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REVIEW ARTICLE

Radiation Treatment in Older Patients: A Framework for Clinical Decision Making

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ABSTRACT

In older patients, radiation treatment plays a vital role in curative and palliative cancer therapy. Radiation treatment recommendations should be informed by a comprehensive, personalized risk-benefit assessment that evaluates treatment efficacy and toxicity. We review several clinical factors that distinctly affect efficacy and toxicity of radiation treatment in older patients. First, locoregional tumor behavior may be more indolent in older patients for some disease sites but more aggressive for other sites. Assessment of expected locoregional relapse risk informs the magnitude and timeframe of expected radiation treatment benefits. Second, assessment of the competing cancer versus noncancer mortality and morbidity risks contextualizes cancer treatment priorities holistically within patients' entire spectrum and time course of health needs. Third, assessment of functional reserve helps predict patients' acute treatment tolerance, differentiating those patients who are unlikely to benefit from treatment or who are at high risk for treatment complications. Potential radiation treatment options include immediate curative treatment, delayed curative treatment, and no treatment, with additional consideration given to altered radiation target, dose, or sequencing with chemotherapy and/or surgery. Finally, when cure is not feasible, palliative radiation therapy remains valuable for managing symptoms and achieving meaningful quality-of-life improvements. Our proposed decision-making framework integrates these factors to help radiation oncologists formulate strategic treatment recommendations within a multidisciplinary context. Future research is still needed to identify how advanced technologies can be judiciously applied in curative and palliative settings to enhance risk-benefit profiles of radiation treatment in older patients and more accurately quantify treatment efficacy in this group.

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INTRODUCTION

In older patients, radiation treatment plays a vital role in curative and palliative cancer therapy. Recommendations for or against radiation treatment should be informed by a comprehensive, personalized risk-benefit assessment that evaluates the expected treatment efficacy and toxicity. The optimal risk-benefit ratio confers maximal treatment efficacy (as determined by locoregional control, cancer survival, and cancer-related symptom management) but simultaneously minimal treatment toxicity.

However, age modifies the efficacy and toxicity profile of radiation treatment for many disease sites, because age itself modifies influential tumor and patient factors. We identify four such factors—locoregional behavior of the tumor as well as the patient's competing cancer versus noncancer mortality and morbidity risks, functional reserve, and palliative needs—and discuss how each of these factors affects the expected magnitude and timeframe of radiation treatment efficacy and toxicity in specific disease sites. Our proposed clinical decision-making framework integrates these four factors into a comprehensive radiation treatment risk-benefit assessment and incorporates the overarching multidisciplinary treatment strategy and a patient's values and preferences into a final treatment recommendation that is tailored to the older patient. Within this framework, viable treatment recommendations include immediate curative treatment, delayed curative treatment, palliative treatment, and no treatment, with additional consideration given to modified radiation target, dose or sequencing with chemotherapy and/or surgery (Fig 1).

LOCOREGIONAL TUMOR BEHAVIOR

Locoregional tumor behavior can vary with age, with tumors behaving either more indolently or aggressively in older patients compared with their younger counterparts. These variations in locoregional behavior affect the expected absolute or relative magnitude of locoregional control benefit from radiation treatment. For example, if absolute risk of

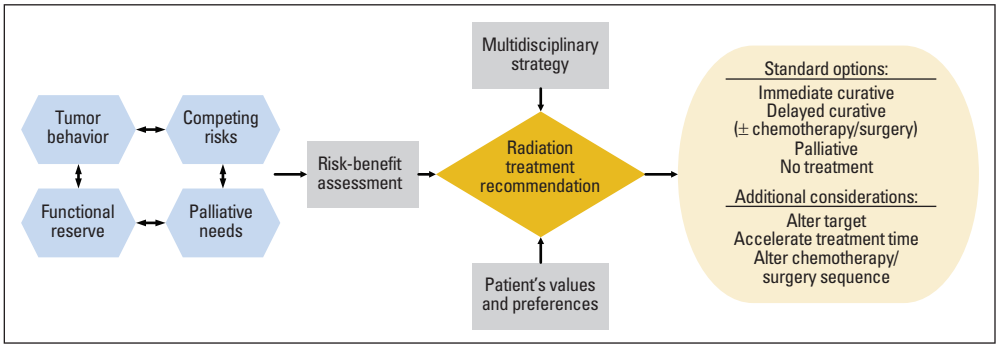

Fig 1. Conceptual framework for radiation oncology decision making for older adults with cancer.

recurrence is extremely low because of an indolent course, absolute benefit of radiation treatment is similarly low, and radiation therapy may not be favored. However, if age inherently decreases the relative radiosensitivity of the tumor, radiation treatment confers smaller relative locoregional control benefit. In this scenario, treatment may still be recommended but is less likely to cure disease.

