Review Article

The role of radiation therapy and systemic therapies in elderly with breast cancer

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Abstract: The focus of this review deals with the management of elderly patients with early stage breast cancer, discussing the role of systemic therapies [endocrine therapy (ET), chemotherapy, novel agents] and radiation therapy (RT). Several studies have evaluated in elderly low risk patients the possibility of omitting the RT but, at the same time, higher locoregional relapse (LR) rates without significant impact on overall survival (OS) were observed in all studies when RT was excluded. Technological improvements [intensity-modulated RT (IMRT), volumetric modulated arc therapy (VMAT), high dose brachy therapy (HDBT)] are very useful in order to reduce cosmetic outcome and improve quality of life of frail patients. The optimal sequence of ET, concomitant or sequential to RT, is currently under investigation, and specifically in the elderly it is questioned the possible choice of prolonged therapy after standard 5 years. Data regarding chemotherapy suggesting no benefit of OS in endocrine responsive diseases, whereas endocrine non-responsive breast cancer still showed a better outcome. Cyclophosphamide, methotrexate and 5-fluorouracil (CMF) regimen is recognized as the standard protocol, although age-dependent increase in therapy related mortality was reported. Neoadjuvant chemotherapy in elderly showed a lower ratio of pathological complete response in comparison to younger patients, but triple negative breast cancer patients showed a good prognosis regarding OS, comparable to younger patients. The risk of cardiotoxicity seems to increase with age, so the use trastuzumab in this setting is much debated. Currently, other anti-HER2 agents (pertuzumab, lapatinib) are used in neoadjuvant setting, but the data on elderly are still premature. Novel molecules are rapidly changing the clinical management of breast cancer patients but are tested especially in locally advanced and metastatic setting. Among these, particularly interesting are inhibitors of CDK4 and 6, alpelisib (PI3K enzymes mutations), immune checkpoint (PD1, PDL1, CTLA4) inhibitors, atezolizumab. Elderly patients are under-represented in clinical trials, although ageing can be frequently correlated with a decrease in the effectiveness of the immune system. For elderly women, treatment decisions should be individually decided, taking into account the geriatric assessment and limited life expectancy and tumor characteristics.

Keywords: Elderly; breast cancer; radiation therapy (RT); adjuvant therapies; novel drugs

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Introduction

In the clinical management of cancer patients, it is of paramount importance to achieve optimal loco-regional control of disease, but at the same time trying to minimize the complications (1).

This recommendation is even stricter in the treatment of

elderly patients.

Age represent the major risk factor for breast cancer, and a significant ratio of this disease is diagnosed in women >70 years (2). At the same time, many elderly women with early stage breast cancer die of other causes (up to 80% in node negative women and 60% in women with positive axillary nodes) (3).

The correct evaluation of the global health status is of paramount importance in older patients, so to avoid aggressive unnecessary treatment in frail patients and to prevent under treatments in fit elderly that can jeopardize the survival (4).

In this particular subset of patients, the scientific literature presents many pitfalls, due to the discrepancies between real life and clinical trials in terms of age and health status of patients (5).

Aim of this review is to depict the optimal adjuvant therapies in the management of elderly patients with breast cancer, focusing on the role of systemic therapies (hormonal therapy, chemotherapy, novel agents) and radiation therapy (RT), through a review of the available literature and the discussion of the various aspects of the clinical management of this defined subset of cancer patients.

Body

It is mandatory in order to correctly stratify breast cancer patients to analyze the hormone receptor status, as well as the HER2 expression. Further stratification relies on anatomic and pathologic characteristics such as size, grading, N status, angiolymphatic invasion.

Several models have been developed in order to estimate outcomes, and a validated model is available online (www.adjuvantonline.com) (6) to estimate disease-free survival (DFS) and overall survival (OS) at 10 years and to measure the expected gain of adjuvant systemic therapies (endocrine and chemotherapy) (7).

It is noteworthy, though, that the accuracy of the estimates for older patients is not very robust, as the algorithm relies on the 1998 meta-analysis of adjuvant trials, in which older patients were under-represented. Currently other methods of tailored medicine are available, through the analysis of individual tumor gene expression profiles. There are many different assays, analyzing a total of 21 genes (8), 50 genes (9) and 70 genes (10), all of them generally validated in older breast cancer patients.

