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Review article

Non-stereotactic radiotherapy in older cancer patients

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ABSTRACT

Old or very old oncological patients represent a heterogeneous and frail population due to concomitant comorbidities. Whether radiotherapy alone or in combination with novel cancer drugs may provide a clear benefit in this setting of patients is still a matter of debate.

The aim of our review is to analyze the evaluation process and the different therapeutic possibilities in older cancer patients, focusing on the different and most disparate applications of radiotherapy. We reviewed the most recent literature on radiotherapy in older patients providing clinical evidence of treatment related toxicity, tolerance and outcomes using standard fractionated and/or hypofractionated irradiation alone or in combination with chemotherapy, targeted and immunotherapy.

In older cancer patients unfit for systemic therapy or surgery, radiotherapy represents a valid therapeutic approach, both with curative and palliative intents, ensuring excellent patient compliance in terms of local toxicity and adherence to therapy.

1. Introduction

The older population is progressively growing due to an increased life expectancy for both sexes: nowadays females at birth have an average life expectancy of 85 years, while males of 80.3 years. According to most definitions, individuals aged ≥65 years are considered as "older" [1]. The lengthening life expectancy allows to identify three different categories according to Balducci classification: young old patients (65–75 years), old patients (76–85 years) and oldest old patients (over 85 years) [2].

In Italy, 35% of all new cancer diagnoses are given to patients over the age of 75 years, but tumour distribution in older patients is different between the two sexes: older males have a higher risk of developing prostate, lung, colon, bladder and stomach cancers; older females, on the other hand, mainly develop breast, gynaecological, colorectal, lung, pancreas and stomach cancers. Furthermore, there is an unequal distribution of the survival rates across the three main Italian geographical areas, with the Southern regions showing lower survival rates compared to the North-Central ones [3]. This trend is probably more related to older population participation in screening programs than to cancer care quality matters.

Old or very old oncological patients represent a heterogeneous and frail population due to concomitant comorbidities, but it is now possible to guarantee them adequate therapies with palliative or curative intent thanks to the newest development of cancer drugs and radiotherapy techniques [4, 5, 6]. Radiation therapy (RT), in particular, is often the only treatment option for older cancer patients unfit for surgery or chemotherapy, though, in this population setting, guidelines still lack and older patients are often excluded from several randomized or prospective studies [7].

In this article, we provide an overview on the most appropriate evaluation process and the different therapeutic possibilities in older cancer patients, focusing on the different and most disparate applications of RT.

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2. Clinical-oncological setting for geriatric patients

Among older patients there is a greater risk of over or under-treatment because of a wrong or incomplete clinical evaluation. Therefore, it is important to distinguish "fit" and "unfit" older patients through a multidimensional analysis that assesses comorbidities, functional and cognitive status, psychological features, and individual social support. In this way it is possible to provide an estimate of the individual life expectancy that will influence the definitive therapeutic choice.

RT can be highly effective with a well-tolerated toxicity and often represents the only alternative treatment for older patients because, compared to systemic therapies, it reaches the oncological target with better patient compliance.

During a personalized RT plan development, it is important to take into account treatment related risks and benefits, performance status (PS) and therapeutic options, considering that tumors are likely to change their biological behaviour in the older population. In fit patients, despite the increased risk of local and systemic toxicities, RT can be administered concomitantly with chemotherapy, and in order to improve the tolerance and avoid an interruption that may negatively affect the treatment outcomes, it is possible to opt for a reduction in the cancer drug dose or, whenever possible, for a sequential scheme. On the other side, in patients with severe functional limitation, RT alone or alternative therapeutic approaches such as supportive therapies should be considered.

2.1. Pre-treatment radiotherapy evaluation and clinical classification of older patient

The clinical evaluation is a crucial moment that will influence the whole therapeutic process and consists of an accurate physical examination and a multimodal analysis of the geriatric patient.

Several methods of screening for older patients have been developed in order to assist decision-making on treatment options, and one of the most validated tools is the Comprehensive Geriatric Assessment (CGA) which includes different criteria such as mental health, functional capacity, medical comorbidities, environmental factors and social supports [8].

2.2. Functional status

Functional status in older patients with cancer disease can be assessed using tools evaluating self-care (KPS – Karnofsky Performance Status), daily activities at home (ADL - Activities of Daily Living) and complex skills necessary to maintain independence in the social field (IADL - Instrumental Activities of Daily Living). In older patients, the need for care coexists with a reduced treatment tolerance and a lower survival rate [9].

The “Timing Up and Go" (TUG) is a rapid screening test used to evaluate the gait speed and the general motor functions of the older, and its score is calculated as the time in seconds taken by an individual to stand up from an arm chair, without using his arms, walk a distance of approximately 10 steps even using some walking devices, turn, walk back to the chair, and sit down. With this test score we can predict the risk for falls that is closely related to a lower tolerance to and/or an interruption of the treatment.

2.3. Cognitive function

Older cancer patients with cognitive disorders have an increased risk of functional dependence, higher incidence of depression and a greater risk of death that compromise therapeutic success.

An essential condition during a RT session is patient's collaboration. The use of anticholinergic drugs, antipsychotics, benzodiazepines, corticosteroids and opioids causes greater cognitive impairment; in particular, antipsychotics are also associated with higher mortality rate in patients with mild-advanced cognitive impairment. The "drug index" has proved to be a useful tool for assessing the effect of these drugs on the older physical and cognitive performance [10].

In case of cognitive impairment, the use of "Mini-Mental State Exam (MMSE)" and of the "Montreal Cognitive Assessment (MoCA)" is highly recommended, while the "Confusion Assessment Method" (CAM) allows the evaluation of a delirium state upon 4 characteristics: acute onset and fluctuating course, inattention, disorganized thinking and altered level of consciousness [11, 12, 13]. As regards depression, the "Geriatric Depression Scale (GDS)" is a reliable tool for both patients without cognitive impairment and patients with mild to moderate cognitive impairment [14]. Finally, it is strongly recommended to treat asthenic disorders as this condition can be often a symptom of depression not related to cancer or current therapies.

2.4. Comorbidities

Major comorbidities can affect prognosis and treatment tolerance as they can worsen the course of cancer disease during RT; cardiovascular diseases, diabetes, renal failure, cognitive impairment, depression, anaemia, chronic infections, osteoporosis, and decubitus ulcers are the most common ones.