In breast cancer, older patients often demonstrate a more indolent underlying tumor biology and lower likelihood of locoregional recurrence. Breast cancers diagnosed in older women are more likely to be estrogen receptor positive and less likely to infiltrate widely through the breast.[1,2] Evidence suggests that older patients have a decreased risk of in-breast recurrence (IBR). In one large European trial, the 10-year risk of IBR was 24% in women age $\leq$ 40 years versus 7% in women age $\geq$ 60 years after adjuvant whole-breast irradiation.[3] Given this finding, other studies have evaluated less aggressive radiation treatment strategies in older patients with breast cancer, including partial breast irradiation,[4] intraoperative radiation treatment,[5] and omission of radiation treatment altogether in favor of endocrine therapy alone.[6] Results indicate that although a less aggressive radiation treatment course may increase IBR risk modestly compared with whole-breast irradiation, low absolute IBR risk justifies consideration of these approaches.[7-9] To promote personalized decision making for older women with breast cancer, our group recently developed a nomogram to predict radiation treatment benefit.[7,10] Similarly, for low- and intermediate-risk prostate cancers diagnosed in older men,[11] local therapy such as radical prostatectomy is unlikely to improve survival in men age $\geq$ 65 years. In contrast, radical prostatectomy does seem to improve survival in men age $<$ 65 years.[12] The mechanisms by which age drives differential local treatment benefits are still unclear, requiring more investigation of age-related variations in tumor biology and host factors.

In contradistinction, for early-stage endometrial cancer, an unfavorable course has been demonstrated in older patients, with more aggressive tumor biology and higher likelihood of locoregional recurrence than younger patients. Consequently, age is directly incorporated into risk stratification schemes that guide decisions for or against postoperative radiation treatment for endometrial cancer.[13] Recent guidelines factor age into both the decision to recommend radiation treatment as well as the determination of target volume. A reduced target volume consisting of only the vaginal cuff may be favored in younger women, whereas irradiation of the whole pelvis may be favored in older women, after considering all aspects of the patient risk profile.[14] Similarly, glioblastoma is another cancer site in which older age is a marker of local aggressiveness and radioresistance. Likewise, age has been incorporated into prognostic schemes for glioblastoma, as developed by the Radiation Therapy Oncology Group (RTOG) and European Organisation for Research and Treatment of Cancer/National Cancer Institute of Canada.[15,16]

For other cancers, such as non–small-cell lung cancer (NSCLC) and GI malignancies, no consistent association between age and locoregional tumor behavior has been established. Given the variable associations between age and tumor behavior, clinicians must carefully consider the impact of age for each particular cancer site. Table 1 summarizes salient findings from randomized trials focused on these issues in older adults.[17-26,28,31]

COMPETING RISKS

In older patients, the competing risks of noncancer death and other morbid events affect radiation treatment decisions, specifically by modifying the timeframe over which patients realize the therapeutic benefits of radiation treatment. If the patient's projected life expectancy is short because of noncancer risks, the relative lifetime gain in overall and cancer-free survival attributable to radiation treatment will be diminished. Alternatively, if the patient's projected life expectancy is long, considerations of the late risks of radiation-associated toxicity in a cancer survivor become increasingly relevant to the overall risk-benefit assessment. An additional consideration is whether the patient's underlying comorbid conditions may worsen or, theoretically, accelerate radiation-associated toxicity (eg, cardiovascular events may be more frequent in patients receiving radiation dose to heart if there is underlying heart disease).[32]

Hence, a thorough competing-risk assessment requires consideration of the patient's age, comorbid status, performance status, functional status, and lifestyle factors such as smoking, all of which can affect life expectancy. These noncancer characteristics must be directly weighed against tumor characteristics, which, along with successful delivery of cancer treatment, predict the likelihood—and expected timeframe—of cancer recurrence and/or death. Because age is consistently the primary factor determining an individual's life expectancy, in healthy younger patients, the competing risk of noncancer death is usually relatively negligible compared with the risk of death as a result of cancer. Consequently, this concept of competing-risk assessment is distinctively relevant to and particularly influential in radiation treatment recommendations for older patients.