Finally, in this subset of patients, it is mandatory to perform a multidimensional geriatric assessment, even with the collaboration of a Geriatrist (11), that can be particularly important in frail patients (12). There are different screening test that can be used to identify patients that would benefit from a more intensive geriatric evaluation (13,14).

We will briefly discuss in different paragraph the different choices of therapies in our selected subgroup of breast cancer patients.

RT

While RT has an established role in the adjuvant setting of treatment of breast cancer, the omission of RT in a particular subgroup of elderly is still a matter of debate.

Several studies have evaluated, in patients older than 65 years treated with conservative surgery, low risk (pT1-2N0-1M0) the possibility of omitting the RT (see *Table 1*) (15-24). At the same time, it's noteworthy that higher local recurrence rates were observed in all studies when RT was excluded.

The overall 5-year survival rate results the same (not statistically significant difference) with adjuvant RT. Some authors (16) concluded that there is clinical evidence of avoiding adjuvant radiotherapy for patients over 75 years with T1–T2 cancer treated with quadrantectomy with a clear excision margin.

Herskovic *et al.* (23) in a retrospective explorative analysis of a large database of over 60.000 patients showed a 5-year overall survival rate of 93.0% in the adjuvant RT group and 83.6% (P=0.0001) in the non-adjuvant RT group. Improved survival is associated with adjuvant RT and endocrine therapy (ET) for older women with early-stage hormone receptor e positive HER2-negative breast cancer.

For frail elderly women, treatment decisions should be individually decided considering geriatric assessment and limited life expectancy and tumor characteristics.

In recent decades, several randomized trials evaluated the role of hypo fractionated RT delivered over a period of 3 weeks *vs.* standard fractionated RT (5 weeks) revealing equivalence in local control and survival without increased toxicity (25-27).

Moreover, APBI is a conservative approach with irradiation of a smaller volume (only the lumpectomy bed plus a 1- to 2-cm margin *vs.* whole breast) in less time. Different APBI methods are available, such as brachytherapy (28,29), intraoperative (30) or external beam radiotherapy.

In order to reduce discomfort of a long treatment of radiotherapy, especially in elderly frail women, APBI is of a special interest in this setting.

Each of these techniques is different from one another

Table 1 Studies that have analyzed the role of adjuvant whole breast radiation therapy (WBRT) versus observation (no RT) in elderly patients

References	Patients	Age	Stage	Treatment	Relapse LR (%)	OS
Fyles 2004	386	≥50 y	Low risk (T1-2N0)	WBRT + TMX	0.5	–
	383			TMX alone	7.7	–
Livi 2005	472	60–92 y	Low risk	Surgery + RT	3.4	–
	755			Surgery	10.6	–
Livi 2006	917	≥65 y	All	Surgery + RT	9.7	65.4% at 10 years
	583			Surgery		72.4% at 10 years
Troung 2006	4,836			Surgery + RT	3	72% at 5 years
		50–89 y	T1-2, N0-1, M0	Surgery	9	90% at 5 years
Potter (ABCSG) 2007	414	66	Low risk	WB ± boost	0.6	97.9% at 5 years
	417			No RT	7.7	94.5% at 5 years
Hughes (CALGB) 2004–2013	636	≥70 y	Stage I	WBRT	2	67% at 10 years
				No RT	9	66% at 10 years
Kunkler (Prime II) 2015	658	≥65 y	Low risk	WBRT	1.3	93.9% at 10 years
	668			No RT	4.1	
Nagar 2017	4,460	≥70 y	Early	WBRT	–	71.5% at 100 months
	1,910			No RT	–	51.3% at 100 months
Herskovic 2018	51,635	≥65 y	T1-T2N0M0 HER negative	RT (WBRT, SBRT…)	–	93.0% at 5 years
	9,760			No RT	–	83.6% at 5 years
Goldberg 2019	1,964	≥65 y	Stage I	Surgery + RT	0.9	99% at 5 years
	1,325			Surgery + RT + ET	1.4	98% at 5 years
	719			Surgery + ET	3.1	97% at 5 years
	1,068			Surgery	9.4	89% at 5 years

RT, radiation therapy; TMX, tamoxifen; WB, whole breast; WBRT, whole breast radiation therapy; SBRT, stereotactic body radiation therapy; ET, endocrine therapy; LR, locoregional relapse.

in terms of degree of invasiveness, radiation delivery, experience of radiation oncologist, and time of treatment.