In a pre-treatment phase, comorbidities effects on life expectancy are commonly calculated with the Charlson Comorbidity Index (CCI) which predicts 10-year survival in patients with multiple comorbidities, and with the Cumulative Illness Rating Scale (CIRS) used for assessing physical impairment [15, 16].

2.5. Nutritional status

Nutritional deficiency or malnutrition are common especially in older cancer patients. A poor nutritional status is associated with an increased risk of severe haematological toxicities during chemotherapy, increased risk of mortality, lower tolerance to RT and higher risk of hospitalization and treatment interruption [17, 18]. Distinguishing cancer-related weight loss from inadequate daily caloric intake is of major relevance. A body mass index (BMI) $\leq$ 22 kg/m^2 and an unintentional weight loss greater than 5% in the last 6 months place the patient in the high-risk class. These patients are also exposed to a greater risk of osteoporosis and fractures due to malnutrition and cancer related lack of vitamin D [19].

2.6. Polypharmacotherapy

Polypharmacotherapy, very common in the older, is described as the use of more than five drugs per prescription and it may influence the choice of the supportive therapy usually prescribed to patients during RT. The supportive therapy usually consists of topical and systemic drugs prescribed to guarantee a better management of local acute toxicities that may occur during treatment, sucha as the radio-induced acute inflammation both of the target organ and of the organs at risk (OARs). This is an inevitable consequence of RT that may cause some discomfort or, in the worst cases, the treatment interruption. To prevent this, radiation oncologists prescribe corticosteroid drugs and non-steroidal anti-inflammatory drugs paying great attention to the pre-existing comorbidities such as diabetes, hypertension and bleeding.

In this context it is necessary to personalize supportive therapy as much as possible considering that older patients are already on drug therapy for several comorbidities.

2.7. Socio-economic issues

Older patients with a low socio-economic level are at higher risk for mortality. During a RT course, patients often need support from family members or caregivers, whose choice is strongly influenced by their financial condition.

3. Planning and treatment in older patients

Surgery may not always be a feasible option for older patients due to associated age-related comorbidities exposing them to high operative

risks. In this context, modulated intensity radiotherapy (IMRT), image-guided radiotherapy (IGRT) and stereotactic radiotherapy (SBRT) are advanced RT techniques that facilitate the delivery of high-dose radiation to well-limited target volumes with a low risk of functional radiation-related damage to surrounding healthy tissues and OARs.

Several studies have shown that in patients defined as unfit for surgery due to age and comorbidities the outcomes in terms of overall survival (OS) and progression free survival (PFS) were comparable both for RT and radical surgery, also providing excellent local control rates in different types of cancer.

Moreover, RT can also be added to surgery to improve its effectiveness. In this regard, Liu et al. evaluated the outcome of radical surgery combined with adjuvant RT in 178 older patients >75 years with stage II or III rectal cancer. Two groups of patients were defined, the adjuvant radiation therapy (ART) group received surgery combined with pelvis RT at a dose of 50 Gy in 25 fractions, and the no radiation therapy (NORT) group that did not receive any irradiation. The 5-year OS rates of the ART and NORT groups were similar, but radical surgery combined with RT resulted in improved local control rates [20].

3.1. Radiotherapy related toxicity and tolerance in older patients: some clinical scenarios using standard fractionated irradiation

If on the one hand there is no indication for a RT dose reduction due to age, on the other hand little is known about RT side effects in this population setting.

Conventionally fractionated curative "involved field" RT seems to be effective along with an acceptable local toxicity in older patients with clinical stage IIIA non-small cell lung cancer (NSCLC), as investigated in some studies reporting a median OS of about 20 months [21, 22, 23].

Curative conformal RT alone has resulted to be a valid therapeutic approach also in muscle invasive bladder cancer (MIBC) older patients defined unfit both for surgery and systemic therapy due to their comorbidities. Indeed, several studies reported [24, 25, 26] the feasibility and the efficacy of RT alone with acceptable gastrointestinal (GI) or genito-urinary (GU) side effects [27].

3.2. Hypofractionated radiation therapy and compliance in older patients

Hypofractionated radiation therapy (HFRT) seems to be more convenient in frail older patients unsuitable for standard fractionated RT because of multiple comorbidities affecting their performance status. A shorter course of RT, by means of accelerated (5–7 fractions) and moderate HFRT, guarantees a major adherence to the therapeutic plan with a concomitant increased tolerance in terms of toxicity regardless of the type of cancer intended to treat.

The accelerated adjuvant HFRT is a feasible therapeutic option for older patients (aged >80 years) with breast cancer previously treated with conservative surgery or mastectomy. Sanz et al. reported in a retrospective study the promising outcomes of once-a-week irradiation at a dose of 5 Gy or 6.25 Gy per 6 fractions (total dose 30–37.5 Gy) of 486 women >80 years unfit for a conventional treatment because of comorbidities or socio-family problems. The only toxicities observed were mild acute G1-3 dermatitis in 75.6% of the patients, and moderate G2 chronic fibrosis in 30.6% of the patients [28].

Regarding prostate cancer, the CHHiP trial compared conventional fractionation (74 Gy in 37 fractions) to moderate HFRT (60 Gy in 20 fractions or 57 Gy in 19 fractions) in 3216 older patients aged ≥75 years who had previously received 3–6 months of androgen deprivation therapy. The incidence of G3 acute GI and GU toxicities was 2% and 7% respectively, so this complex study proved that the hypofractionated schedules are highly effective with a few long-term side effects [29].

The safety of HFRT has also been demonstrated in several studies that enrolled older patients with basal cell carcinoma obtaining similar survival and local control rates compared to standard fractionation [30, 31, 32]. In this regard, a retrospective analysis of 117 frail older patients (CCI>5) with facial basal cell carcinoma treated with the once-weekly schedule (5 Gy per week up to 25–30 Gy) reported that all patients completed the treatment showing a complete tumor response in 98.3% with no G3 acute toxicities, late toxicities or hospitalization [33].

Older patients with bladder cancer unfit for long periods of daily irradiation may benefit from HFRT. In a study conducted by Dirix et al. a hypofractionated schedule of 34.5 Gy in six weekly fractions was successful in the long-term management of hematuria with acceptable acute and late G ≥ 3 urinary toxicity [34]. Accelerated HFRT, as recently reported by Hammer et al., provides good local control with no G4 toxicity and acceptable G3 GI or GU side effects also in older patients with muscle invasive bladder cancer unfit for chemoradiotherapy [35].