Table 1. Key Randomized Trials Evaluating Radiotherapy in Older Adults

Trial	Patient Population	Clinical Question	Key Results
Breast cancer			
CALGB 9343[6]	Women age ≥ 70 years with small (≤ 2 cm), clinically node-negative, estrogen receptor–positive breast cancer treated with margin-negative lumpectomy	Does radiation to breast improve outcomes?	At 10 years, radiation therapy lowered risk of locoregional recurrence from 10% to 2% but did not improve OS or likelihood of breast preservation
Danish Breast Cancer Group 82c[17]	Postmenopausal women age < 70 years with breast cancer that was node positive, large (> 5 cm), or invading skin or chest wall; all patients treated with mastectomy and tamoxifen	Does post-mastectomy radiotherapy improve OS?	At 10 years, survival was 45% in radiotherapy group and 36% in no-radiotherapy group
Canadian hypofractionation trial[18]	Women of any age (48% were age ≥ 60 years) with pT1-2 N0 breast cancer treated with conservative surgery	Are whole-breast fractionation schemes of 42.5 Gy in 16 fractions and 50 Gy in 25 fractions equivalent with respect to in-breast tumor control and cosmesis?	No difference in in-breast tumor control or cosmesis at 11-year follow-up
START B trial[19]	Women of any age (40% were age ≥ 60 years) with pT1-3a pN0-1 breast cancer treated with conservative surgery or mastectomy	Are whole-breast fractionation schemes of 40 Gy in 15 fractions and 50 Gy in 25 fractions equivalent with respect to in-breast tumor control and cosmesis?	No difference in in-breast tumor control for two groups, but late normal tissue effects were less common with 40 Gy at 10-year median follow-up
Prostate cancer			
EORTC 22863[20]	Men age < 80 years (median age, 70 years) with cT3-4 prostate cancer of any Gleason score or cT1-2 with Gleason score 8-10	Does addition of goserelin acetate for 3 years beginning at time of radiotherapy improve OS?	Addition of goserelin markedly improved survival, with 10-year OS of 58% in goserelin arm compared with 40% in control arm
Scandinavian Prostate Cancer Group study No. 7[21]	Men age < 76 years (mean age, 66 years) with T3 any-grade or T1/2 intermediate- to high-grade prostate cancer	Does prostate irradiation (70 Gy) improve cancer-specific survival for men receiving leuprorelin for 3 months and flutamide until progression or death?	Prostate irradiation improved prostate cancer–specific survival, with prostate cancer mortality of 23.9% with endocrine therapy alone compared with 11.9% with addition of radiotherapy
Lung cancer			
RTOG 88-08[22]	Patients of any age with stage II or III NSCLC	Does addition of two cycles of cisplatin plus etoposide chemotherapy before radiotherapy improve survival?	Median survival was 13 months for chemotherapy arm compared with 11 months for standard radiotherapy arm; however, for patients age ≥ 70 years, standard radiotherapy was best arm because of chemotherapy-induced toxicity and death
EORTC 08941[23]	Patients of any age (median age, 61 years) with unresectable stage IIIA-N2 non–small-cell carcinoma who responded to three cycles of platinum-based chemotherapy	Does surgical excision or radiotherapy confer better outcome?	No difference in survival between two arms, with 5-year OS of 16% in surgical group versus 14% in radiotherapy group
Intergroup 0096[24,25]	Patients of any age (median age, 62 years) with limited-stage small-cell lung carcinoma treated with four cycles of cisplatin plus etoposide chemotherapy and prophylactic cranial radiotherapy	Does thoracic radiotherapy to dose of 45 Gy in 30 fractions over 3 weeks improve outcomes compared with 45 Gy in 25 fractions over 5 weeks?	Survival was improved in 3-week arm, with 5-year OS of 26% for 45 Gy in 3 weeks compared with 16% for 45 Gy in 5 weeks; although patients age ≥ 70 years seemed to benefit from 45 Gy in 3 weeks, risk of fatal lung toxicity was 10% for older patients compared with 1% for younger patients

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Table 1. Key Randomized Trials Evaluating Radiotherapy in Older Adults (continued)

Trial	Patient Population	Clinical Question	Key Results
Intergroup 0139[26]	Patients of any age (median age, 59 years) with T1-3 pN2 M0 NSCLC treated with cisplatin plus etoposide and 45-Gy concurrent radiotherapy	Does resection improve outcomes compared with additional chemoradiation to dose of 61 Gy?	OS was not statistically different for two arms; however, in post hoc analysis, survival was improved in patients who underwent lobectomy compared with matched controls who underwent chemoradiation to 61 Gy; age was not predictive of survival
RTOG 0617[27]	Patients with stage III NSCLC receiving concurrent chemoradiation with carboplatin and paclitaxel	Does high-dose (74 Gy) radiotherapy improve survival compared with standard dose (60 Gy)?	OS was not improved with high-dose radiotherapy; additional data regarding effect of age on outcomes are awaited
Glioblastoma multiforme			
ANOCEF radiotherapy for glioblastoma in the elderly study[28]	Patients age ≥ 70 years with newly diagnosed glioblastoma and Karnofsky performance status ≥ 70	Does radiotherapy (50.4 Gy in 28 fractions) improve survival compared with best supportive care?	Radiotherapy improved OS, with median survival of 29 weeks in radiotherapy arm compared with 17 weeks in best supportive care arm; no significant measurable differences in quality of life between two arms
Canadian hypofractionation trial[18]	Patients age ≥ 60 years with newly diagnosed glioblastoma multiforme and Karnofsky performance status ≥ 50	Is there difference in OS between 60 Gy in 30 fractions compared with 40 Gy in 15 fractions?	Median survival was 6 months in each arm; patients who received 40 Gy in 3 weeks had lower corticosteroid requirement
German NOA-08 trial[29]	Patients age ≥ 65 years with newly diagnosed anaplastic astrocytoma or glioblastoma	Is TMZ alone inferior to standard radiotherapy alone (60 Gy)?	TMZ was not inferior to standard radiotherapy; TMZ alone was particularly beneficial in patients with *MGMT* promoter methylation
NCBTSG trial[30]	Patients age ≥ 60 years with newly diagnosed glioblastoma	Are there differences in OS with standard radiotherapy (60 Gy), hypofractionated radiotherapy (34 Gy), or TMZ alone?	OS was improved with TMZ alone compared with standard radiotherapy; for patients age ≥ 70 years, both hypofractionated radiotherapy and TMZ alone were superior to standard radiotherapy
NHL			
GELA elderly radiotherapy trial[31]	Patients age ≥ 61 years with stage I or II histologically aggressive NHL and no adverse factors on age-adjusted IPI; all patients received four cycles of CHOP chemotherapy	Does involved-field radiotherapy to 39.6 Gy in 22 fractions improve outcomes?	Radiotherapy did not improve EFS or OS