Today APBI is not the gold standard but it was largely used in clinical trial and also in clinical practice especially in low risk elderly women in terms of efficacy, quality of life outcomes, and cost-effectiveness *vs.* whole breast standard RT.

Lately, technological improvements in modern radiotherapy are very useful in order to reduce cosmetic outcome. Intensity-modulated RT (IMRT) or volumetric modulated arc therapy (VMAT) results to give advantages over three-dimensional conformal RT in terms of a better homogeneity of dose distribution within the target volume and a reduction in high doses to organs at risk (31).

Although the advantage of these new techniques IMRT are still not considered a standard of care as they have no impact on local control or patients' quality of life (32,33).

Some studies noted a fair aesthetic outcome after IMRT that results feasible and well tolerated in elderly breast cancer patients (see *Table 2*) (28,29,34-37).

Concluding this paragraph, while the previous cited clinical trials have provided information regarding the omission of adjuvant RT for women with favorable characteristics, they still contain many limitations.

First, CALGB and Fyles trials do not include information regarding HER2 status and oncotype score, as they were not available. Similarly, the PRIME II and ABCSG Study

Table 2 Special radiation therapy techniques adopted in treating elderly patients

References	Patients	Age (years)	Stage	Treatment	Cosmetic outcome
Genebes 2014	70	62–93	All	HIBT: 32–34 Gy/10 fx	Complication G1 80.8%; G2 19.2%. 95.7% good cosmetic outcomes
GERICO-03 trial 2013	40	70–87	pT1-2 N0	HIBT: 34 Gy/10 fx	G1 59%; G2 28%; G3 2%
Jagsi 2010	32	40–80	Stage 0–1	APBI-IMRT 38.5 Gy bid—DIBH	Good 79.5%
Bougier 2012	48	52–79	pT1N0	3D Hypo 40 Gy/1	G2 erythema no statistically
				3D Hypo 42 Gy/10	G2 desquamation more in 42 Gy
Riou 2015	9	44–85	pT1N0	APBI-VMAT: 40 Gy/4 bid	Only G1 acute and late
Fiorentino 2018	40	≥70	Early (pT1-2N0-1)	IMRT: 60 Gy/30	Good 92.5%
	40			HypoVMAT: 48 Gy/15	Acute and late toxicity better; good 97.5%

HIBT, high-dose-rate interstitial multi-catheter brachytherapy; APBI, accelerated partial breast irradiation; IMRT, intensity-modulated RT; DIBH, deep inspiration breath hold; VMAT, volumetric modulated arc therapy.

trials did not specifically include or exclude HER2-positive patients, or patients who received chemotherapy. Most importantly, the previous trials could be not statistically powered enough to detect a potential OS benefit for adjuvant RT in favorable-risk patients (15,19,21,22,38-40).

This last point is supported by the Early Breast Cancer Trialists' Collaborative Group Oxford meta-analysis, which found that 1 breast cancer death could be avoided for every 4 local recurrences prevented over 15 years. The absolute risk reduction in cancer mortality risk was 5.4% at 15 years in that analysis (41).

ET

In patients with endocrine responsive breast cancer, hormonal therapy has provided evidence to increase both disease free survival and overall survival (42,43).

The optimal sequence of hormonal therapies is currently under investigation, and specifically in the elderly it is questioned the possible choice of prolonged therapy after 5 years of hormonal therapy.

Two studies have compared tamoxifen (TAM) versus aromatase inhibitor (AI) as first choice of adjuvant therapy in postmenopausal women (44,45), and they found that AI arm showed fewer recurrences, although no differences in survival were reported.

At the same time, a significant increase of fractures was reported in older patients undergoing letrozole (11.6%) versus tamoxifen (5.4%).

