Combined Modality Therapy in the Elderly Population

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Opinion statement

The incidence of cancer among older patients continues to rise. The use of combined modality therapy has improved survival in a variety of malignancies, including rectal, head and neck, and lung cancer; however, the addition of chemotherapy increases substantially the toxicities of treatment. Elderly patients have generally been excluded from prospective clinical trials and as such, there is a lack of evidence-based data with regards to the most appropriate treatment. Age itself should not be used as a criterion for foregoing combined modality therapy in elderly patients. Due to the increased toxicity of therapy, patients must be carefully selected. Any medical intervention should account for life expectancy, performance status, tolerance to therapy, and presence of medical or social conditions that may impact therapy. We encourage a comprehensive geriatric assessment to evaluate functional status, comorbidities, mental status, psychological state, social support, nutritional status, polypharmacy, and geriatric conditions in order to improve a patient's overall functional status during the course of therapy. Fit elderly patients should be considered candidates for combined modality therapy, however, because they are potentially more vulnerable to therapy, careful attention should be paid to hydration and nutritional status with early intervention when necessary. Investigators should be encouraged to expand eligibility to include elderly patients on non age-related clinical trials. Additionally, therapy-related clinical trials directed at the elderly should be developed.

Introduction

The use of combined modality therapy (CMT) has led to improvements in disease free and overall survival in a variety of malignancies including lung, esophagus, rectal, and head and neck cancer [1–4]. Appropriately selecting patients for CMT can be challenging especially for the elder population who are often denied combined treatment due to concerns of additional toxicity. Many of the clinical trials that established the standard of care in oncology have generally excluded older patients, thus limiting the ability to extrapolate the use of these treatments to all patients. Additionally, patients with advanced age may have substantial comorbidities that can affect their life expectancy and the effectiveness and tolerance of chemoradiotherapy and/or surgery. From small prospective and retrospective

reviews of large patient series, external beam radiotherapy alone is well tolerated even in patients over 80 with as high as 90% of patients being able to complete therapy [5–8]. In this review, we discuss the potential challenges of CMT in older patients in select tumor sites.

Head and neck cancer

- The use of concurrent chemoradiotherapy for locoregionally advanced head and neck cancer allows for functional organ preservation and improved locoregional control (LRC) and overall survival compared with radiotherapy alone [9–11]. Additionally, concomitant chemoradiotherapy has had a significant impact on organ preservation in patients with laryngeal cancer [12–14]. For patients with high-risk features after surgical resection, concurrent cisplatin chemotherapy in addition to radiotherapy is considered standard treatment [15–17]. The use of standard therapy in older patients, however, warrants serious forethought given the potential for higher toxicity. As the population ages, the number of patients over the age of 70 with head and neck cancers is increasing and now account for approximately one quarter of all new patients [18]. External beam radiotherapy with conventional fractionation is now the most widely used form of treatment in head and neck cancer patients. The use of radiotherapy alone in elderly patients with locally advanced head and neck cancers has been evaluated by several groups [19–21]. In an analysis by Pignon et al. [21], there was no difference in terms of response and survival between younger and older patients enrolled on EORTC clinical trials. Acute mucositis and weight loss in elderly patients (≥70 years) was similar to that of younger patients; however, the incidence of grade 3 or 4 functional acute toxicity was significantly higher. The LRC and cancer-specific survival were similar in all age groups in this analysis, where patients who were enrolled were those with good performance status without significant comorbid conditions.
- Surgery has an important role for the treatment of head and neck cancers. Elderly patients, however, have a higher potential for morbidity and mortality associated with surgery due to the presence of comorbidities and reduced physiologic reserve. In a retrospective analysis, Clayman et al. [22] compared the outcomes of 43 patients older than 80 years and 79 patients younger than 65 years. There was a higher prevalence of systemic complications, particularly cardiovascular and pulmonary complications in the older group, and a higher prevalence of local complications in the younger group. Postoperative mortality was 2% in the older group and absent in the younger group. LRC was similar between both groups; however, overall survival was significantly different at 5 years (33% vs. 63%, $P < 0.001$), and was comparable to an age matched group [22]. The use of minimally invasive techniques may be feasible options for elderly patients as this requires less operative and recovery time [23].
- Chemotherapy combined with radiotherapy has particular importance in the era of organ preservation. The use of chemoradiotherapy in patients with head and neck carcinomas involves a combination of cisplatin and infusional 5-fluorouracil (5FU), although the optimal regimen continues to evolve. The altered functional reserve of elderly patients can change the pharmacokinetics of cytotoxic drugs and can result in enhanced toxicity. Mucositis is generally more severe and persists longer in older patients. Reduction of chemotherapy dose has been studied as one option to adjust for the altered physiology in elderly patients; however, in a small study by Schneider et al. [24],