Even though in older patients these short-course RT schedules play a major role as palliative treatments, HFRT is indicated for many types of cancer involving different body districts for palliative, symptomatic and cytoreductive purposes, achieving good local control rates with improved compliance and minimal treatment related morbidity [36].

Table 1 reports a summary of the main studies on conventionally fractionated and hypofractionated RT in older patients.

3.3. RT and chemotherapy in older patients

Several studies have investigated the combined use of chemo-radiotherapy (CRT) in older patients showing improved clinical outcomes such as OS and PFS. However, caution is recommended considering the decreased reserve of stem cells and the pre-existing comorbidities affecting drug absorption and metabolism [37].

From November 2007 to September 2013, Perry et al. enrolled 562 patients with a median age of 73 years and a new diagnosis of glioblastoma randomly divided in two groups; one group received a short-course RT alone (40 Gy in 15 fractions over a period of 3 weeks) whereas the other one received a short-course RT plus concurrent and adjuvant temozolomide for up to 12 cycles or until radiologically defined disease progression occurred. The OS and PFS rates were more promising in the second group though, as expected, greater hematologic toxicities were found. Moreover, in methylated MGMT patients undergoing CRT survival was nearly double compared to the unmethylated MGMT patients [38].

The advantage of CRT in terms of survival has been proved also in several studies on unresectable stage III NSCLC older patients. The first prospective randomised clinical trial designed for this aim was run by the Japanese Clinical Oncology Group that recruited 200 patients older than 70 years and randomly assigned half of them to CRT (60 Gy plus concurrent low-dose daily carboplatin) and the other half to RT alone. The median OS was 22.4 months versus 16.9 months respectively, thus even though in the CRT group 61/100 patients reported G3-G4 haematological toxicities, CRT was considered a valid therapeutic option for this population [39]. In keeping with this study, the EORTC Elderly Task Force and International Society for Geriatric Oncology (SIOG) and a systematic review by Dawe et al. recommend CRT for the treatment of older patients with NSCLC whose KPS and comorbidities are acceptable [40, 41]. Miller et al. supported this evidence too, as they recently conducted the largest comparative effectiveness study to date collecting two cohorts of ≥70-year-old patients in stage III NSCLC treated with definitive RT or CRT [42].

Despite the onset of acute toxicities, CRT is an accepted standard treatment also for older patients with inoperable esophageal cancer and adequate functional status, as suggested by a phase II single-arm study published by Servagi-Vernat et al. [43] and confirmed by a review of the National Cancer Database conducted by Vlacich et al. in 2017 [44].

A comparison in terms of OS and side effects between CRT and RT alone has highlighted the benefit of the combined treatment also in older patients with uterine cervical cancer, despite the different characteristics of the treatment-related toxicities occurred in this population compared to those typical of young patients [45].

Definitive CRT is a feasible and effective therapeutic choice even in older patients affected by squamous cell carcinoma of the head and neck.

Table 1. Summary of the main studies on conventionally fractionated and hypofractionated RT in older patients. Survival outcomes and complications are reported. Abbreviations: P prospective, R retrospective, NSCLC non-small cell lung cancer, MIBC muscle invasive bladder cancer, BCC basal cell carcinoma, CFRT conventional fractionated radiotherapy, HFRT hypofractionated radiation therapy, FU follow-up, OS overall survival, RFS recurrence-free survival, LC local control, BCF biochemical or clinical failure, GI gastrointestinal, GU genitourinary.

Authors	Year	Type of study	N. Pts	Median age (range)	Histology	Type of RT	Dose range Gy/fxs	Median FU (months)	Outcomes	Acute toxicities (%)	Late toxicities (%)
Pergolizzi et al. [22]	2002	P	40	77 (75–83)	NSCLC	CFRT	54-64/27-32	54	Median OS 19 months	G1/2 esophagitis (70)	Radiation pneumonia (5)
Santacaterina et al. [24]	2002	R	45	75 (70–85)	MIBC	CFRT	56-64/28-32	63	Median OS 21.5 months	G1/2 GI and/or GU toxicity (100)	-
Santacaterina et al. [25]	2015	R	27	84.5 (81–91)	MIBC	CFRT	60-64/30-32	17.5	Mean OS 23.5 months	G1/2 GI and/or GU toxicity (55.5)	G1/2 GI and/or GU toxicity (11)
Wujanto et al. [27]	2019	R	45	77 (65–95)	MIBC	CFRT	50–69.8/30-40	31	Median OS 56 months	G1/2 GI and/or GU toxicity (89)	G3 cystitis (2.2)
Soyfer et al. [60]	2013	R	21	80	Soft-tissue sarcoma	HFRT	39-48/13-16	26	-	G2/3 toxicity (3.75)	G2/3 toxicity (3.75)
Kouloulias et al. [30]	2014	R	38	78 (64–91)	BCC	HFRT	30/5 once weekly	48	Local RFS 92.1%	G1/2 skin toxicity (92.2)	-
Marriappan et al. [31]	2014	R	25	89 (83–103)	BCC	HFRT	42/7 once weekly	15	LC 95%	-	-
Pelissero et al. [33]	2015	R	117	82 (75–103)	BCC	HFRT	25-30/5–6 once weekly	61	3-year RFS 96.4%; 5-year RFS 94.5%	G1/2 skin toxicity (30.7)	-
Russi et al. [32]	2015	R	134	82.5 (75–103)	BCC	HFRT	25-30/5–6 once weekly	64.5	3-year RFS 97.3%; 5-year RFS 92.7%	G1/2 skin toxicity (30.6)	-
Dirix et al. [34]	2016	R	44	72	MIBC	HFRT	34.5/6	10	Mean OS 10.5 months; mean hematuria-free survival 13 months	G3 GU toxicity (9)	G3 GU toxicity (19)
Sanz et al. [28]	2018	R	486	79	Breast cancer	HFRT	30–37.5/6	51	5-year OS 74.2%; local RFS 96.5%	G1 dermatitis (52)	G1 fibrosis (68)
Wilson et al. [29]	2018	P	491	75	Prostate cancer	HFRT	57-60/19-20	60	5-year BCF-free rates 87.7–91%	G3 GI and/or GU toxicity (10)	G2 GI toxicity (12.5) and GU toxicity (9.2)
Hammer et al. [35]	2019	R	17	87 (81–95)	MIBC	HFRT	45/15	65.3	1-year OS 47%; 2-year OS 23%	G3 GI toxicity (6) and GU toxicity (24)	G3 GU toxicity (5.8)

In this regard a single-centre retrospective study compared the OS, the local and distant tumour control and the treatment-related adverse events separately for patients aged ≥65, ≥70, and ≥75 years without observing any significant differences for any of the aforementioned groups [46]. More recently, CRT provided longer OS than RT alone (53.7% vs 36.9%, $P = 0.002$) in 455 patients with nasopharyngeal carcinoma aged ≥65 years [47]. Both studies concluded that chronological age itself is not a sufficient parameter to take treatment decisions.

