found to be superior to RT alone already during the 1990s,[75] but came along with increased toxicity. Consequently, subsequent trials included only small numbers of elderly patients. First, Atagi et al investigated the role of chemoradiation in patients ≥70 years.[76–78] OS benefit for chemoradiation was confirmed, although the applied regimen (carboplatin only) was less intensive than usually used doublets. Similar results were shown in a meta-analysis for combined treatments despite increased toxicity.[79] Esophageal and pulmonary toxicities are usually the clinically most relevant side effects with regard to treatment compliance and Qol and are clearly increased within combination approaches.[80,81] Therefore, sequential chemoradiation or (hypofractionated) RT are still reasonable treatment options in elderly patients deemed unfit for concurrent chemoradiation, showing limited toxicity and promising results.[74,81,82] A clinical trial comparing concurrent and sequential chemoradiation in patients ≥75 years regarding quality-adjusted survival is ongoing. Patients are stratified into frail, vulnerable and fit groups based on geriatric assessment.[83]

Immunotherapy has gained attraction also in non-metastatic NSCLC patients since the PACIFIC trial showed an OS benefit for adding consolidation therapy with Durvalumab after chemoradiation compared to chemoradiation alone.[84,85] Immunotherapy generally inherits a different safety profile, which is not affected by age[86,87] at least if used as a sole treatment. Therefore, checkpoint inhibitors seem worth to be evaluated either as a substitute for concomitant chemotherapy during chemoradiation or as an adjunct after less intensive chemoradiation specifically in elderly patients. The first approach is currently evaluated in the randomized Phase II TRADE-hypo trial (NCT04351256). It includes patients >70 years, ECOG 1/2 with locally advanced, unresectable NSCLC, who are unfit for chemotherapy because of age and/or frailty and compares concomitant durvalumab with either conventionally (60Gy in 30 fractions) or hypofractionated (55Gy in 20 fractions) RT.[62] Moreover, a Japanese prospective trial evaluating conventionally fractionated RT with low-dose carboplatin and Durvalumab followed by Durvalumab consolidation in frail/elderly stage III NSCLC patients is ongoing.[88] Efficacy and toxicity results, especially regarding pneumonitis rates with simultaneous application, are awaited.

NSCLC Stage IV (Metastatic)

If RT is used for palliation or prevention of symptoms (pain, bleeding, obstruction), hypofractionated regimens are clearly preferable. In case of oligometastatic disease, the individual situation has to be evaluated. Palma et al showed[89] in his prospective trial that SABR in oligometastatic patients may improve OS with minimal toxicity compared to chemotherapy alone. Furthermore, SABR may help to avoid or delay the need for systemic therapies, which can improve Qol especially in frail/elderly patients. Adding RT to Pembrolizumab is also a promising option with improved outcome in metastatic lung cancer.[90]

Breast Cancer

Breast cancer (BC) remains the most common cancer diagnosis in women. Of those diagnosed with BC, about 30% are ≥70 years.[91] In early stage BC, breast conserving surgery (BCS) is the first and one of the main pillars in oncological

treatment. Even though RT is seen as a standard treatment after BCS,[92] the treatment of elderly BC patients differs from the treatment of younger ones due to geriatric frailty or comorbidities – especially in low-risk constellations. Nevertheless, the range of general conditions in elderly patients is wide – from highly morbid patients in their early 70s to athletic patients in their late 80s – leaving the establishment of a standardized procedure hardly achievable. Especially in radiation oncology, where the side effects of a breast treatment decreased continually over the last decades, critical selection of patients is crucial, yet not always easy.

If patients are not eligible for postoperative RT, mastectomy was historically considered as the alternative surgical treatment.[93] This dogma, that all patients who cannot receive postoperative radiotherapy have to undergo mastectomy, falters in low-risk constellations (pT1, pN0, ER/PR+, Her2-). Several analyses showed that in those situations, RT can most likely be dispensed – even after BCS. Hughes et al reported on the results of the CALGB 9343 trial, which showed an advantage of tamoxifen and postoperative RT compared to tamoxifen alone after 10 years (local control 98% vs 90%, sig.). Nevertheless, this did not translate in a significant difference in time to mastectomy, time to distant metastasis, cancer-specific survival or OS.[94] A more recent analysis by Stueber et al came to similar conclusions with a chance of relapse within 5 years of <3% in patients aged 70 years and older with low-risk features.[95] Furthermore, the authors recommend to spare elderly low-risk patients from mastectomy with the intention of avoiding postoperative RT. In elderly high-risk patients, RT following BCS is recommended. The recent NCCN-guidelines also feature the recommendation to consider omitting breast irradiation in patients aged 70 years and older with ER-positive, cN0, pT1 tumors who receive adjuvant endocrine therapy.[96] The same is true for the national German guideline.[92]