Cardiovascular events of high grade, similarly, were increased in letrozole arm (2.4%) versus tamoxifen arm (1.4%), although the overall low incidence (46). Hypertension and prior cardiac events were recognized as risk factors, and the risk seems to be greater in the range 65–74 years (44,47).

Conversely, the use of tamoxifen could increase the risk of endometrial cancer and thromboembolic complications, and increasing age is an independent risk for these complications (48). For this reason, generally, AI is the preferred option as first choice of hormonal therapy in elderly patients (49).

Several trials have analyzed the various combinations of HT in elderly patients, with comparable results (see *Table 3*) (45,50-53).

At the same time, the Clinician should also take in consideration the comorbidities and should discuss with older patients the optimal choice of adjuvant hormonal therapies, due to the different toxicities of AI and TAM.

The concurrent use of hormonal agents and radiotherapy have been analyzed in the meta-analysis of Li *et al.* (54), that found no difference in any of the clinical endpoint (toxicity, local recurrence, distant metastases and overall survival) for the concurrent approach. Although this study does not present a subgroup analysis for the elderly patients, the median age of concurrent approach was older than sequential approach.

The avoidance of some "invasive" treatment in elderly, with a minimalistic approach, on the other hand, is currently under investigation in many trials.

Table 3 Studies that have analyzed various combinations of adjuvant hormone therapies in elderly patients with breast cancer

References	Patients	Age	Stage	Treatment for 5 years	DFS (%)	OS (%)	Other outcomes
TEAM trial, 2017	3,075	Post-menopausal	Early stage	Exemestane 25 mg	67% at 10 years	–	–
	3,045			Tamoxifen 20 → exemestane 25	67% at 10 years	–	–
TEAM trial, 2018	3,369	<65 years		Exemestane 25 mg		–	BCM at 10 years 11.7%
	1,896	65–74 years	All	*vs.*		–	BCM at 10 years 12.7%
	854	>75 years		Tamoxifen 20 → exemestane 25		–	BCM at 10 years 15.6%
IES trial, 2012	507	Post-menopausal	Early stage	Tamoxifen	27%	17.6	BCM =1.2%
	423			Tamoxifen → exemestane	23.1%	15.3	BCM =1.6%
ATAC trial, 2010	3,125	Post-menopausal	Early stage	Anastrozole	80.3% at 10 years	–	BCM =14.2%
	3,116			Tamoxifen	76% at 10 years	–	BCM =12.6%
	3,125			Anastrozole + TAM	NA	NA	NA
BIG1-98, 2011	911+1,548	Post-menopausal	Early stage	Tamoxifen	81.4% at 5 years	–	–
	917+1,546			Letrozole	84% at 5 years	–	–
	1,548			Tamoxifen → letrozole	86.2%	–	–
	1,540			Letrozole → tamoxifen	87.20%	–	–

DFS, disease-free survival; OS, overall survival; TAM, tamoxifen; BCM, breast cancer mortality; NA, not available.

Specifically, the ET when used as a sole agent to treat breast cancer is defined as primary endocrine therapy (PET) and is greatly used in clinical practice for elderly patients (2), reaching over 60% of patients over 80 years in UK.

The Cochrane review of Hind *et al.* found no overall survival benefit in comparison to surgery for patients older than 75 years, although a worse local control (55). The study by Fennessy *et al.* compared TAM versus surgery and TAM, and found a significant benefit for surgery in the subgroup 70–75 years, a trend towards a benefit for the subgroup 75–80 and no benefit of survival for patients older than 80 years, although the numbers were small (56). Mustacchi *et al.* analyzed in a randomized multicenter controlled GRETA trial the same approach with TAM versus surgery and TAM (57). Similarly, after a follow up of 80 months, they did not found a significant difference in OS for patients older than 70 years.

Another approach is to treat only with hormonal therapy, avoiding adjuvant radiotherapy after surgery. Chesney *et al.* have published recently a meta-analysis of four randomized controlled trials in a subset of elderly breast cancer patients (>70 years). They concluded that radiotherapy can reduce local recurrences (breast and axilla), but it does not impact distant recurrence or overall survival in this particular subgroup (58). Wickberg *et al.* (59), similarly, analyzed a cohort of 603 breast cancer women (age >65 years), and found that breast conservative surgery and ET without RT seem to be a safe treatment option, with only 1.2% recurrence at five years.