Abbreviations: ANOCEF, Association of French-Speaking Neuro-Oncologists; CALGB, Cancer and Leukemia Group B; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; EFS, event-free survival; EORTC, European Organisation for Research and Treatment of Cancer; GELA, Groupe d'Etude des Lymphomes de l'Adulte; IPI, International Prognostic Index; NCBTSG, Nordic Clinical Brain Tumor Study Group; NOA, Neuro-Oncology Working Group; NSCLC, non–small-cell lung cancer; NHL, non-Hodgkin lymphoma; OS, overall survival; RTOG, Radiation Therapy Oncology Group; START, Standardisation of Breast Radiotherapy; TMZ, temozolomide.

In prostate cancer, predicted life expectancy has been directly incorporated into treatment guidelines.[33] Such an approach is especially relevant for this disease site given the increased incidence of prostate cancer with older age, combined with its relatively indolent trajectory and long timeframe for recurrence and death, at least for low- to intermediate-risk disease.[34] Because guidelines combine noncancer risk stratification (life expectancy) with cancer risk stratification (low-, intermediate-, and high-risk prostate cancer based on tumor characteristics), the end result, ideally at least, creates a treatment strategy that is patient centered and minimizes the potential for overtreatment as well as undertreatment.[34]

Although life expectancy–based guidelines explicitly inform primary prostate cancer treatment options (ie, observation, active surveillance, radiation treatment, or radical prostatectomy), conversely, it is less clear whether life expectancy should modulate recommendations for or against adjuvant prostate irradiation after radical prostatectomy. Current recommendations for adjuvant prostate irradiation are largely determined by the presence of positive surgical margins, extraprostatic extension, and prostate-specific antigen nadir, but not age.[35,36] Nonetheless, because a substantial number of patients—anywhere between 15% and 60%—with high-risk pathologic features after radical prostatectomy demonstrate biochemical relapse within 5 years,[37] life expectancy $\leq$ 5 years is a specific setting in which the competing noncancer risks would prominently influence the risk-benefit assessment of adjuvant radiotherapy. Notably, in the postprostatectomy setting, adjuvant radiation therapy could be delivered immediately, but it could also acceptably be delayed until definite recurrence. As a result, any decision for delayed treatment must not overlook the tempo or severity of the patient's noncancer comorbidities. A patient who delays treatment may ultimately have more difficulty completing the delayed treatment course compared with an upfront treatment course because of progressively older age, frailty, or worsening comorbid disease at the time of recurrence. Furthermore, a salvage approach may require treatment intensification involving higher radiation dose, larger irradiation field, or concomitant systemic therapy.

For older patients with cancers of other sites, site-specific life expectancy nomograms and guidelines are comparatively lacking. In this circumstance, the clinician must empirically weigh the anticipated timeframe, trajectory, and tempo of risks for noncancer mortality, noncancer morbidity (disease, symptoms, and impact on health and function), cancer mortality, cancer morbidity, and treatment morbidity. Weighing these competing risks contextualizes a patient's cancer treatment priorities holistically within his or her entire spectrum and time course of health needs. In certain disease sites (eg, lymphoma and early-stage endometrial cancer), adjuvant radiation therapy is found to benefit event-free survival but not necessarily overall survival. In this circumstance, a competing-risk assessment remains relevant, but it should be modified. Here, the clinician should emphasize the impact of radiation treatment on the timeframe and trajectory of the event-free survival curve as opposed to overall survival curve, also balanced against noncancer mortality and morbidity risks over time.

A thorough assessment of radiation-associated toxicity should consider both short- and long-term risks. Radiation treatment toxicity is typically categorized within two timeframes: acute (occurring during treatment to within months after treatment) and late (sometimes not manifesting until years after treatment is complete). In this context, the heterogeneity of radiation treatment toxicity profile by anatomic site and dose must be carefully considered. The recently published Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) tables demonstrate a systematic attempt to quantify such risks.[38] Radiation-associated toxicities are known to be dose dependent and strongly and steadily dependent on the volume of normal tissue exposed to radiation as well as the physiologic function of the exposed normal tissue. In general, however, published risks are not systematically adjusted for age, because the severity of toxicities is not consistently associated with age.[38] How normal tissue tolerance changes by age is unclear (Appendix, online only).