If the omission of radiotherapy is no option, several hypofractionated options are eligible. The most elegant option is an intraoperative single-dose radiotherapy in which the "adjuvant" treatment is already completed intraoperatively. A major disadvantage may be that the full pathological report is not available at the time of the radiotherapy and that this option is not available in all centers. Nevertheless, the randomized TARGIT-IORT trial showed a comparable long-term control to the classic RT.[97] Accelerated breast irradiation over the course of one week was also described as non-inferior to the standard treatment course of three weeks, though long-term follow-up concerning cosmesis is still pending.[98] Partial breast irradiation after BCS is also often discussed as an additional RT technique. However, one meta-analysis reported on significantly higher rates of in breast recurrences.[99] In cases with higher risk constellations (T3/T4, N+, ER/PR-, Her2+, TNBC) radiotherapy according to guidelines is clearly recommended with a significant effect on recurrence-free survival being proven and confirmed by a recent analysis.[95]

The variety of treatment options (especially in low-risk constellations) is wide and needs to be discussed in detail with the patient, desirably before surgery. The patient's clinical condition and the patient's preferences must be taken into account to reach an informed consent on the best possible treatment for the individual case.

Gastrointestinal Cancer

Curative intent RT for gastrointestinal cancers is usually not used as a sole modality but often within a bimodal (combined with simultaneous chemotherapy) or even trimodal (followed by surgery) approach. This complicates the evaluation of its role in elderly patients. A relevant part of toxicities and treatment compliance will be related to the concurrently applied chemotherapy rather than to RT alone. Detailed discussion of all combination approaches within gastrointestinal cancer would exceed the scope of this review. Therefore, we focused on three major gastrointestinal entities with (chemo)radiation as a major part of curative intent therapy strategies.

Esophageal Cancer

Neoadjuvant or definitive chemoradiation represents the current standard of care in locally advanced esophageal cancer (EC) based on resectability, while RT alone has to be considered a palliative treatment.[100] Although the median age at diagnosis for EC is 68–70 years and roughly 30–40% of patients will be ≥75 years,[101,102] elderly patients are still underrepresented in randomized trials. This seems to be partly related to the inclusion of surgery into the treatment approach. For example, the median age within the CROSS trial (setting the standard of neoadjuvant chemoradiation followed by surgery in resectable locally advanced EC) was only 60 years.[103] However, modern trials focusing on definitive chemoradiation analysed cohorts comparable to the general age distribution. In the randomized SCOPE-1 and

ARTDECO trials,[104,105] median age was 67 and 71 years, with the latter including patients up to 90 years. Nevertheless, two SEER analyses focusing on patients ≥65 years showed an underutilization of treatment in older patients per se:[106,107] 34% of patients ≥65 years did not receive any treatment, which was significantly correlated with decreased OS. Interestingly, increasing age was associated with the non-receipt of surgery or chemotherapy but not RT.

Trimodal Therapy

Several studies showed that trimodal therapy (chemoradiation followed by surgery) results in improved OS also in selected elderly patients compared to surgery alone.[108–110] Guttman et al[109] analysed 1364 patients >70 years and found lower R+ resection and increased OS rates with the addition of neoadjuvant chemoradiation. Postoperative morbidity and mortality were similar. However, most studies analyzing age-dependent outcomes after trimodal therapy or resection alone showed an increase in postoperative cardiopulmonary toxicity[108,109,111] in elderly patients. This finding translated into consecutively increased postoperative mortality at least in some of the trials.[108,109] Cardiopulmonary toxicity after trimodal therapy increased roughly linear with age in a pooled US analysis (+61% per decade).[108] Similarly, postop. mortality after resection increased with age (65–69 yrs: 9%, 70–79 yrs: 13%, >80 yrs: 20%) in a large population-based study.[112] However, this might be rather related to comorbidity than age, as a significant association between an increased Charlson score (CCI >2) with postoperative mortality was described in the latter analysis.[112]

Definitive Chemoradiation

Data on definitive chemoradiation focusing on elderly patients are limited and mainly retrospective. Some reports found decreased survival rates and increased major toxicities.[113,114] However, most data suggest that chemoradiation is equally effective compared to younger patients without a major increase in adverse events.[115–117] Clinical complete remissions (cCR) are achieved in 50–65% of the patients with median OS times of 12–26 months and 2-year OS-rates of 30–40%.[118] Moreover, in the prospective SCOPE-1 trial, age (< vs ≥ 65 years) had no statistical impact on PFS or OS according to multivariate analyses.[104] Only one prospective trial specifically addressed chemoradiation feasibility in (selected) elderly patients: Servagi-Vernat et al[119] included 22 patients (mean 79 years) if they had a CCI ≤4, a baseline weight loss <15% and ECOG ≤2. They were treated with 50Gy and concurrent cisplatin. The treatment compliance was 100%, 64% achieved cCR at 6 weeks and 1-year OS was 62% with no acute grade 4 toxicities. The authors concluded that chemoradiation is well tolerated using these inclusion criteria, however some data suggest an increase in pulmonary complications in patients ≥80 years.[120] Tolerability of chemoradiation may depend also on several treatment factors. Carboplatin/Paclitaxel has shown similar OS and DFS with lower toxicity rates compared to the long-time standard of Cisplatin/5-FU also in the definitive setting.[121] The introduction of modern radiation techniques (namely image-guided intensity-modulated RT) has resulted in similar or improved outcomes with clearly reduced side effects in patients of all age groups.[122,123] The issue of the necessity of elective nodal irradiation is not finally solved in the absence of randomized trials. Indeed, increasing evidence suggests the use of smaller treatment volumes confined to the areas of gross disease because of increased tolerability.[123,124] A recent randomized trial further suggests that dose escalation beyond 50Gy to the primary tumor does not result in significantly improved outcome, but may result in increased toxicity.[105] Therefore, it seems reasonable to restrict the total dose in elderly/frail patients to 50Gy. Nutritional status (based on nutritional risk index) or weight loss at baseline have been identified as major prognostic factors for DFS and OS in large retrospective series.[125,126] There is no clear evidence supporting the prognostic value of further weight loss or deterioration of nutritional status nor its therapeutic correction during chemoradiation. Nevertheless, care should be taken to ensure adequate nutritional support especially in elderly patients.