reduction in chemotherapy dose was found to seriously mitigate the efficacy of treatment. For patients who are functionally able to receive therapy, they should be treated in the same manner as younger patients, but supportive care must be increased including administration of growth factor support. One method to prevent acute mucositis from chemoradiotherapy is the use of amifostine [25, 26].

- More recently, the use of concomitant weekly cetuximab 250 mg/m^2 after an initial 400 mg/m^2 loading dose with radiation has been recently demonstrated to enhance LRC and overall survival [27] and may be an appropriate treatment option for elderly patients who cannot tolerate standard chemotherapy. Combination therapy in this study conferred a 13% absolute improvement in 3 year LRC and a 10% improvement in OS at 3 years (45% vs. 55%, $P = 0.05$). They included patients with Karnofsky performance scores ranging from 60 to 100, and age was not a criteria for eligibility. No significant difference in acute toxicity was noted in patients receiving cetuximab/RT vs. RT alone, indicating that these results are applicable to most patients with locally advanced disease, including older patients.

- In a study by Derk *et al.*, they analyzed the influence of age, comorbidity, social support, and quality of life on treatment of choice in 266 patients with advanced head and neck cancer. Patients 70 years of age and older received standard treatment less often than younger patients. In patients 80 years and older, the use of standard therapy was even less often with 36% of patients receiving standard therapy, while 18% received no treatment at all. In patients 70 and older, old age, stage IV, tumor site (pharynx), marital status (widowed), more comorbidity, poor physical functioning, less pain, less social support, and giving longer life less priority were predictive for receiving nonstandard therapy. They found that a higher comorbidity index, social factors, and poor physical functioning were associated with nonstandard treatment.

- Concurrent cisplatin and radiotherapy is the treatment of choice for appropriate patients with squamous cell carcinoma of the head and neck. Cetuximab concurrently with radiation therapy demonstrated clear progression free and overall survival benefits; however, a comparison of radiation and conventional chemotherapy with radiation and cetuximab has not yet been performed. For those patients who cannot tolerate high-dose cisplatin therapy concurrently with radiation therapy, cetuximab is a potential option. For select patients, transoral laser surgery may be an option. Selection of therapy for elderly patients is based upon a multitude of factors. Elderly patients who reported less social support and younger patients who had similar issues receive standard treatment less often. Among the elderly patients, factors such as tumor stage, marital status, comorbidities, pain, physical functioning, social support, and opinions about the length of life were all determinants for nonstandard therapy [28]. Decisions regarding treatments should be based on a complete medical evaluation and on patient preference; however, we must be mindful that older patients may reject standard therapies as a result of misinformation or a lack of social support.

Lung

- The use of chemoradiotherapy either sequential or concurrent has been demonstrated to improve survival in patients with locally advanced nonsmall cell lung cancer (NSCLCa) compared to radiotherapy alone