Several other points related to the concept of competing risks are worth noting. First, treating clinicians should be aware of both the potential to overtreat elderly patients with significant competing noncancer mortality risk as well as the potential to undertreat patients. Undertreatment can result either from underestimating the patient's true life expectancy (eg, by assuming that age alone predicts high risk of death without consideration of comorbid disease, functional status, and so on) or from underestimating the aggressiveness of the cancer.[34] Second, although estimating expected noncancer versus cancer mortality risks seems straightforward in principle, in practice, life expectancy is notoriously difficult to calculate. Life tables are based on population data and therefore predict average life expectancies based on age (in addition to other covariates such as sex and comorbid health status) for a group of patients, but they do not necessarily accurately predict individual outcomes. Alternatively, numerous nomograms (eg, in patients with prostate cancer) have been published, as derived from various cohort data with long-term follow-up, but nonetheless, the accuracy, external validity, and practicality of these instruments have been debated.[39-41]

Accordingly, another concept, as previously demonstrated in studies of radiation treatment in patients with breast cancer, can be further considered in this context. The number needed to treat (NNT) is the number of patients requiring the treatment to prevent a certain event of interest (eg, death, cancer recurrence, and so on). This concept is frequently used outside of oncology to justify interventions. For example, in patients with hypertension, the NNT is 11 men or 21 women treated for 10 years with antihypertensive pharmacotherapy to prevent one cardiac event.[42] In patients with osteoporosis receiving a bisphosphonate, the NNT is 39 women over 3 years to prevent one fracture.[43]

Similarly, the NNT with adjuvant irradiation to prevent recurrence can also be calculated in patients with cancer. However, because locoregional recurrence may not occur for many years after diagnosis, the NNT must be adjusted to account for competing risk of death before recurrence. For example, in a prior study of older women with ductal carcinoma in situ of the breast, we calculated the NNT adjusted for patient age and comorbidity. For patients with higher-risk ductal carcinoma in situ, the NNT with radiation treatment ranged from 11 to 22 to prevent a local breast event, whereas lower-risk patients had overall increased NNT ranging from 15 to 29 after 5-year follow-up (Table 2).[44] In another cohort of patients with breast cancer age $\geq$ 70 years with early-stage but invasive disease, the NNT ranged from 21 to 125 over 8 years of follow-up. Only in patients age $\geq$ 85 years was the NNT highly unfavorable ($\geq$ 53), suggesting that in this group, risks of noncancer adverse outcomes prevail, and adjuvant irradiation is typically not warranted (Table 3).[45] However, for the vast majority of

Table 2. Adjusted NNT for Older Women With Ductal Carcinoma in Situ

Age (years)	Charlson Comorbidity Index*	5-Year OS		Adjusted NNT			
				Low Risk†		High Risk‡	
		%	95% CI	Events (per 100 persons)	95% CI	Events (per 100 persons)	95% CI
66-69	0	96	94 to 97			11	8 to 16
	1	93	88 to 97			11	8 to 17
	2-9	77	66 to 89			13	10 to 20
70-74	0	95	93 to 96	15	10 to 29	11	8 to 16
	1	88	84 to 93	16	10 to 32	11	9 to 17
	2-9	69	58 to 79	20	13 to 41	15	11 to 22
75-79	0	89	86 to 92	15	10 to 31	11	9 to 17
	1	90	86 to 95	15	10 to 31	11	8 to 17
	2-9	68	57 to 78	20	14 to 41	15	11 to 23
80-84	0	81	77 to 86	17	11 to 34	13	9 to 19
	1	68	60 to 77	20	13 to 41	15	11 to 22
	2-9	58	45 to 72	24	16 to 48	17	13 to 26
≥ 85	0	65	56 to 74	21	14 to 43	16	12 to 24
	1	66	52 to 80	21	14 to 42	15	11 to 23
	2-9	47	26 to 69	29	19 to 59	22	16 to 32

NOTE. Data adapted.[44]
Abbreviations: NNT, number needed to treat; OS, overall survival.
*Charlson comorbidity score of 0 indicates no significant comorbidity; 1, mild comorbidity; and 2-9, moderate to severe comorbidity.
†Low-risk group includes patients age ≥ 70 years with tumor size ≤ 2.5 cm, noncomedo histology, and non–high-grade disease.
‡High-risk group includes any of the following: age 66-69 years, tumor size > 2.5 cm, comedo histology, and/or high-grade disease.

older patients in these studies, the NNT with irradiation approximates the magnitude of the NNT for accepted pharmacotherapy interventions for hypertension and osteoporosis. As with life expectancy calculations, the NNT approach to competing-risk assessment strongly considers age and comorbid status. Given that similar NNT data for older patients have not necessarily been calculated for radiation treatment of every disease site, these general principles can be empirically applied in the clinical setting.