In summary, elderly patients in good shape (especially with no or limited cardiopulmonary comorbidity) might be selected for trimodal therapy. For most patients, definitive chemoradiation (with selective reevaluation for surgery) should be preferred because of better treatment compliance and less treatment-related mortality. Chemoradiation should be performed preferably with limited treatment volumes and total doses not exceeding 50Gy. Modern imaging for treatment planning and modern RT techniques should be used. Care should be taken especially for adequate nutritional support. Future trials specifically designed for elderly cohorts are warranted. They should include the evaluation of geriatric assessment tools for the prediction of chemoradiation outcomes as for example in the ongoing OSAGE trial.[127]

Rectal Cancer

Neoadjuvant (short course) RT or chemoradiation therapy represents the current standard of care in locally advanced rectal cancer (LARC) to improve locoregional control and/or resectability.[128] Recently, neoadjuvant (chemo)radiation has been incorporated into so-called total neoadjuvant therapy (TNT) concepts combined with induction or consolidation chemotherapy prior to surgery.[128] Several randomized trials have shown increased overall response, pathologic complete remissions (pCR) and distant control rates compared to the standard approach.[129,130] In parallel, so-called NOM approaches omitting surgery in cases of cCR after neoadjuvant chemoradiation or TNT have gained attraction, especially if sphincter-sparing surgery seems not possible.[131] Both concepts have not been specifically studied in elderly patients. As TNT concepts usually include doublet or triplet consolidation or induction chemotherapy regimens, they seem hardly suitable for the majority of elderly patients. Nevertheless, alternative (non-surgical) treatment concepts might offer new options in elderly patients hardly suitable for extended surgery.

Median age at diagnosis of rectal cancer is roughly 70 years with a peak incidence at 80–85 years, which also represents the peak prevalence age for comorbidities.[132,133] In comparison, median age in major landmark trials was roughly 10 years less.[134,135] Moreover, several population-based or retrospective studies showed an underutilization of surgery, neoadjuvant radiotherapy and palliative systemic treatment with less adherence to guidelines compared to younger patients (<70–75 years).[136–141] In contrast, elderly patients received more often palliative and/or hypofractionated RT.[140,141] While treatment outcome in terms of OS has clearly improved in the last decades in younger patients (5y-OS increased from 60% to 70%), this was not the case in patients aged >75 years (5-year OS remained stable at around 40%).[142]

As the vast majority of LARC patients is treated within multimodal concepts, suitability for subsequent treatments has to be included into the evaluation of radiation approaches. Most available data indicate no distinct differences in treatment compliance or tolerance within neoadjuvant (chemo)radiation concepts comparing younger and older patients (cutoff typically 70–75 years).[143–147] Some trials showed higher rates of acute G3+ toxicity with limited clinical consequences. In contrast, a large Dutch study found a clear and steady increase in 1- and 6-month mortality after surgery with increasing age starting at 75 years.[133,142] While postoperative complication rates per se showed no significant difference, the onset of a complication resulted in clearly worse outcome in elderly patients.[133,142] For example, anastomotic leakage occurred at a rate of roughly 10% but resulted in a mortality rate of 8% in younger vs 57% in older patients.[133] Interestingly, the same studies did not find a significant association of preoperative RT with postoperative complication rates.[133,142] However, they showed an improved outcome with the addition of RT to surgery in elderly, which is also supported by a SEER analysis.[148] The authors concluded that RT had little or no impact on postoperative complication rates or mortality, while the surgical trauma itself remains most important.[133] In contrast, comorbidity seems to be clearly linked with postoperative complications and 30-day-mortality. A Dutch study restricted to patients >75 years showed only a moderate difference in postoperative complication rates and none in 30- day-mortality with or without neoadjuvant short-course RT in the entire cohort. However, they described a roughly 5-fold increase in complication rates and a more than 10-fold increase in 30- day-mortality, if severe comorbidity like COPD, diabetes or cerebrovascular disease was present.[149] Therefore, the most important question to answer prior to RT is suitability for major pelvic surgery. If a patient is deemed suitable, indication for neoadjuvant (chemo)radiation can usually follow standard recommendations. Several retrospective studies showed high compliance rates and similar results in patients aged >70 and deemed fit for surgery compared to younger ones.[143,146] There is no clear evidence for a distinctly different outcome comparing neoadjuvant short-course RT with long-course chemoradiation specifically in elderly patients, thus the indication may follow the institutional standards and general recommendations. However, short-course RT might be preferred with regard to patient's convenience.