Chemotherapy

As the magnitude of the effect of chemotherapy in terms of recurrences and survival generally decrease with elderly patients, the decision whether to use systemic cytotoxic therapy in the management of breast cancer in older patients is very complex (41), especially if comorbidities that can exacerbate the toxicity of chemotherapy are present (60).

At the same time, the bio molecular characteristics associated with a worse outcome are the same markers

of increased benefit from systemic therapy (nodal status, negative hormonal receptors). Conversely, shorter remaining life expectancy, positive estrogen receptor as well as the necessity of decreasing chemotherapy doses due to comorbidities require to seriously consider the effective necessity of a systemic approach (61,62).

Actually, data regarding older women are limited (41), suggesting no benefit of survival in endocrine responsive diseases, whereas endocrine non responsive breast cancer still showed a better outcomes (63,64).

In regards of the chemotherapy regimen, the combination of cyclophosphamide, methotrexate and 5-fluorouracil (CMF) is recognized as the standard protocol, although age-dependent increase in therapy related mortality was reported (65). Capecitabine has shown to be inferior to standard CMF or Adriamycin cyclophosphamide combination (AC) (66), although the enrollment was discontinued early, so that these results need to be interpreted with great caution. Anthracycline, at the same time, carry on an increased risk of heart failure in the treatment of elderly people (67), thus docetaxel and carboplatin combination could represent an alternative regimen (68).

The large meta-analysis of Early Breast Cancer Trialists' Collaborative Group (69) concluded that taxane and/or anthracycline-based regimens reduced breast cancer mortality by, on average, about one-third. Their data, though, are limited in patients older than 70 years. The SEER registries analysis, conversely, has demonstrated a benefit of survival in elderly patients with non-endocrine positive breast cancer, and this gain in OS was higher if the axillary nodes were positive (64).

A recent pooled analysis by von Waldenfels *et al.* analyzed individual patients data from eight randomized controlled trials in order to investigate the outcome after neoadjuvant chemotherapy in elderly patients (>65 years) (70). They concluded that elderly showed a lower ratio of pathological complete response in comparison to younger patients, but triple negative breast cancer patients showed a good prognosis regarding overall survival, comparable to younger patients. This approach, thus, could be useful in a selected elderly population.

The combination with RT, at the same time, is still poorly investigated in elderly. A recent work by Huang *et al.* has analyzed radiotherapy concurrent versus adjuvant standard anthracycline based chemotherapy, concluding that the concurrent strategy was superior to the sequential administration in loco-regional recurrence-free survival for node positive patients, although with an high risk of lymphedema (71). There are, unfortunately, no information regarding the age of patients enrolled in the meta-analysis, so that these results cannot be safely assumed for older breast cancer patients.

Other approaches in order to determine the frailty of elderly patients undergoing chemotherapy are currently under investigation. Bailur *et al.* have recently performed an analysis of the immune profiling in breast cancer patients receiving chemotherapy. This profiling was correlated with unexpected hospitalizations, and could be useful to select the most appropriate tailored strategy (72).

Concluding this paragraph, actually there are insufficient data to extrapolate chemotherapy recommendations in older women, thus the treatment needs to be individualized, taking into consideration the comorbidities and the bio molecular characteristics of the disease.

Targeted agents

Trastuzumab is a humanized monoclonal antibody with a selective specificity for the extracellular domain of HER2, that has shown an improvement in both DFS and OS, although with an increase of heart failures (73).

Unfortunately, in this particular subgroup of patients, the frequency of HER2 positivity tends to decrease with age. At the same time, the first trials evaluating this drug did not include elderly women. The Finnish trial included women <66 years, whereas the median age in the HERA trial was 49 years (73-75). Additionally, the risk of cardio toxicity seems to increase with age (>60 years), so that the decision whether to use trastuzumab in elderly patients is much debated.