Despite multiple studies have shown higher toxicity rates especially haematological with CRT compared to RT alone both in young and older population, an adapted geriatric selection and a strict monitoring may help decreasing toxicity. In this view, the Concurrent Once-Daily Versus Twice-Daily Radiotherapy (CONVERT) Trial is the largest randomized trial to date comparing CRT outcomes of limited-stage SCLC patients aged ≥70 years versus younger patients showing comparable survival and toxicity [48].

To facilitate decision making for older adults, chemotherapy toxicity risk can be predicted by parameters included in the Cancer and Aging Research Group (CARG) Chemo Toxicity Calculator and in the Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH) [49].

3.4. RT and targeted therapy/immunotherapy in older patients

The recent introduction of targeted therapies (TT) and immunotherapy (IT) has radically changed the outcome of various cancer treatments, but unfortunately sufficient data on the safety and efficacy of TT/IT alone and in association with RT in older patients are still lacking [50]. It is established that severe recruitment criteria are necessary especially in case of several comorbidities coexisting. In fact, though in this frail population the effectiveness of these treatments is comparable to the younger counterpart and tolerance is better than cytotoxic treatment, specific adverse events might occur [51, 52, 53].

Literature data suggest that RT has immunostimulatory properties by priming and homing activated immune cells in the irradiated area in addition to systemic and distant antitumor effects such as the abscopal effect [54, 55, 56, 57].

In a case report on a 80-year-old patient with a pretreated advanced squamous cell lung cancer who had a poor response to RT, Lazzari et al. found that RT plus sequential nivolumab as a second line therapy provided local and systemic disease control at 24 months [58]. In addition, 81 studies have been included in the most recent and complete review on the concurrent administration of TT/IT and RT in over 65 years of age cancer patients [59].

Despite the association of RT and TT/IT is a crucial arm for fighting cancer in older patients, safety and efficacy of this innovative treatment option in this frail population is still a matter of debate and further studies should be fostered in order to better elucidate its feasibility.

A summary of the main studies on CRT and RT plus TT/IT in older patients is reported in Table 2.

Table 2. Summary of the main studies on RT + chemotherapy (CRT) and RT + targeted therapy (TT)/immunotherapy (IT) in older patients. Survival outcomes and complications are reported. Abbreviations: R retrospective, NSCLC non-small cell lung cancer, HNC head and neck cancer, FU follow-up, OS overall survival, GI gastrointestinal, GU genitourinary.

Authors	Year	Type of study	N. Pts	Median age (range)	Histology	Type of therapy	Dose range Gy/fxs	Median FU (months)	Outcomes	Acute toxicities (%)	Late toxicities (%)
Cai et al. [61]	2013	R	126	75 (70–92)	Rectal cancer	CRT	52.2	19	3-year OS 48.1%	-	-
Servagi-Vernat et al. [43]	2015	Phase 2 study	30	85.2 (79.4–92)	Esophageal cancer	CRT	50/25	36	3-year OS 22.2%	G > 4 toxicity (38)	-
Nosaka et al. [45]	2016	R	49	75.4 (70–89)	Cervical cancer	CRT	50.4/28 + 18–24	25.5	Median OS 66.9 vs 60.1 months (CRT vs RT group)	G3/4 acute toxicities: hyponatremia (35), neutropenia (15), diarrhea (10)	-
Perry et al. [38]	2017	Trial	562	73 (65–90)	Glioblastoma	CRT	40/15	17	Median OS 9.3 vs 7.6 months (CRT vs RT group)	G3/4 hematological toxicity (46.6)	-
Atagi et al. [62]	2018	Phase 3 trial	200	77	NSCLC	CRT	60/30	19.4	Median OS 22.4 vs 16.9 months (CRT vs RT group)	G4 hematological toxicity (26.4)	G3/4 lung toxicity (6.5)
Miller et al. [42]	2018	R	23229	77.6	NSCLC	CRT	64.8/33	15.5	Median OS 18.1 vs 12.2 (CRT vs RT group)	G > 3 hematological toxicity (89.9)	-
Lazzari et al. [58]	2018	Case report	1	80	NSCLC	RT + IT	66/33	36	-	G2 anemia and G3 febrile neutropenia	-
Müller von der Grün et al. [46]	2018	R	158	65	HNC	CRT	70.6	29	3-year OS 50%	G > 3 hematological toxicity (18)	-
Lai et al. [63]	2018	R	70	75	HNC	CRT	60-74/ 30-37	-	Median OS 10.8 vs 11.4 months (CRT vs RT group)	G3/4 hematological toxicities: neutropenia (13.2), thrombocytopenia (5.3)	-
Wang et al. [64]	2019	R	1061	74 (70–88)	Cervical cancer	CRT	50.4/28 + 30-36/ 5-7	28.9	3-year OS 71.9%	G3/4 hematological toxicity (58.1)	G3/4 GI toxicity (8.6)
Jingu et al. [65]	2020	R	358	80	Esophageal cancer	CRT	50–60	-	3-year OS 22%	-	-
Lu et al. [47]	2021	R	272	72 (65–88)	HNC	CRT	-	-	5-year OS 61.8 vs 51.7 (CRT vs RT group)	-	-

4. Conclusions

Nowadays older patients still represent a therapeutic challenge. The complex approach to this vulnerable population occurs in a context of multiple comorbidities, increased risk of complications and limited life expectancy. Furthermore, several studies have shown that older patients poorly refer to specialists, often receive suboptimal therapies or, even worse, refuse any kind of treatment.

Innovative techniques and fractionation schedules have made radiotherapy as a valid therapeutic option with both curative and palliative intents even in patients unfit for systemic therapy or surgery, ensuring optimal patient compliance in terms of toxicity and adherence to therapy.