In elderly patients deemed less suitable for major pelvic surgery, several algorithms have been proposed.[132,150] Paradoxically, some include treatment intensification of chemoradiation because of a higher likeliness of response. Moderate treatment intensification by localized dose escalation either via external beam RT or addition of brachytherapy can usually be achieved without a major increase in side effects.[151] A consequently pronounced response then might enable local excision (LE) or even omission of surgery without compromising the overall results. Several trials suggested

similar local control rates at least in node-negative patients with chemoradiation followed by LE in responding patients compared to more extended surgery,[152–154] although not specifically for elderly patients. Short-course RT seems less suitable for this approach because several reports suggest increased complication rates with LE after short-course RT compared to chemoradiation.[153–155] In frail (medically inoperable) patients, chemoradiation alone[132,150] or EBRT with or without brachytherapy are reasonable options.[150,156–158] If RT alone is used, hypofractionation should be strongly considered, because it achieved similar results to conventional fractionation.[159] Short-course RT is an effective regimen for palliation with >80% complete or partial symptom relief at four weeks and reasonable rates of colostomy-free and overall survival.[160] The addition of brachytherapy may further enhance the results as shown by a recent Phase I trial: increasing weekly doses of brachytherapy were added to a moderately hypofractionated EBRT concept and resulted in good response rates (cCR 61%) and acceptable OS.[161] However, within the MTD cohort of this trial, rectal grade 3+ toxicity was roughly 30% prompting the authors to recommend some form of optimization.

Several structured reviews have proposed similar treatment algorithms for elderly patients with rectal cancer.[132,150] Based on the available evidence, elderly patients in good shape (suitable for major pelvic surgery) should be preferably treated according to standard recommendations. Patients with intermediate features (some comorbidity, less suitable for major surgery) might be treated with chemoradiation (with or without dose escalation) and LE or omission or surgery in case of partial or complete response. In patients with severe comorbidity (unlikely to undergo surgery at all), hypofractionated radiotherapy achieves good palliation and seems feasible in most cases. Addition of brachytherapy can improve results but has to be weighed against increased complications risks.

Anal Cancer

In contrast to many other gastrointestinal malignancies, most patients with anal cancer are managed without surgery. The cornerstone of treatment is definitive chemoradiation with curative intent. Chemoradiation results in significantly improved outcomes compared to RT alone based on randomized trials.[162–164] The median age at diagnosis is 60–65 years and roughly onethird of the patients are aged ≥70 years.[165,166] Standard treatment usually includes a doublet chemotherapy regimen (Mitomycin C or Cisplatin combined with 5-FU or capecitabine) simultaneously applied to RT. This may result in considerable rates of acute gastrointestinal, hematological and skin toxicities. Therefore, its suitability to elderly patients is often questioned by clinicians. Data specifically addressing elderly patients are rare, mainly retrospective and therefore susceptible for selection biases. Moreover, the vast majority of published series used outdated staging modalities and radiation techniques (2D- or 3D-conformal RT). In contrast, modern techniques like intensity-modulated RT (IMRT) have shown clearly reduced rates of side effects in younger populations.[167] Nevertheless, most published data suggest that age per se is not limiting the capability to tolerate standard therapy. In a large population-based analysis of roughly 12,000 patients treated with curative intent, age was not an independent factor for receiving chemoradiation in multivariate analysis.[168] However, patients with two or more comorbidities were more likely to receive RT alone.[168] Several authors analyzed elderly cohorts with cutoffs of 70–80 years treated by chemoradiation or RT alone.[169–172] They showed high treatment compliance for RT but 25–50% of the patients needed dose reductions of chemotherapy, especially if comorbidity was present.[169,170] Addition of chemotherapy resulted in significantly increased toxicity but also in improved outcome in most reports, including colostomy-free survival.[169–171] Some investigators analyzed patients treated with either RT or chemoradiation according to age.[173,174] They observed less CHT use in elderly patients, which showed also worse performance scores. If only patients with chemoradiation were compared, overall toxicity was not clearly increased in elderly patients, but they tended to have less skin but more hematological side effects. Outcome parameters were reported only for the overall cohorts. While cCR, colostomy and LC rates were similar, MFS, DFS and OS were worse in older patients, probably related to less chemotherapy use and increased mortality by other causes.[173,174] Recent studies analyzed larger cohorts receiving chemoradiation by age groups.[165,175] They consistently found reduced treatment compliance (mainly to chemotherapy) with increasing age but no clear difference in overall toxicity. However, none of the measured outcome parameters was associated with age, while comorbidity was associated with more toxicity, more dose reductions and worse LC.[175] Thus, it seems reasonable to offer standard regimens also to elderly patients at least if performance score is good and no severe comorbidity is present.