[29]. Furthermore, concurrent chemoradiotherapy has improved survival in patients with locally advanced NSCLCa as demonstrated by the results of several recent randomized clinical trials [2, 30, 31]. Patients with advanced age, low Karnofsky performance status, or concomitant comorbidities were excluded, however. Relatively few prospective studies have investigated the feasibility of combination chemotherapy radiotherapy in older patients with locally advanced NSCLCa. The Japan Clinical Oncology Group (JCOG) attempted a phase III randomized study in elderly (>70 years) patients with locally advanced NSCLCa [32]. Patients were randomized to radiotherapy or radiotherapy with concurrent daily carboplatin (JCOG 9812). The trial was stopped early after four patients died due to treatment-related toxicity (one on the radiotherapy alone arm and three on the radiotherapy and carboplatin arm). Three of the deaths were attributed to radiation pneumonitis. Upon review of the radiotherapy portals, two of the patients were found to have protocol violations. The overall incidence of radiation pneumonitis in their study was 8.7%, which is higher than the observed incidence of radiation pneumonitis in other trials [33, 34]. At the time the study was terminated, 46 patients had been registered; median survival was 428 days for patients who received radiotherapy alone vs. 554 days for patients who received carboplatin and radiotherapy (P = NS). The authors concluded that the efficacy of concurrent chemotherapy and radiotherapy in elderly patients remains unanswered and an important clinical question.

- Several retrospective analyses of randomized studies have analyzed the outcome of elderly vs. younger patients with locally advanced NSCLCa with conflicting conclusions. In an analysis of 6 phase II and III RTOG (Radiation Therapy Oncology Group) studies performed by Movsas *et al.* [35], patients <70 had improved survival with either induction chemotherapy and standard radiotherapy or concurrent chemotherapy with hyperfractionated radiotherapy. Patients over 70 had longer median survival times with standard radiotherapy alone. This is in contrast to results of a secondary analysis of NCCTG (North Central Cancer Therapy Group) 94-24-52 performed by Schild *et al.* [36]. Two hundred forty-six patients were randomized to receive etoposide plus cisplatin and either radiotherapy daily or split-course RT twice a day (bid). Of the 244 assessable patients, 26% were elderly. The 5-year survival rates 18% vs. 13% in patients younger than 70 years vs. patients 70 years and older, respectively (P = 0.4). Performance status was found to be associated with survival. Higher rates of toxicity were found in older patients; 62% of patients younger than 70 vs. 81% of elderly patients experienced grade 4 or higher toxicity (P = 0.007). Grade 4 or higher hematologic toxicity occurred in 56% of patients younger than 70 compared with 78% in elderly patients (P = 0.003). The authors concluded that overall survival in elderly patients was equivalent to younger patients; however, toxicity, specifically myelosuppression and pneumonitis, was higher in elderly patients receiving CMT.

- These results are similar to results by Langer *et al.* [34]. Fit elderly patients seemed to benefit from concurrent chemotherapy and daily radiotherapy. Patients were enrolled on RTOG (Radiation Therapy Oncology Group) 9410, a phase III randomized study in which patients received either sequential chemoradiotherapy daily or concurrent chemotherapy with daily radiotherapy, or concurrent chemotherapy and twice daily radiotherapy [30]. Of the 595 assessable patients on the study, 17% were 70 years or older. The median

survival in elderly patients was higher in patients who received concurrent chemoradiotherapy (median survival 22.4 months with concurrent daily radiotherapy, 16.4 months with concurrent bid radiotherapy, and 10.8 months with sequential daily radiotherapy). Grade 3 or higher neutropenia, and grade 3 or higher esophagitis, occurred significantly more often in elderly patients; however, there was no difference in long-term toxicity. The authors concluded that fit elderly patients with locally advanced NSCLCa were candidates for CMT.

- Rocha Lima *et al.* [37] retrospectively evaluated the effect of age on the outcome and toxicity of patients enrolled on two CALGB prospective phase III studies. On CALGB 9130, patients with stage III NSLCCa were randomized to receive induction chemotherapy using vinblastine and cisplatin followed by either thoracic radiotherapy alone (60 Gy in 30 fractions) or thoracic radiotherapy (60 Gy) and weekly carboplatin. The rate of severe hematologic toxicity and renal toxicity during induction chemotherapy was significantly higher among elderly patients, $P = 0.028$ and $P = 0.0025$, respectively. There was no significant difference in median survival or response rate, $P = 0.8$ and $P = 0.3$, respectively.