It is important to point out that a careful patient evaluation is always required to personalize the therapeutic plan and to minimize as much as possible the risk of under- or over-treatment. Therefore, either a holistic approach to older patients or a multidisciplinary collaboration involving geriatricians and other health professionals are essential to provide the best cancer care to this vulnerable population for which trials, evidence-based data and guidelines are still scarce.

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References

[1] H. Orimo, H. Ito, T. Suzuki, A. Araki, T. Hosoi, M. Sawabe, Reviewing the definition of elderly, Geriatr. Gerontol. Int. 43 (2006) 27–34.
[2] L. Balducci, G.H. Lyman, W.B. Ershler, M. Extermann, Comprehensive Geriatric Oncology, 2004.
[3] A.I.O.M. Linee guida, Tumori Dell'anziano, 2017.
[4] E. Amato, A. Italiano, S. Pergolizzi, Gold nanoparticles as a sensitising agent in external beam radiotherapy and brachytherapy: a feasibility study through Monte Carlo simulation, Int. J. Nanotechnol. 10 (2013) 1045.

[5] A. Sindoni, F. Minutoli, A. Pontoriero, G. Iatì, S. Baldari, S. Pergolizzi, Usefulness of four dimensional (4D) PET/CT imaging in the evaluation of thoracic lesions and in radiotherapy planning: review of the literature, Lung Cancer 96 (2016) 78–86.

[6] A. Cacciola, S. Parisi, C. Tamburella, S. Lillo, G. Ferini, L. Molino, G. Iatì, A. Pontoriero, A. Bottari, S. Mazziotti, G. Cicero, F. Minutoli, A. Blandino, S. Pergolizzi, Stereotactic body radiation therapy and radiofrequency ablation for the treatment of liver metastases: how and when? Rep. Practical Oncol. Radiother. 25 (2020) 299–306.

[7] E. Soto-Perez-De-Celis, S.M. Lichtman, Considerations for clinical trial design in older adults with cancer, Expet Opin. Invest. Drugs 26 (2017) 1099–1102.

[8] British Geriatrics Society, Comprehensive Geriatric Assessment Toolkit for Primary Care Practitioners, (n.d.).

[9] P. Maione, F. Perrone, C. Gallo, L. Manzione, F. Piantedosi, S. Barbera, S. Cigolari, F. Rosetti, E. Piazza, S.F. Robbiati, O. Bertetto, S. Novello, M.R. Migliorino, A. Favaretto, M. Spatafora, F. Ferraù, L. Frontini, A. Bearz, L. Repetto, C. Gridelli, E. Barletta, M.L. Barzelloni, R.V. Iaffaioli, E. De Maio, M. Di Maio, G. De Feo, G. Sigoriello, P. Chiodini, A. Cioffi, V. Guardasole, V. Angelini, A. Rossi, D. Bilancia, D. Germano, A. Lamberti, V. Pontillo, L. Brancaccio, F. Renda, F. Romano, G. Esani, A. Gambaro, O. Vinante, G. Azzarello, M. Clerici, R. Bollina, P. Belloni, M. Sannicolò, L. Ciuffreda, G. Parello, M. Cabiddu, C. Sacco, A. Sibau, G. Porcile, F. Castiglione, O. Ostellino, S. Monfardini, M. Stefani, G. Scagliotti, G. Selvaggi, F. De Marinis, O. Martelli, G. Gasparini, A. Morabito, D. Gattuso, G. Colucci, D. Galetta, F. Giotta, V. Gebbia, N. Borsellino, A. Testa, E. Malaponte, M.A. Capuano, M. Angiolillo, F. Sollitto, U. Tirelli, S. Spazzapan, V. Adamo, G. Altavilla, A. Scimone, M.R. Hopps, F. Tartamella, G. Pietro Ianniello, V. Tinessa, G. Failla, R. Bordonaro, N. Gebbia, M.R. Valerio, M. D'Aprile, E. Veltri, M. Tonato, S. Darwish, S. Romito, F. Carrozza, S. Barni, A. Ardizzoia, G.M. Corradini, G. Pavia, M. Belli, G. Colantuoni, E. Galligioni, O. Caffo, R. Labianca, A. Quadri, E. Cortesi, G. D'Auria, S. Fava, A. Calcagno, G. Luporini, M.C. Locatelli, F. Di Costanzo, S. Gasperoni, L. Isa, P. Candido, F. Gaion, G. Palazzolo, G. Nettis, A. Annamaria, M. Rinaldi, M. Lopez, R. Felletti, G.B. Di Negro, N. Rossi, A. Calandriello, L. Maiorino, R. Mattioli, A. Celano, S. Schiavon, A. Illiano, C.A. Raucci, M. Caruso, P. Foa, G. Tonini, C. Curcio, M. Cazzaniga, Pretreatment quality of life and functional status assessment significantly predict survival of elderly patients with advanced non-small-cell lung cancer receiving chemotherapy: a prognostic analysis of the multicenter Italian lung cancer in the elderly s, J. Clin. Oncol. 23 (2005) 6865–6872.

[10] S.N. Hilmer, D.E. Mager, E.M. Simonsick, S.M. Ling, B.G. Windham, T.B. Harris, R.I. Shorr, D.C. Bauer, D.R. Abernethy, Health ABC study, drug burden index score and functional decline in older people, Am. J. Med. 122 (2009) 1142–1149, e2.

[11] T. Monroe, M. Carter, Using the Folstein Mini Mental State Exam (MMSE) to explore methodological issues in cognitive aging research, Eur. J. Ageing 9 (2012) 265–274.

[12] B.T. Mast, A. Gerstenecker, Screening instruments and brief batteries for dementia, Handb. Assess. Clin. Gerontol. (2010) 503–530.

[13] S.K. Inouye, L. Leo-Summers, Y. Zhang, S.T. Bogardus, D.L. Leslie, J.V. Agostini, A chart-based method for identification of delirium: validation compared with interviewer ratings using the confusion assessment method, J. Am. Geriatr. Soc. 53 (2005) 312–318.

[14] J.A. Yasavage, J.I. Sheikh, 9/Geriatric depression scale (GDS) recent evidence and development of a shorter version, Clin. Gerontol. 5 (1986) 119–136.