In patients with comorbidities or limited performance status, several adjustments are possible with still curative intent. Chemoradiation can be performed using only one sensitizing agent (either 5-FU, Mitomycin or Cisplatin). Although chemoradiation with simultaneous doublet therapy (MMC/5-FU) was superior to 5-FU mono regarding LC, MFS and DFS in RTOG 87–04, no significant survival difference was reported.[176] However, patients with cardiopulmonary comorbidities might be less suitable for 5-FU or capecitabine therapy. In those patients, MMC or Cisplatin mono may represent a reasonable alternative, although not supported by sufficient data. In patients deemed unsuitable for chemotherapy at all, conventionally fractionated RT alone may still result in good outcome with less toxicity. In the RT only arms of both randomized trials showing superiority of chemoradiation, 5-year OS was still >50%. RT alone can be tolerated by most patients of advanced age even in the presence of comorbidities,[169–171,173] especially if modern radiation techniques are used. RTOG 0529[167] evaluated IMRT for anal cancer in a single-arm phase II design and demonstrated significant reductions in acute toxicity compared to historic data from RTOG 98–11.[177] Moreover, they showed that moderate de-escalation of dose did not result in decreased outcome. Therefore, the use of modern RT techniques should be mandatory in elderly patients. In frail patients, further adjustments can be made regarding target volume and dose. Charnley et al[178] reported the results of limited treatment (30Gy in 10 fractions to the primary tumor excluding elective nodal irradiation combined with low-dose 5-FU) in frail patients and found 100% treatment compliance with low toxicity and still tolerable outcomes.

In summary, elderly patients in good shape should be preferably treated according to standard recommendations. In patients with comorbidities or limited performance status, stepwise adjustments can be made, ranging from chemoradiation with a single agent to standard RT alone. While toxicity will be clearly reduced with every step, long-term survival is still likely in the majority of patients. In patients with severe comorbidity, hypofractionated radiotherapy with limited volumes still achieves good palliation. The use of modern RT techniques like IMRT is strongly recommended to reduce acute and late side effects.

Gynecological Cancer

RT is an integral part of the treatment in many gynecological cancers, however often used as an adjunct to surgery. We therefore focused on cervical cancer as the main entity using nonsurgical radiation-containing approaches. Recently, the American Cancer Society reported that more than 15% of cervical cancer cases were found in women aged over 65 years.[179] In large clinical studies, only a few elderly patients were included. Venkatesulu et al conducted a systematic review about patterns of care of cervical cancer in elderly and found only 24 out of 17,338 publications addressing the outcome in elderly cohorts.[180] In these publications, 11,279 out of 14,479 patients aged ≥60 years (78%) received EBRT with or without concurrent chemotherapy and/or brachytherapy. With regard to the latter, low dose rate (LDR) was the most common modality, followed by high dose rate (HDR). However, in some studies with scheduled brachytherapy, up to 30% of the patients did not receive it due technical reasons (48.7%), comorbidities (69.4%) or patient refusal (38.3%). Five-year OS was generally inferior (27–69%) for elderly patients compared to younger populations (58–75%). Suboptimal radiation dose resulted in clearly reduced 5-year OS (11%) compared to patients treated with chemoradiation followed by brachytherapy (74%). However, it remains unclear if elderly patients with cervical cancer have a worse prognosis per se, due to comorbidity or limited performance scores or due to limited treatment application or tolerability. Limited historical data showed inconsistent results regarding generally worse[181,182] or similar[183,184] survival outcomes in elderly compared to younger patients. The performance status has been reported as a significant prognostic factor for OS and PFS.[185–187] However, a retrospective registry-based study showed that patients ≥60 years were less likely to receive standard therapy compared to younger ones, mainly because treatment was not recommended.[188] In a Japanese study, some elderly patients experienced severe toxicity, although radiotherapy was generally effective for them.[189] These conditions might further contribute to the adverse effect on the prognosis of elderly patients.[190] Interestingly, Hou et al[191] reported comparable treatment outcomes with regard to CSS and loco-regional control in elderly patients with cervical cancer despite receiving less comprehensive treatment (including less concurrent chemoradiation, less brachytherapy, lower total RT dose and limited EBRT volumes). The authors concluded that, for patients ≥70 years a conservative treatment strategy with RT alone could be appropriate, especially in those with a favorable stage or histopathology. Similarly, Shimamoto et al[192] found equivalent DFS but worse OS in patients aged ≥65 years compared to younger ones.