Table 3. Adjusted NNT for Older Women With Early Invasive Breast Cancer

Age (years)	Charlson Comorbidity Index*	8-Year Survival†		Adjusted NNT	
		%	95% CI	Events (per 100 persons)	95% CI
70-74	0	84	83 to 86	21	16 to 31
	1	72	68 to 76	24	18 to 36
	2-9	47	40 to 55	37	28 to 55
75-79	0	79	76 to 81	22	17 to 33
	1	62	58 to 67	28	21 to 42
	2-9	43	36 to 51	41	31 to 60
80-84	0	61	57 to 64	29	22 to 43
	1	47	40 to 53	38	28 to 56
	2-9	29	21 to 36	61	46 to 90
≥ 85	0	33	29 to 38	53	40 to 78
	1	18	13 to 24	97	73 to 143
	2-9	14	7.2 to 21	125	94 to 185

NOTE. Data adapted.[45]
Abbreviation: NNT, number needed to treat.
*Charlson comorbidity score of 0 indicates no significant comorbidity; 1, mild comorbidity; and 2-9, moderate to severe comorbidity.
†Expected survival calculated with Kaplan-Meier method.

FUNCTIONAL RESERVE

Functional reserve assessment is essential for estimating the magnitude and timeframe of anticipated toxicity risks of radiation treatment in older patients. Functional reserve reflects a patient's physiologic (as opposed to strict chronologic) age and predicts the patient's tolerance of cytotoxic interventions. Functional reserve is multidimensional, signifying the underlying degree of vulnerability in major organs, cognition, immunity, and psychological and nutritional status and is also related to capability of maintaining daily activities and independence in a setting of injury or impairment.[46] Thus, a functional reserve assessment should serve as an instrumental factor for predicting a patient's radiation treatment tolerance acutely. This assessment should aid the clinician in differentiating those patients who are unlikely to benefit from radiation treatment because of intrinsic patient characteristics, as opposed to tumor characteristics.[47]

Functional reserve is one domain evaluated by the comprehensive geriatric assessment (CGA) for patients with cancer,[46] separately discussed in *Journal of Clinical Oncology*. Fundamentally, however, functional reserve as a concept is often more explicitly considered in recommendations for chemotherapy rather than radiation therapy, informing proposed strategies for chemotherapeutic dose adjustment and supportive (growth factor and transfusion) therapy use. The role of a CGA in patients undergoing radiation treatment is the topic of ongoing investigation.[48]

Functional reserve is likely to influence analogous facets of radiation treatment, specifically the patient's ability to complete the intended radiation treatment duration and dose and his or her anticipated need for acute supportive care to manage toxicities. Anticipating whether a patient can tolerate a definitive (curative) radiation treatment course that will typically last several weeks is important,

given that there is a relatively limited therapeutic window for dose adjustment or dose-intensity adjustment in radiation treatment. Radiobiologically, the dose gradients considered adequate for eradicating microscopic and gross disease are narrow and depend on both sufficient daily fractionated dose delivered as well as cumulative dose over a limited time window. For example, in NSCLC, daily doses of 1.8 to 2.0 Gy to a total dose $\geq$ 50 Gy are considered adequate for microscopic disease, whereas at least 60 Gy is necessary for gross disease. Breaks in treatment markedly diminish efficacy.

Therefore, delivering an incomplete radiation treatment course to a suboptimal dose creates a clinical conundrum, because an inadequate course not only fails to eradicate residual disease, allowing for tumor repopulation, but also exhausts neighboring normal tissue radiation tolerance—potentially prohibiting a future course of local radiation treatment. Accordingly, in a patient with extremely limited functional reserve, in whom a standard radiation treatment regimen is unlikely to be completed, recommendations advocating radiation treatment must be rendered judiciously, and alternative treatment options should be considered accordingly, particularly if there is curative intent. When a patient with limited reserve undergoes treatment, prophylaxis and anticipation of severe reactions involve thoughtful upfront planning to support hydration, nutrition, and pain status if mucositis is expected, as well as attentive monitoring to proactively manage infection and organ decompensation (neurologic or hematologic). Maximizing supportive care to preserve and enhance functional reserve is essential for delivering high-quality radiation treatment, because acute complications can cause difficulty with setup and targeting or result in treatment interruption and incompletion.

Studies of radiation treatment in older patients with glioblastoma illustrate many of these considerations. In glioblastoma, standard therapy consists of maximal surgical resection followed by adjuvant radiation to 60 Gy in 30 fractions delivered over 6 weeks with concurrent and adjuvant temozolomide (TMZ). Survival benefits are attributed both to addition of radiation treatment as well as TMZ. However, a growing body of studies has focused on defining an optimal treatment strategy for older patients, who comprise approximately 50% of patients but tend to have aggressive disease and short median survival.[16] A Canadian randomized trial included patients with glioblastoma age $\geq$ 60 years and compared a radiation treatment course of 60 Gy in 30 fractions (over 6 weeks) versus 40 Gy in 15 fractions (over 3 weeks).[49] Patients experienced a median survival of 6 months, with no significant survival differences by treatment arm. Notably, patients receiving the short course demonstrated lower steroid requirements, suggesting less toxicity, lower morbidity, and possibly better quality of life with the shorter treatment course.[49] Two recent studies compared outcomes in older patients treated with radiation therapy versus TMZ alone. In the German NOA-08 (Neuro-Oncology Working Group) trial, median survival was 9.6 months with standard radiation treatment (60 Gy in 30 fractions) compared with 8.6 months with TMZ, and this comparison was reported to be noninferior.[29] In the Nordic trial, three arms were compared: standard radiation treatment to 60 Gy in 30 fractions versus short-course radiation treatment to 34 Gy in 10 fractions versus TMZ alone, with median survival of 6.0, 7.5, and 8.3 months, respectively. Standard-course radiation treatment was associated with significantly worse survival, particularly in patients age $\geq$ 70 years; only 72% of patients in this arm completed the intended course (Table 1).[30]