- Together these results demonstrate that fit elderly patients may benefit from aggressive therapy. There is potential selection bias that may affect the enrollment of patients on cooperative group studies and thus the interpretation of retrospective analyses. As Rocha Lima *et al.* [37] reported, older patients were underrepresented with patients 70 and older representing only 22% of the total studied group and may not be directly applicable to older patients. We are in need of prospective clinical studies targeted at the elderly population to evaluate the benefits of an aggressive concurrent combined modality approach and until then selection of patients for this approach should be made judiciously.

Rectal cancer

- Colorectal cancer is the second most common cause of cancer-related death in industrialized nations [38]. The mainstay of treatment for colorectal cancer is surgery. The addition of (neo)adjuvant radiotherapy or chemoradiotherapy has led to improvements in both local control and survival [4, 39]. Preoperative chemoradiotherapy in patients with locally advanced rectal cancer is now considered to be standard of care based on an improvement in local control as well as a decrease in acute and late toxicity as compared to postoperative chemoradiotherapy [40].

- Another explanation for the improvement in survival from rectal cancer is the introduction of the total mesorectal excision (TME). The Dutch have conducted a trial comparing TME with and without a short course of preoperative radiotherapy (5 Gy × 5 fractions) [41, 42]. The findings support the combination of preoperative radiotherapy and TME as the standard treatment for rectal cancer. However, the mean age of patients included in the trial was only 63, as elderly patients were underrepresented. In a recent analysis of two datasets (Dutch TME study and the Dutch Comprehensive Cancer Centers) by Rutten *et al.* [43], the impact of TME on survival based on age group was analyzed. The combined dataset failed to demonstrate a beneficial effect on overall survival in elderly patients. Elderly patients were much more likely to suffer complications than younger patients, and the complications were more severe. Complications including

sepsis, cardiac or pulmonary problems, and abscesses were also related to a significantly increased risk of dying within 6 months post surgery in elderly patients. The increased mortality rate was directly attributable to the surgery and not radiotherapy; disease free survival in elderly patients was significantly improved in the group that received preoperative radiotherapy (five fractions of 5 Gy), whereas younger patients did not benefit from the addition of RT.

- Despite data demonstrating the benefits to adjuvant radiotherapy or chemoradiotherapy, population-based studies have generally shown that increasing age is associated with less (neo)adjuvant treatment [44–46]. In a population-based analysis of data from the California Cancer Registry from 1996 to 1997, older patients were significantly less likely to receive radiation therapy. Combination chemoradiotherapy was also delivered significantly more often in patients younger than 55 years of age (OR, 2.7; 95% CI, 1.3–5.6) than to patients 75–84 years of age (OR, 0.3; 95% CI, 0.2–0.5) and 85 years of age and older (OR, 0.1; 95% CI, 0.0–0.2), relative to patients 65–74 years of age. These results are consistent with other studies that have significantly correlated age at diagnosis with receipt of radiation therapy [47]. Among patients aged 65–69, 73% received radiation therapy, whereas only 66% among those aged 70–74, 52% of those aged 75–79, and 39% of those aged 80–84 received treatment. Non-use of radiotherapy or chemotherapy in these studies may be related to comorbidities or other barriers to medical cares such as lack of transportation or absence of caregivers.

- Among elderly patients that do receive appropriate therapy, the benefits to (neo)adjuvant therapy have been described. In a SEER Medicare analysis of 2886 patients with stage II and III rectal cancer, stage II patients were less likely to receive chemoradiation compared to stage III patients, but within both groups a clear cancer specific survival benefit was seen among those patients who completed a full course of chemoradiation [48]. Data from Pignon et al. [49] do not substantiate the claim that elderly patients do not tolerate pelvic radiotherapy as well as younger patients, as age was not a limiting factor. The complication rate from treatment was found to be two-fold higher in patients over 70 in an analysis by Shahir et al. [50]; however, there was no association made between age and radiotherapy. The goal of radiation therapy in patients with rectal cancer is to decrease the incidence of local recurrence, which can cause a significant degree of discomfort. Therefore, use of radiation therapy may be appropriate even for patients with a short life expectancy, with limited additional toxicity.