Modern EBRT techniques with a reduction of treatment-related side effects might be helpful for elderly patients to improve outcomes and RT completion rates. Several studies have confirmed clearly reduced side effects with IMRT techniques compared to conventional 2D- or 3D-conformal treatments.[180,193] Brachytherapy was also often refused in elderly patients due to fear of toxicities or other reasons in elderly patients,[180,183,191] but seems applicable with acceptable toxicity using modern image-guided approaches. In a prospective cohort study, Seppenwoolde et al[194] analyzed morbidity and dose–volume effects in definitive radiochemotherapy for locally advanced cervical cancer. This cohort was treated with modern treatment techniques according to the EMBRACE protocol (94% received IMRT techniques). Most common gastrointestinal toxicities were low-grade diarrhea, stool urgency, rectal incontinence, rectal bleeding and weight loss. Most common genitourinary toxicities were dysuria and bladder incontinence. Only stool urgency, rectal or bladder incontinence and weight loss showed significantly increasing rates over the entire dose range. Correlations of toxicities with certain dose-volume factors (V40Gy) were observed, linking dysuria to bladder dose and stool urgency and rectal incontinence to bowel and rectum doses. Based on these data, the following treatment planning objectives were recommended to minimize stool urgency, rectal and urinary incontinence: bowel V40Gy≤250cm^3, rectum V40Gy≤80% and bladder V40Gy≤80–90%, respectively.[194] Using modern EBRT techniques considering those assumptions during treatment planning will likely increase treatment tolerability and ensure treatment completion in a larger proportion of elderly patients in the future.

In summary, age influences treatment strategies for cervical cancer world-wide, although based on scarce evidence. Only very few studies addressed treatment outcome in elderly patients with cervical cancer. However, most elderly patients may be treated with curative intent using modern radiation techniques with adequate supportive care. Recent studies have provided more insights into dose constraints for organs at risk to minimize acute and late toxicity by sophisticated treatment planning. The use of concurrent chemotherapy should be carefully evaluated based on patients´ performance status and comorbidities balancing possible benefit and harms. Brachytherapy should be an integral part of the treatment regimens in elderly patients as it can be safely applied by modern image-guided approaches with acceptable toxicities.

Prostate Cancer

Prostate cancer is a disease of the elderly and age remains to be the most important risk factor for its development. Due to its high prevalence and since the population will continue to grow older, prostate cancer and its management is a major health and socioeconomic factor.

The population-wide PSA screening combined with the good prognosis of prostate cancer carries the inherent risk of overtreatment, which is aggravated in elderly patients with a limited life span due to comorbidities or frailty. This has to be taken into account in screening strategies and treatment decisions. EAU, S3 as well as international NCCN guidelines have abandoned general population-based PSA screening in favor of offering early detection programs to select patients after discussion of pros and cons. For men ≥70 years, EAU guidelines for example give a grade D recommendation (rather than C for men aged 55–69) to inform about the possibility of PSA screening.[195] A definition of 'select patients' is not provided, but data from the ERSPC and PIVOT trial suggest that men with a life expectancy of ≤15 years are unlikely to benefit from screening.[196,197] However, after decades of routine PSA screening of men aged ≥45, the current recommendations do not seem to be fully adopted in clinical practice yet.

The same is true for the primary treatment of elderly patients with very low risk and low risk prostate cancer for whom active surveillance is the preferred approach when the life expectancy is below 20 and 10 years, respectively. The ProtecT trial has shown that active surveillance had similar very high 10-year-OS compared to surgery or primary RT.[198] For patients with a life expectancy below 5 years, observation (not active surveillance!) is suggested in NCCN guidelines.[199]

The dependency on life expectancy underlines the importance of geriatric assessment of prostate cancer patients as a basis of treatment decisions. The task force of the International Society of Geriatric Oncology has issued recommendations for the management of prostate cancer in elderly patients.[200] They emphasize that patients should be managed according to their individual health status rather than age. Therefore, initial evaluation of health status is mandatory.

A two-step process is suggested using the validated G8 screening tool which identifies patients who should undergo full comprehensive geriatric assessment (CGA).

For elderly patients having aggressive (Gleason grade 8–10) or locally advanced disease, immediate treatment is usually warranted. Local complications such as bleeding, urinary retention and problems arising from distant metastases may occur within a short timeframe. In these patients, EBRT is the treatment of choice since it is less invasive and can be better tailored to the individual situation in terms of total dose and treatment time. For such patients, ultrahypofractionated radiation schedules, using 4–7 high-dose fractions daily or every other day, may be the preferred treatment. Such regimens reduce strain on patients in terms of required hospital visits (and transportation) and have been shown to be non-inferior to moderate or normofractionated schedules in randomized Phase III trials[201,202] and metaanalyses.[203] Androgen deprivation therapy (ADT) should be added according to current guidelines. However, cardiovascular risk and long-term complications as a result of reduced bone density need to be considered in the elderly. Notably, Qol (hot flashes, depression, fatigue) is typically less affected by long-term ADT in elderly patients than in younger patients featuring higher testosterone levels.