The physiopathology of cardio toxicity of this drug is classified as a chemotherapy related cardiac dysfunction of type II (CRCD II) and induce a reduced contractility of myocyte cells, through the blockade of HER2 signaling of cardiomyocytes (76).

It is usually reversible with discontinuation of the treatment, and it differs with cardiac dysfunction of type I, usually induced by anthracyclines, that is related to the total dose and induces irreversible loss of myocyte cells.

Several studies have investigated the use of trastuzumab in elderly (77-79), finding significant association with clinical variables and comorbidities (age, adjuvant chemo, history of cardiac disease, diabetes, renal failure).

Usually, adjuvant trastuzumab was used for one year, although improvement of outcomes was observed with only 9 weeks of treatment (80,81), an approach that must be further

validated but could be interesting for our particular subset.

Currently, other anti-HER2 agents (pertuzumab, lapatinib) are used in neoadjuvant setting, but the data on elderly are still premature. In the "Aphinity" that investigated the use of double HER2 blocking with trastuzumab and pertuzumab, only 13% of the patients (315 patients) were older than 65 years, and the subset analysis did not show difference in DFS (82).

Concluding this paragraph, age should not be the only parameter in the decision-making process for women with HER2 positive breast cancer. At the same time, the prevention of cardiac risk among elderly breast cancer patients receiving trastuzumab is of paramount importance.

Novel agents

Novel molecules are rapidly changing the clinical management of breast cancer patients, although their use is currently limited to locally advanced and metastatic setting.

At the same time, there are many clinical trials enrolling early stage breast cancer patients in order to investigate the efficacy in earlier stage of disease, so in this paragraph we will briefly comment these approaches in elderly, with a particular emphasis on the combination with RT.

At this regard, the role of RT especially for oligometastatic breast cancer patients, has shown to be able to achieve long term progression free survival, without significant treatment related toxicities, as in other pathologies (83). Its investigation with the novel molecules will be necessary in the next future for the optimal management of breast cancer patients, elderly included.

Inhibitors of cycle-dependent kinases (CDK) 4 and 6 seem one of the most promising drug in this setting. Normal cell replication progresses are regulated by a number of proteins including cyclin-dependent-kinases (CDKs). CDK 4/6 inhibitors target the formation of the CDK 4/6-cyclin D1 complex and block the phosphorylation of Rb to effect cell cycle arrest (84).

Their efficacy has been tested in many clinical trials (85-88), and is currently used for post-menopausal, HER2-, advanced breast cancer in combination, either with AI or with Fulvestrant. At the same time, as with previous drugs, specific data regarding efficacy and safety in elderly are limited and mostly extrapolated by subgroup analysis of randomized controlled trials. According to these trials, CDK seem to have similar efficacy with a slight increase of toxicity (89).

The combination with RT is still investigational and is currently tested in clinical trials. There are only small series published (90-92), and a case report of severe radiation induced enter colitis in a patient undergoing palliative RT to bone metastases (93).

In the same setting, after treatment with AI, everolimus with exemestane has been shown to improve PFS as compared to exemestane alone (94), regardless of age.

Everolimus is an oral inhibitor of mammalian target of rapamycin (mTOR) pathway, an important intracellular signal that promotes cell growth and proliferation.

The toxicity of this drug included infections, rash, pneumonitis, stomatitis and hyperglycemia, and elderly patients seem to have similar incidence of these side effects, with more weight loss and anemia, but had more deaths on-treatment (95,96).

The combination with RT has been tested in different diseases, especially in glioblastoma (97-99), but currently there are no sufficient data to estimate risks and benefits of the concurrent approach, especially in breast cancer. Particular caution should be given when RT involves gastrointestinal tracts, due to case reports in literature.

On the other hand, the analysis of phosphatidylinositol 3-Kinase (PI3K) enzymes mutations, that occur in almost 40% of breast cancer patients, has led to the development of Alpelisib that was very recently approved by FDA in combination with fulvestrant, to treat post-menopausal women with hormone receptor positive, HER2 negative advanced or metastatic breast cancer following progression after endocrine-based regimen (SOLAR 1 trial). The cohort of PI3K mutated patients treated with Alpelisib had a PFS of 11 months versus 5.7 months ($P<0.001$). The most frequent adverse events were hyperglycemia, rash, diarrhea (100).