- The improvement in surgical techniques for the treatment of rectal cancer is obscured by the increase in treatment-related mortality in elderly patients. Comprehensive assessment of relevant patient parameters including social, mental, functional, and medical will help in defining the most appropriate treatment. Less invasive treatment options should be explored in the frail, elderly patients; however, as the above studies have demonstrated, age alone should not be used as a factor in limiting therapy to this population.

Treating the elderly with CMT

- In all patients, and particularly elderly patients, close attention should be paid to the maintenance of nutritional support as malnutrition can affect the efficacy of therapy as well as decrease patients' survival [51, 52•]. Radiotherapy to any part of the gastrointestinal tract or

adjacent organs may result in enteritis, mucosal ulcers, difficulty swallowing or decreased saliva which can contribute to poor overall nutrition and dehydration. The addition of concurrent chemotherapy can help potentiate the effects of radiotherapy. The frequency of weight loss or dehydration related to chemoradiotherapy varies according to site treated. When present, elderly patients are more likely to ignore symptoms of dehydration and weight loss for longer and may present with acute electrolyte imbalances if not followed closely and with early intervention. When chemotherapy or radiation induced nausea and vomiting is high, the preventive rather than symptomatic use of antiemetics is recommended. Additionally, anti-spasmodics or anti-cholinergics are recommended for treatment-related enteritis. Nutritional support is especially important in patients receiving therapy to the chest or head and neck and may require the placement of a gastrostomy tube for feeding if weight loss is significant. Studies on cancer patients unselected on the basis of nutritional status and age failed to demonstrate a clear benefit of artificial nutrition on postoperative mortality and on the effects of radiotherapy and chemotherapy [53–55]. However, both parenteral and enteral nutrition have been demonstrated to be effective in improving the nutritional status of malnourished cancer patients [56, 57]. Weight loss and decreased nutrition in cancer patients are unfavorable prognostic factors that negatively affect survival, and patients must be closely followed during therapy to maintain an optimal nutritional status [58]. No data are currently available regarding the effects of oral nutritional support and its effects on nutritional status and the clinical course of older patients with cancer; however, early consultation with a nutritional specialist is advised to assist in recommendations for improved support. Hematologic toxicity may also be increased and interventions to mitigate the impact include transfusions and use of growth factor support (Table 1).

- Age itself should not be used as a selection criterion for foregoing CMT in elderly patients. Because the addition of chemotherapy to radiotherapy increases substantially the toxicities to treatment, patients must be carefully selected. Any medical intervention in this patient population needs to account for life expectancy, tolerance to therapy, and presence of medical or social conditions that may impact therapy. One method to do so is to conduct a comprehensive geriatric assessment that evaluates functional status, comorbidities, mental status, psychological state, social support, nutritional status, polypharmacy, and geriatric conditions. An expert task force of the International Society of Geriatric Oncology recommended using a Comprehensive Geriatric Assessment (CGA) in older cancer patients to understand problems and to recommend interventions to improve

Table 1. Management of toxicities in the elderly

Toxicity	Treatment
Mucositis	Amifostine, oral gargles
Enteritis	Anti-spasmodics/anti-cholingergics, aggressive hydration and nutritional support
Hematologic toxicity	Growth factor support/transfusions
Nausea	5-Hydroxytryptamine 3 receptor antagonists (preventive rather than symptomatic administration)
Depression	Comprehensive geriatric assessment/supportive care

a patient's functional status and perhaps ultimately survival [59•]. Widespread use of a CGA approach has not been readily implanted because it is time-consuming and not yet validated.

• We must also emphasize the need for further data on the effectiveness, acute and late toxicity, and survival of elderly patients that receive CMT integrating a comprehensive geriatric assessment tool. Such data could help us identify patients for whom standard of care treatment is acceptable vs. patients for whom standard treatment poses a high degree of risk. Additionally, we must strive to include elderly patients in non age-specific clinical trials.

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