In the oligometastatic setting, data have shown OS benefits for both, RT of the primary tumor[204–206] as well as metastases directed therapy[89] for patients with low-volume disease. These treatments should not be held back thoughtlessly in elderly patients. They inherit a very low risk of severe toxicity, especially when delivered via SBRT. Thus, elderly patients will likely benefit in a similar range than younger ones. If life expectancy is severely impaired by comorbidities such as secondary cancers, palliative androgen deprivation monotherapy may be considered.

Discussion

Generally, RT is an important tool in the treatment of cancer patients. It has been estimated that more than 50% of all cancer patients benefit from some form of RT.[207] With the latest improvements in radiation technique, cure rates have further increased, paralleled by a reduction in side effects. Thus, RT is a particularly attractive local treatment in elderly patients because of its non-invasive nature with limited systemic toxicities.[207] Recently, hypofractionated regimens using higher single doses but fewer fractions have been established in many cancer entities. They achieved similar rates of tumor control and toxicity compared to conventionally fractionated approaches.[8] This seems specifically relevant for older and/or frail patients with lack of social, financial or practical support for transportation and may further improve patient's acceptance and tolerance of RT.

However, many curative intent radiation therapies still involve simultaneous applications of chemotherapy (Chemoradiation), which impedes strong hypofractionation approaches. Nevertheless, many older patients can tolerate conventionally fractionated chemoradiation regimens without increased side effects as shown by our summarized data. This is especially true, if older patients present in good performance score without significant comorbidities. Therefore, age alone should not be a decisive factor for treatment assignment. However, some of the mentioned studies also showed decreased treatment tolerance or the need for treatment adaptions, especially within combination approaches in relevant parts of elderly cohorts. Therefore, tools for an adequate selection of elderly patients for standard regimens as well as for adapted regimens or even omission of RT are urgently needed.

Several authors have used different assessment tools to predict treatment tolerance or side effects in elderly cancer patients with regard to surgery, chemotherapy and RT.[208–210] The most sophisticated tool is a comprehensive geriatric assessment (CGA). This includes a multidisciplinary diagnostic process that evaluates medical, psychological, social and functional capacity.[211] However, CGA is time consuming (it takes roughly two hours) and therefore unlikely to be applied in a relevant proportion of elderly patients in daily routine practice prior to RT.[211] Therefore, screening tools have been developed either as surrogate markers to guide treatment decisions directly or at least to reduce the proportion of elderly patients amended to a full CGA. For example, Hurria et al[209] developed an 11-item scale that correctly predicted the risk of severe toxicities in the majority of patients treated with chemotherapy in an external validation cohort. However, most of these screening tools still lack adequate discriminative power for the prediction of tolerability according to a recent review.[208] Moreover, most of the studies did not involve patients with combined chemoradiation approaches. In studies specifically addressing elderly patients with planned RT, the use of either screening tools or CGA was even less promising. Szumacher et al[211] performed a systematic review and found no significant association with RT-related toxicity in the majority of the included studies. One possible reason lies within the different spectrum of acute side effects caused by RT. In contrast to chemotherapy, most severe side effects are locoregionally limited, site-specific

and depend on irradiated volume, total dose and fractionation. For example, lung cancer treatment by a small-volume SABR in 3 fractions with total doses equivalent to ≥80Gy in conventional fractionation will hardly result in any severe acute toxicity. Therefore, it can be used even in very old, frail patients with severe pulmonal comorbidity. In contrast, large field chemoradiation for lung cancer (even with much lower equivalent doses) will likely result in unacceptable side effects in similar patients. Moreover, RT inherits the risk of causing late toxicities possibly limiting long-term Qol. Again, those are site-specific, depend on volume, dose and fractionation and additionally on preexisting mainly organ-specific comorbidities. While an older or frail patient with limited pulmonary reserve will be at higher risk for all major surgeries, this is not true for all high-dose radiation treatments. Moreover, the timely onset of late radiation toxicities is highly variable and their detection needs long and careful follow-up strategies. Taken together, it is unlikely that common CGA or screening tests will be able to accurately predict tolerability or toxicity caused by RT, because they do not include site-specific and treatment-specific variables. Therefore, one key priority of future radiation research must be the development of modified evaluation tools taken the specific conditions of RT into account. Ideally, they would use at least some information already ascertained during routine RT planning.[207] Prediction tools using such information could be more conveniently incorporated into daily routine compared to long lasting assessments. For example, radiomics and deep-learning algorithms might be used to gain more site-specific information already inherited in routinely performed treatment planning CTs. The latter methods also allow the incorporation of multiple information into new models.[207] This may include site-specific clinical information, molecular data, imaging and (RT)-treatment-related factors resulting in more complex, nevertheless easily usable models.