The median age in the SOLAR trial was 63 years (range, 25–87 years), but unfortunately there is not a subgroup analysis for the elderly patients. These drugs, thus, should be used with caution in elderly patients. The combination with RT, also, needs to be further studied, although PIK3CA seems to be a part of biological pathways impacting the radio sensitivity (101).

Immune checkpoint inhibitors, finally, represent an immunotherapy approach that include molecules targeting programmed cell death type I (PD1) or death ligand type I (PDL1) and cytotoxic T lymphocyte antigen 4 pathways (CTLA4). This strategy has demonstrated a dramatic efficacy for several cancer diseases and many drugs are currently used in oncological clinical practice. Elderly patients, again, are under-represented in clinical trials, although ageing can be frequently correlated with a decrease in the effectiveness of the immune system (102).

These agents are usually better tolerated than cytotoxic chemotherapies and the side effects are mainly immune-related adverse events that can develop in different organs.

Few clinical trials have analyzed the toxicity in elderly people, and the results must be treated with caution due to the small sample size of older patient's subgroups. Diarrhea/colitis and rash seem to be more frequent in elderly, and particular vigilance is required for the risk of dehydration and renal failure (103,104).

Actually, atezolizumab was recently approved by the FDA due to the prolonged PFS in patient with metastatic triple-negative breast cancer, in combination with nab-paclitaxel (105). The use in neoadjuvant setting of Pembrolizumab is currently under investigation in clinical trials (Keynote-756 trial).

The combination of immunotherapy with RT is very interesting, as also RT is able to induce immunological effects (106): mole first described tumor shrinking, distant from other irradiated cancer sites, a phenomenon called "abscopal effect" (107), and Demaria *et al.* demonstrated that this effect was immune-mediated, through a specific immune response (108). The irradiated tumor cells release a pool of antigens, in addition the RT also induces an increase in MHC-I expression on tumor cells and up-regulation of death receptors (e.g., FAS, NKG2DL) (109). RT can also induce immunogenic cell death (ICD) (109), characterized by the release of "Damage-Associated Molecular Patterns" (DAMPs) acting as an endogenous adjuvant. DAMPs, which include HMGB1 and Calreticulin, act as activation and maturation signal on DCs, increasing the processing and antigenic presentation to cytotoxic T lymphocytes (109). Finally, RT induces an increase in the expression of adhesion molecules on tumor cells and endothelial cells such as VCAM-I and ICAM-I (109), thus inducing an increase of the infiltration of the immune cells into the tumor site. All these mechanisms are believed to underlie the abscopal effect, although this effect is rarely seen, with fewer than 50 documented cases in the literature (110). Preclinical studies, also, showed that RT is able to induce an increase of expression of PD-L1 on tumor cells (111), blocking the induced immune response. This is the preclinical rationale of the combined use of radiotherapy and immunotherapy.

Clinical studies show encouraging results of the use of combined RT and immunotherapy (112-115): RT seems to prolong the survival of advanced NSCLC patients undergone immune modulating treatment (113) or to checkpoint inhibitors (116). The most impressive results were shown in the PACIFIC trial, a phase III study for stage III unresectable NSCLC, whose experimental arm patients received CHT/RT followed by Durvalumab (117).

At the same time, in breast cancer patients, there are no data regarding a concurrent approach.

Conclusions

Age per se should be evaluated together with many other parameters in the decision-making process for elderly patients with breast cancer. Specifically, the overall individual performance status, more than the age, should be considered when treatment options are being evaluated.

Acute and chronic comorbidities, nutritional status, fitness, and disease-specific symptomatology all need to be taken into consideration. All the Clinicians involved in the management of elderly cancer patients should be familiar with geriatric screening test that can be used to identify patients that would benefit from a more intensive geriatric.

On the other hand, the goals of treatment in elderly patients should be always the same as those in younger patients, with an emphasis on the global care of the patients more than the cure of the disease. Finally, studies including elderly people as well as patients with comorbidities need to be considered in future, as the treatment of these subgroups represent the major medical challenge of the next future.

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