[15] M.E. Charlson, P. Pompei, K.L. Ales, C.R. MacKenzie, A new method of classifying prognostic comorbidity in longitudinal studies: development and validation, J. Chron. Dis. 40 (1987) 373–383.

[16] B.S. Linn, M.W. Linn, L. Gurel, Cumulative illness rating scale, J. Am. Geriatr. Soc. 16 (1968) 622–626.

[17] J. Alexandre, M. Gross-Goupil, B. Falissard, M.L. Nguyen, J.M. Gornet, J.L. Misset, F. Goldwasser, Evaluation of the nutritional and inflammatory status in cancer patients for the risk assessment of severe haematological toxicity following chemotherapy, Ann. Oncol. 14 (2003) 36–41.

[18] A.A. Aaldriks, L.G.M. van der Geest, E.J. Giltay, S. le Cessie, J.E.A. Portielje, B.C. Tanis, J.W.R. Nortier, E. Maartense, Frailty and malnutrition predictive of mortality risk in older patients with advanced colorectal cancer receiving chemotherapy, J. Geriatr. Oncol. 4 (2013) 218–226.

[19] F. Landi, G. Zuccalà, G. Gambassi, R.A. Incalzi, L. Manigrasso, F. Pagano, P.U. Carbonin, R. Bernabei, Body mass index and mortality among older people living in the community, J. Am. Geriatr. Soc. 47 (1999) 1072–1076.

[20] W. Liu, J. Jin, Y. Li, S. Wang, Y. Song, Y. Liu, W. Wang, H. Ren, H. Fang, N. Li, Y. Tang, X. Wang, Y. Tang, N. Lu, Q. Xiao, Y. Feng, J. Wang, L. Deng, H. Jing, X. Liu, Z. Yu, Radical surgery combined with adjuvant radiotherapy for elderly patients aged over 75 years with stage II(or III) rectal cancer: a retrospective study from a single center, Zhonghua Wei Chang Wai Ke Za Zhi 21 (2018) 654–659.

[21] F. Lonardi, M. Coeli, G. Pavanato, F. Adami, G. Gioga, F. Campostrini, Radiotherapy for non-small cell lung cancer in patients aged 75 and over: safety, effectiveness and possible impact on survival, Lung Cancer 28 (2000) 43–50.

[22] S. Pergolizzi, A. Santacaterina, C. De Renzis, N. Settineri, M. Gaeta, P. Frosina, E.G. Russi, G. Altavilla, Older people with non small cell lung cancer in clinical stage IIIA and co-morbid conditions: is curative irradiation feasible? Final results of a prospective study, Lung Cancer 37 (2002) 201–206.

[23] P.D. Soni, P.S. Boonstra, M.J. Schipper, L. Bazzi, R.T. Dess, M.M. Matuszak, F.M. Kong, J.A. Hayman, R.K. Ten Haken, T.S. Lawrence, G.P. Kalemkerian, S. Jolly, Lower incidence of esophagitis in the elderly undergoing definitive radiation therapy for lung cancer, J. Thorac. Oncol. 12 (2017) 539–546.

[24] A. Santacaterina, N. Settineri, C. De Renzis, P. Frosina, A. Brancati, P. Delia, C. Palazzolo, A. Romeo, G. Sansotta, S. Pergolizzi, Muscle-invasive bladder cancer in elderly-unfit patients with concomitant illness: can a curative radiation therapy be delivered? Tumori 88 (2002) 390–394.

[25] A. Santacaterina, A. Platania, C. Palazzolo, C. Spatola, G. Acquaviva, M. Crispi, G. Privitera, N. Settineri, S. Pergolizzi, Very elderly (>80 years), frail patients with muscle-invasive bladder cancer and comorbidities: is curative irradiation feasible? Tumori 101 (2015) 609–613.

[26] G. Ferini, A. Cacciola, S. Parisi, S. Lillo, L. Molino, C. Tamburella, V. Davi, I. Napoli, A. Platania, N. Settineri, G. Iati, A. Pontoriero, S. Pergolizzi, A. Santacaterina, Curative radiotherapy in elderly patients with muscle invasive bladder cancer: the prognostic role of sarcopenia, Vivo (Brooklyn) 35 (2021) 571–578.

[27] C. Wujanto, J. Tey, D. Chia, F. Ho, K.H. Ooi, A.S. Wong, Y.Y. Soon, K. Lim, Radical radiotherapy in older patients with muscle invasive bladder cancer, J. Geriatr. Oncol. 10 (2019) 292–297.

[28] J. Sanz, M. Zhao, N. Rodríguez, R. Granado, P. Foro, A. Reig, I. Membrive, M. Algara, Once-weekly hypofractionated radiotherapy for breast cancer in elderly patients: efficacy and tolerance in 486 patients, BioMed Res. Int. 2018 (2018), 8321871.

[29] J.M. Wilson, D.P. Dearnaley, I. Syndikus, V. Khoo, A. Birtle, D. Bloomfield, A. Choudhury, J. Graham, C. Ferguson, Z. Malik, J. Money-Kyrle, J.M. O'Sullivan, M. Panades, C. Parker, Y. Rimmer, C. Scrase, J. Staffurth, A. Stockdale, C. Cruickshank, C. Griffin, E. Hall, The efficacy and safety of conventional and hypofractionated high-dose radiation therapy for prostate cancer in an elderly population: a subgroup Analysis of the CHHiP trial, Int. J. Radiat. Oncol. Biol. Phys. 100 (2018) 1179–1189.

[30] V. Kouloulias, E. Papadavid, E. Mosa, K. Platoni, O. Papadopoulos, D. Rigopoulos, J. Georgakopoulos, I. Beli, F. Karantonis, O. Castana, M. Dalamaga, N. Kelekis, A new hypofractionated schedule of weekly irradiation for basal cell carcinoma of the head and neck skin area in elderly patients, Dermatol. Ther. 27 (2014) 127–130.

[31] L. Marriappan, S. Ramasamy, F. Robert, Weekly radiotherapy for basal cell carcinoma in the frail and elderly, Br. J. Dermatol. 171 (2014) 1237–1239.

[32] E.G. Russi, A. Pelissero, A. Melano, C. Fillini, R. Vigna-Taglianti, L. Gianello, F. Lucio, N. Settineri, A. Santacaterina, A. Pontoriero, G. Iati, S. Pergolizzi, Facial basal cell carcinomas in elderly frail patients treated with low total-dose radiotherapy, Anticancer Res. 35 (2015) 4949–4953.