Aside from patient selection for standard treatments, underrepresentation of elderly and/or comorbid patients in clinical trials is a major issue. Some progress has been made since major study groups recommended to skip an upper age limit within the eligibility criteria of randomized trials.[3] This has already resulted in an increased rate of protocols allowing the inclusion of older patients.[3] However, real inclusion of those patients is far from being adequate.[4,212] Several patient-related barriers for study participation of elderly patients have been suggested: poor performance status, number of comorbidities, need for emergent therapy, lack of social support, reluctance to travel or difficulties due to travel distance (especially regarding fractionated RT), unwillingness to participate in trials per se, unability to manage the intensified follow-up procedures.[213] While some of these factors may truly prevent patients from entering trials or from being eligible, there is no reliable evidence of a distinctly different attitude of elderly patients towards study participation.[214] In fact, physicians recommendations and bias may play a more important role.[214] Restrictive inclusion criteria regarding organ function, comorbidity and performance status[215] and/or complex trial designs with multiple endpoints and/or additional preclinical research[213] may further reduce trial participation of elderly patients. Moreover, most trials rarely address endpoints of particular interest for older adults such as preservation of physical or cognitive function.[6,213]

While there is clearly a need to generate more high-level evidence regarding the optimal treatment for elderly patients, the way to do so is challenging and debatable. One option would be to establish general rules for trials to ensure enrolling of a particular percentage of older patients.[207] However, this may lengthen the trial period or increase the number of prematurely stopped trials if accrual in the elderly age group is slower than in younger patients. Even if achieved, subgroup analyses according to age will often lack statistical power for definitive conclusions. Another option is the design of trials specifically addressing elderly patients.[213] This approach would allow adaptions of the study design: inclusion of geriatric assessments and recording of parameters related to frailty, but less complex trial procedures and more adequate endpoints to increase the willingness to participate. Several studies suggest that age-specific trials will result in the inclusion of much older patients, many of whom otherwise will not have entered a clinical trial.[216,217] Moreover, tailored treatment regimens based on combinations of age, performance status, comorbidity and results of geriatric assessments could be evaluated. However, caution is mandatory in exploring tailored treatment approaches: age-specific trials should aim at defining an optimal treatment rather than simply testing less aggressive interventions.[216] Otherwise, undertreatment may result in suboptimal outcomes. Consensus recommendations for the design of therapeutic trials in older and frail patients have been already published.[213]

In summary, RT plays an important role in the treatment of elderly patients because of its noninvasive nature. In several situations, RT can replace surgical interventions with lower risks for severe complications but similar outcome. Most treatments using RT as the sole modality are well tolerated by elderly patients. If RT is embedded into multimodal treatment approaches (for example combined with simultaneous chemotherapy or as neoadjuvant/adjuvant treatment), tolerability of the overall treatment is mainly dependent on the systemic or surgical therapy. Nevertheless, the (limited) available data suggest that standard treatments

including RT are feasible and well tolerated in a large proportion of elderly patient with similar outcomes to younger ones. Therefore, age alone should not be a decisive factor with regard to treatment selection. Geriatric assessments or screening might be used for patient selection. However, the value of the available tests is limited with regard to predictability of specific RT side effects. Care should be taken to use modern radiation techniques, which clearly have reduced toxicity rates. Hypofractionated regimens might be preferred due to a reduction in socioeconomic burden for the patients. Future research should focus on the development of specific assessment tools for RT and improved representation of elderly patients in randomized trials. Moreover, specific trials addressing the optimal treatment strategy for elderly patients including endpoints of particular interest for elderly should be developed and conducted.

Abbreviations

RT, Radiation therapy; OS, overall survival; Qol, quality of life; RPA, recursive partitioning analysis; MGMT, O-6-methylguanine-DNA methyltransferase; CCNU, lomustine; Gy, Gray; EORTC, European Organisation for Research and Treatment of Cancer; BSC, best supportive care; HNSCC, head and neck squamous cell cancer; SEER, surveillance, epidemiology, and end results; 5-FU, 5-fluorouracil; RTOG, Radiation Therapy Oncology Group; CRP, C-reactive protein; SCLC, small cell lung cancer; NSCLC, non-small cell lung cancer; SABR, stereotactic ablative radiation therapy; ECOG, Eastern Cooperative Group performance score; BC, breast cancer; BCS, breast conserving surgery; ER, estrogen receptor; PR, progesterone receptor; Her2, human epidermal growth factor receptor 2; CALGB, Cancer and leukemia group B; NCCN, National Comprehensive Cancer network; N+, node-positive; EC, esophageal cancer; R+, margin-positive resection US, United States; yrs, years; CCI, Charlson comorbidity score; cCR, clinical complete remission PFS, progression-free survival; DFS, disease-free survival; LARC, locally advanced rectal cancer TNT, total neoadjuvant therapy pCR, pathologic complete remission NOM, non-operative management; COPD, chronic obstructive pulmonal disease; LE, local excision; EBRT, external beam radiation therapy; MTD, maximum tolerated dose; IMRT, intensity-modulated radiation therapy; 2D, two-dimensional; 3D, three-dimensional; LC, local control; MFS, metastases-free survival; MMC, Mitomycin C; LDR, low dose rate; HDR, high dose rate; CSS, cancer-specific survival; PSA, prostate-specific antigen; EAU, European Association of Urology; CGA, comprehensive geriatric assessment; ADT, androgen deprivation therapy; CT, computed tomography.

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