Although consensus on the best treatment approach for older patients with glioblastoma has yet to be reached,[50] there are important general implications to be drawn from this collective body of evidence. First, the substantial rate of incompletion of radiation treatment in these elderly patients likely contributed to poorer outcomes in the standard arm. Second, results raise the concern that the logistic challenges of radiation treatment delivery in a frail patient—including the need for daily transportation, social support, and sufficient patient mobility to comply with treatment positioning—may represent stressors that in and of themselves can consume limited functional reserve. Third, in patients with limited expected survival, the risk-benefit assessment must weigh the expected survival gain from radiation treatment against the time spent on treatment itself.

For other disease sites, the functional reserve assessment is directly relevant to the recommendations for or against combined-modality therapy (ie, concurrent chemotherapy plus radiation treatment). For many disease sites, chemotherapy delivered concurrently with radiation treatment not only acts synergistically to increase local tumor control and survival but also translates to increased treatment toxicity burden. In patients with limited reserve, this burden may be prohibitive, and alternative strategies to optimize treatment must be considered.

For example, growing evidence suggests that patients with advanced-stage endometrial cancer experience improved survival with concurrent chemotherapy and radiation treatment after surgery, compared with either adjuvant therapy alone.[51,52] Unfortunately, patterns-of-care studies demonstrate that older patients with endometrial cancer have lower completion rates for surgery, radiation treatment, and chemotherapy, despite a higher frequency of presentation with advanced-stage and higher-grade disease.[53,54] Combined therapy demonstrates higher risks of acute toxicity than single-modality therapy, particularly hematologic toxicity.[55] Thus, in a patient with limited functional reserve, other standard options include postoperative chemotherapy alone, radiation treatment alone, or consecutively sequenced therapies. However, another strategy to consider is judiciously employing advanced technologies to allow delivery of concurrent therapy by minimizing toxicities in a compromised patient. In patients with endometrial cancer, the advent of intensity-modulated radiation therapy (IMRT) has allowed for decreased radiation doses to normal tissues at risk while concomitantly allowing for dose painting—a tailored technique that targets the highest radiation doses to the highest-risk tumor targets. A recent analysis of patients with endometrial cancer enrolled onto RTOG 0418 demonstrated that using IMRT to treat the whole pelvis, bone marrow radiation doses could be carefully limited and minimized, resulting in lower risks of grade $\geq$ 2 hematologic toxicities.[56] Other data suggest IMRT can similarly help minimize acute GI toxicities in advanced endometrial cancer.[57,58] Results demonstrate the feasibility of exploiting advanced radiation treatment technologies to accomplish multidisciplinary treatment objectives, because preserving bone marrow and overall functional reserve also allows for future cytotoxic treatments.

Evolving treatment strategies in advanced NSCLC are similarly illustrative. In advanced-stage unresectable NSCLC, concurrent chemoradiotherapy to 60 Gy in 30 fractions is standard,[27] although studies of elderly patients with NSCLC, especially those age $\geq$ 70 years,

consistently demonstrate high risks of toxicity, particularly hematologic and neuropsychiatric toxicities.[59-61] However, concurrent chemoradiotherapy with a platinum-based doublet yields the best survival outcomes, and age alone should not preclude such an approach. Nonetheless, chemotherapy-associated toxicity is limiting, especially because of concern for toxicity risks from doublet chemotherapy in patients with advanced NSCLC with poor baseline performance status.[62-65]

In practice, a substantial proportion of patients with NSCLC are considered poor candidates for concurrent treatment because of insufficient functional reserve. Alternative treatment options include radiation treatment alone or sequential radiation therapy and chemotherapy. However, a recently proposed approach—hypofractionation—has also undergone investigation. Here, larger doses per fraction shorten the overall radiation treatment course while simultaneously intensifying the biologically effective dose to the highest-risk radiation targets (eg, gross or bulky disease).[66] Carefully combining this fractionation approach with improved targeting via advanced technologies (eg, IMRT, proton therapy, respiratory gating, and/or image guidance) likely adds to the benefit of dose escalation for high-risk tumor targets, thereby helping to compensate for omission of chemotherapy while simultaneously minimizing normal tissue toxicity, especially in anatomically complicated sites. The additional benefit of shorter treatment time for compromised patients with NSCLC may help preserve functional reserve (as hypothesized in patients with glioblastoma) by minimizing stressors resulting from the daily delivery of radiation treatment in this frail population.