[33] A. Pelissero, E.G. Russi, A. Melano, C. Fillini, R. Vigna-Taglianti, N. Settineri, F. Lucio, G. Girolomoni, S. Pergolizzi, Facial basal cell carcinomas treated with hypo-fractionated radiotherapy: a retrospective analysis in 117 elderly patients, J. Am. Acad. Dermatol. 73 (2015) 166–168.

[34] P. Dirix, S. Vingerhoedt, S. Joniau, B. Van Cleynenbreugel, K. Haustermans, Hypofractionated palliative radiotherapy for bladder cancer, Support. Care Cancer 24 (2016) 181–186.

[35] L. Hammer, M. Laufer, Z. Dotan, R. Leibowitz-Amit, R. Berger, S. Felder, I. Weiss, Y.R. Lawrence, Z. Symon, Accelerated hypofractionated radiation therapy for elderly frail bladder cancer patients unfit for surgery or chemotherapy, Am. J. Clin. Oncol. 42 (2019) 179–183.

[36] V. Donato, M. Valeriani, A. Zurlo, Short course radiation therapy for elderly cancer patients. Evidences from the literature review, Crit. Rev. Oncol. Hematol. 45 (2003) 305–311.

[37] T. Wasil, Clinical pharmacology issues relevant to the dosing and toxicity of chemotherapy drugs in the elderly, Oncol. 10 (2005) 602–612.

[38] J.R. Perry, N. Laperriere, C.J. O'Callaghan, A.A. Brandes, J. Menten, C. Phillips, M. Fay, R. Nishikawa, J.G. Cairncross, W. Roa, D. Osoba, J.P. Rossiter, A. Sahgal, H. Hirte, F. Laigle-Donadey, E. Franceschi, O. Chinot, V. Golfinopoulos, L. Fariselli, A. Wick, L. Feuvret, M. Back, M. Tills, C. Winch, B.G. Baumert, W. Wick, K. Ding, W.P. Mason, Short-course radiation plus temozolomide in elderly patients with glioblastoma, N. Engl. J. Med. 376 (2017) 1027–1037.

[39] S. Atagi, M. Kawahara, A. Yokoyama, H. Okamoto, N. Yamamoto, Y. Ohe, T. Sawa, S. Ishikura, T. Shibata, H. Fukuda, N. Saijo, T. Tamura, Japan Clinical Oncology Group Lung Cancer Study Group, Thoracic radiotherapy with or without daily low-dose carboplatin in elderly patients with non-small-cell lung cancer: a randomised, controlled, phase 3 trial by the Japan Clinical Oncology Group (JCOG0301), Lancet Oncol. 13 (2012) 671–678.

[40] A.G. Pallis, C. Gridelli, J.P. van Meerbeeck, L. Greillier, U. Wedding, D. Lacombe, J. Welch, C.P. Belani, M. Aapro, EORTC elderly Task Force and lung cancer group and international society for geriatric oncology (SIOG) experts' opinion for the treatment of non-small-cell lung cancer in an elderly population, Ann. Oncol. 21 (2010) 692–706.

[41] D.E. Dawe, D. Christiansen, A. Swaminath, P.M. Ellis, J. Rothney, R. Rabbani, A.M. Abou-Setta, R. Zarychanski, S.M. Mahmud, Chemoradiotherapy versus radiotherapy alone in elderly patients with stage III non-small cell lung cancer: a systematic review and meta-analysis, Lung Cancer 99 (2016) 180–185.

[42] E.D. Miller, J.L. Fisher, K.E. Haglund, J.C. Grecula, M. Xu-Welliver, E.M. Bertino, K. He, P.G. Shields, D.P. Carbone, T.M. Williams, G.A. Otterson, J.G. Bazan, The addition of chemotherapy to radiation therapy improves survival in elderly patients with stage III non–small cell lung cancer, J. Thorac. Oncol. 13 (2018) 426–435.

[43] S. Servagi-Vernat, G. Créhange, B. Roullet, V. Guimas, P. Maingon, M. Puyraveau, J.F. Bosset, Phase II study of a platinum-based adapted chemotherapy regimen combined with radiotherapy in patients 75 Years and older with esophageal cancer, Drugs Aging 32 (2015) 487–493.

[44] G. Vlacich, P.P. Samson, S.M. Perkins, M.C. Roach, P.J. Parikh, J.D. Bradley, A.C. Lockhart, V. Puri, B.F. Meyers, B. Kozower, C.G. Robinson, Treatment utilization and outcomes in elderly patients with locally advanced esophageal carcinoma: a review of the National Cancer Database, Cancer Med. 6 (2017) 2886–2896.

[45] K. Nosaka, K. Shibata, F. Utsumi, K. Yoshida, K. Niimi, R. Sekiya, S. Suzuki, H. Kajiyama, F. Kikkawa, Feasibility and benefit of concurrent chemoradiotherapy for elderly patients with uterine cervical cancer, Tumori J 102 (2016) 600–605.
[46] J. Müller von der Grün, D. Martin, T. Stöver, S. Ghanaati, C. Rödel, P. Balermpas, Chemoradiotherapy as definitive treatment for elderly patients with head and neck cancer, BioMed Res. Int. 2018 (2018) 1–9.
[47] Y. Lu, J. Hua, F. Yan, C. Jiang, Y. Piao, Z. Ye, Z. Fu, H. Jiang, F. Wang, Y. Jiang, Combined radiotherapy and chemotherapy versus radiotherapy alone in elderly patients with nasopharyngeal carcinoma: a SEER population-based study, Medicine (Baltim.) 100 (2021), e26629.
[48] M. Christodoulou, F. Blackhall, H. Mistry, A. Leylek, J. Knegjens, V. Remouchamps, I. Martel-Lafay, N. Farré, M. Zwitter, D. Lerouge, N. Pourel, H. Janicot, A. Scherpereel, C. Tissing-Tan, K. Peignaux, X. Geets, K. Konopa, C. Faivre-Finn, Compliance and outcome of elderly patients treated in the concurrent once-daily versus twice-daily radiotherapy (CONVERT) trial, J. Thorac. Oncol. 14 (2019) 63–71.
[49] NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®), Older Adult Oncology, 2017.
[50] S. Parisi, I. Napoli, S. Lillo, A. Cacciola, G. Ferini, G. Iatì, A. Pontoriero, C. Tamburella, V. Davì, S. Pergolizzi, Vaginal mucosal melanoma: a complete remission after immunotherapy and "0-7-21" radiotherapy regimen (24 Gy/3 fractions/21 days), Folia Med. (Plovdiv) 62 (2020) 605–609.
[51] A. Daste, C. Chakiba, C. Domblides, M. Gross-goupil, A. Quivy, A. Ravaud, P. Soubeyran, Targeted therapy and elderly people: a review, Eur. J. Cancer 69 (2016) 199–215.
[52] A. Daste, C. Domblides, M. Gross-goupil, C. Chakiba, A. Quivy, V. Cochin, E. de Mones, N. Larmonier, P. Soubeyran, A. Ravaud, Immune checkpoint inhibitors and elderly people: a review, Eur. J. Cancer 82 (2017) 155–166.
[53] G. Ferini, V. Valenti, A. Tripoli, S.I. Illari, L. Molino, S. Parisi, A. Cacciola, S. Lillo, D. Giuffrida, S. Pergolizzi, Lattice or oxygen-guided radiotherapy: what if they converge? Possible future directions in the era of immunotherapy, Cancers 13 (2021).
[54] A. Sindoni, F. Minutoli, G. Ascenti, S. Pergolizzi, Combination of immune checkpoint inhibitors and radiotherapy: review of the literature, Crit. Rev. Oncol. Hematol. 113 (2017) 63–70.
[55] S. Arcangeli, B.A. Jereczek-Fossa, F. Alongi, C. Aristei, C. Becherini, L. Belgioia, M. Buglione, L. Caravatta, R.M. D'Angelillo, A.R. Filippi, M. Fiore, D. Genovesi, C. Greco, L. Livi, S.M. Magrini, G. Marvaso, R. Mazzola, I. Meattini, A. Merlotti, I. Palumbo, S. Pergolizzi, S. Ramella, U. Ricardi, E. Russi, M. Trovò, A. Sindoni, V. Valentini, R. Corvò, Combination of novel systemic agents and radiotherapy for solid tumors – Part II: an AIRO (Italian association of radiotherapy and clinical oncology) overview focused on treatment toxicity, Crit. Rev. Oncol. Hematol. 134 (2019) 104–119.
[56] S. Arcangeli, B.A. Jereczek-Fossa, F. Alongi, C. Aristei, C. Becherini, L. Belgioia, M. Buglione, L. Caravatta, R.M. D'Angelillo, A.R. Filippi, M. Fiore, D. Genovesi, C. Greco, L. Livi, S.M. Magrini, G. Marvaso, R. Mazzola, I. Meattini, A. Merlotti, I. Palumbo, S. Pergolizzi, S. Ramella, U. Ricardi, E. Russi, M. Trovò, A. Sindoni, V. Valentini, R. Corvò, Combination of novel systemic agents and radiotherapy for solid tumors – part I: an AIRO (Italian association of radiotherapy and clinical oncology) overview focused on treatment efficacy, Crit. Rev. Oncol. Hematol. 134 (2019) 87–103.
[57] S. Parisi, I. Napoli, S. Lillo, A. Cacciola, G. Ferini, G. Iatì, A. Pontoriero, C. Tamburella, V. Davì, S. Pergolizzi, Spine eburnation in a metastatic lung cancer patient treated with immunotherapy and radiotherapy. The first case report of bystander effect on bone, J. Oncol. Pharm. Pract. (2021).
[58] G. Lazzari, A. Terlizzi, G. Porrazzo, S. Devicienti, F. Perri, G. Della Vittoria Scarpati, G. Silvano, Effective nivolumab sequential thoracic radiotherapy in elderly patients with advanced squamous cell lung cancer: did radiation therapy play a role? A case report, OncoTargets Ther. 11 (2018) 4621–4629.
[59] L. Belgioia, I. Desideri, A. Errico, C. Franzese, A. Daidone, L. Marino, M. Fiore, P. Borghetti, D. Greto, A. Fiorentino, Safety and efficacy of combined radiotherapy, immunotherapy and targeted agents in elderly patients: a literature review, Crit. Rev. Oncol. Hematol. 133 (2019) 163–170.
[60] V. Soyfer, B.W. Corn, Y. Kollender, J. Issakov, S. Dadia, G. Flusser, J. Bickels, I. Meller, O. Merimsky, Hypofractionated adjuvant radiation therapy of soft-tissue sarcoma achieves excellent results in elderly patients, Br. J. Radiol. 86 (2013), 20130258.
[61] X. Cai, H. Wu, J. Peng, J. Zhu, S. Cai, G. Cai, Z. Zhang, Tolerability and outcomes of radiotherapy or chemoradiotherapy for rectal cancer in elderly patients aged 70 years and older, Radiat. Oncol. 8 (2013).
[62] S. Atagi, J. Mizusawa, S. Ishikura, T. Takahashi, H. Okamoto, H. Tanaka, K. Goto, K. Nakagawa, M. Harada, Y. Takeda, N. Nogami, Y. Fujita, T. Kasai, K. Kishi, T. Sawa, K. Takeda, K. Tomii, M. Satouchi, T. Seto, Y. Ohe, Chemoradiotherapy in elderly patients with non–small-cell lung cancer: long-term follow-up of a randomized trial (JCOG0301), Clin. Lung Cancer 19 (2018) e619–e627.
[63] K. Lai, J. Lin, H. Lu, C. Liang, M. Chen, Is definitive concurrent chemoradiotherapy effective for locally advanced head and neck cancer in the elderly aged $\geq$ 75 years: a single-institute, retrospective, cohort study, Asia, Pac. J. Clin. Oncol. 14 (2018) 247–255.
[64] W. Wang, X. Liu, Q. Meng, F. Zhang, K. Hu, Comparisons of survivals and toxicities between young and elderly patients with cervical cancer treated with definitive radiotherapy or concurrent chemoradiotherapy, Taiwan, J. Obstet. Gynecol. 58 (2019) 364–369.
[65] K. Jingu, H. Numasaki, Y. Toh, K. Nemoto, T. Uno, Y. Doki, H. Matsubara, Chemoradiotherapy and radiotherapy alone in patients with esophageal cancer aged 80 years or older based on the Comprehensive Registry of Esophageal Cancer in Japan, Esophagus 17 (2020) 223–229.