PALLIATION

When cancer is incurable, the treatment goal shifts to palliative management of symptoms. Occasionally, however, despite a technically curable setting (nonmetastatic tumor), a patient's life expectancy and/or functional reserve are so compromised that the oncologic treatment goal also shifts to palliation. A CGA in this setting is important for prioritizing the patient's goals for pain (or other symptom) control, preservation of function and independence, and time spent receiving treatment.

Common sites for palliative radiation treatment include brain, bone, and thoracic metastases. Proposed treatment guidelines for each of these sites demonstrate a range of acceptable dose-fractionation schemes and technical approaches.[67,68] However, palliative radiation can have a role in the treatment of a wide variety of anatomic sites.[69] Notably, clinically appreciable acute palliative benefit can be obtained in many sites within as few as one to five treatment sessions, suggesting excellent feasibility and utility of radiation treatment as a palliative tool. Nonetheless, a recent study suggested a low frequency (8%) of radiation treatment use in the last 30 days of life, despite substantial decreases in total cost of hospice care when radiation treatment was used.[70] The utility of applying advanced technologies such as IMRT and stereotactic ablative radiotherapy in the palliative setting remains an ongoing question. As with definitive treatment application of advanced technologies, use in palliative settings should be judicious, given the associated potential increased cost and resource burden.[71]

FUTURE DIRECTIONS

Priorities for future research include: one, continued analyses of radiation treatment efficacy and effectiveness in older patients with cancers of various sites; two, validation of existing functional assessment tools or development of new assessment tools to aid in risk stratification and intervention for patients technically eligible for radiation treatment but potentially facing obstacles to treatment because of impaired reserve; three, identification of how advanced technologies can be judiciously applied in curative and palliative settings to enhance risk-benefit profiles of radiation treatment in older patients; and four, evaluation of the clinical and biologic underpinnings of radiation-associated toxicity in older adults. Ultimately, recommendations for or against radiation treatment made in partnership with the older patient and a multidisciplinary oncologic team are best poised to balance the multidimensional treatment considerations.

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Appendix

Aging and Radiation-Associated Toxicity

There is no fully developed conceptual model to inform an understanding of the relationship between aging and radiation-associated toxicity. It may seem self-evident that the decrease in physiologic reserve attendant with the aging process would, by definition, render normal tissues more sensitive to the adverse effects of radiation therapy. Nevertheless, this has yet to be definitively proven in the literature. Perhaps the most elucidating finding to support this hypothesis stems from the study of prophylactic cranial irradiation (PCI) in the treatment of small-cell lung cancer. Specifically, the RTOG (Radiation Therapy Oncology Group) 02-12 trial compared three different dose-fractionation schemes for PCI and found that chronic neurotoxicity was more common with higher doses of PCI (Wolfson AH et al: Int J Radiat Oncol Biol Phys 81:77-84, 2011). In addition, in multivariate modeling, increasing age was the most significant predictor of neurotoxicity, with odds of neurotoxicity increasing by 12% per year of age. Such a finding supports the hypothesis that advancing age sensitizes patients to the adverse effects of radiation treatment, at least with respect to the adverse cognitive effects of whole-brain irradiation.

A more extreme example is the use of whole-brain irradiation for patients with primary CNS lymphoma. Radiation treatment caries a relatively high risk of severe leukoencephalopathy in treatment of this disease, perhaps in part because of sensitization from CNS-active chemotherapy such as high-dose methotrexate and perhaps in part because of effects from the disease itself. In the RTOG 93-10 study of induction chemotherapy followed by whole-brain irradiation to 45 Gy, the risk of severe leukoencephalopathy was 14% in patients age $<$ 60 years and 19% in patients age $>$ 60 years, suggesting that both young and old patients were at similar risk of toxicity in the brain (DeAngelis LM et al: J Clin Oncol 20:4643-4648, 2002). However, death resulting from toxicity in the brain was numerically higher in older rather than younger patients, with 16% of older patients dying as a result of leukoencephalopathy compared with 6% of younger patients. Collectively, these studies suggest that age could modify toxicity risks of whole-brain irradiation, although young age itself is not completely protective against toxicity.

For other disease sites such as the lung, breast, or prostate, to our knowledge, there is no clear evidence suggesting a higher risk of normal tissue toxicity solely attributable to age. Within this context, it is worth noting that known rare genetic syndromes associated with premature aging, known as progeria syndromes, are frequently attributable to mutations in genes involved in DNA damage repair (Burtner CR et al: Nat Rev Mol Cell Biol 11:567-578, 2010). Thus, there is an interesting overlap between heritable syndromes associated with premature aging and heritable syndromes associated with radiosensitivity. A classic example is the genetic syndrome ataxia telangiectasia, which is associated with both premature aging and radiosensitivity. An intriguing hypothesis related to this observation is that longevity may be a phenotype that indicates a patient has robust intrinsic DNA repair capability. If true, healthy older adults demonstrating significant longevity may be relatively more tolerant to the adverse normal tissue effects of ionizing radiation treatment. Further molecular and clinical research may be helpful in exploring this hypothesis.