Updated recommendations regarding the management of older patients with breast cancer: a joint paper from the European Society of Breast Cancer Specialists (EUSOMA) and the International Society of Geriatric Oncology (SIOG)

Dr. Laura Biganzoli, MD
"Sandro Pitigliani" Department of Medical Oncology, Hospital of Prato, Prato, Italy

Dr. Nicolò Matteo Luca Battisti, MD
Breast Unit - Department of Medicine, The Royal Marsden NHS Foundation Trust, Downs Road, Sutton, London, United Kingdom
Breast Cancer Research Division, The Institute of Cancer Research, 15 Cotswold Road, Sutton, London, United Kingdom

Prof. Hans Wildiers, PhD
Department of General Medical Oncology, University Hospitals Leuven, Leuven, Belgium

Dr. Amelia McCartney, MBBS
"Sandro Pitigliani" Department of Medical Oncology, Hospital of Prato, Prato, Italy

Dr. Giuseppe Colloca, PhD
Unità Operativa Complessa di Radioterapia Oncologica, Dipartimento di Diagnostica per Immagini, Radioterapia Oncologica ed Ematologia, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy

Prof. Ian H. Kunkler, FRCR
Institute of Genetics and Molecular Medicine, Western General Hospital Campus, Crewe Road, Edinburgh, United Kingdom

Prof. Maria-João Cardoso, PhD
Breast Unit, Champalimaud Clinical Center, Champalimaud Foundation and Nova Medical School, Lisbon, Portugal

Prof. Kwok-Leung Cheung, MD
School of Medicine, University of Nottingham, United Kingdom

Dr. Nienke Aafke de Glas, PhD
Leiden University Medical Center, Department of Medical Oncology, P.O. Box 9600, 2300 RC Leiden, The Netherlands

Dr. Rubina M. Trimboli, MD
Unit of Radiology, Humanitas Clinical and Research Center, Rozzano, Italy

Prof. Beatriz Korc-Grodzicki, PhD
Memorial Sloan Kettering Cancer Center, New York, United States of America

Dr. Enrique Soto-Perez-de-Celis, MD
Department of Geriatrics, Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Mexico City, Mexico

Dr. Antonio Ponti, MD
CPO Piemonte, AOU Città della salute e della scienza, Turin, Italy

Dr. Janice Tsang, MD
Hong Kong Breast Oncology Group, Li Ka Shing Faculty of Medicine, University of Hong Kong, Hong Kong

Dr. Lorenza Marotti, PhD
European Society of Breast Cancer Specialists (EUSOMA), Florence, Italy

Ms Karen Benn, BA
EUROPA DONNA - The European Breast Cancer Coalition, Milan, Italy

Dr. Matti S. Aapro, MD
Genolier Cancer Center, Clinique de Genolier, Switzerland

Dr. Etienne G.C. Brain, MD
Department of Medical Oncology, Institut Curie, Saint-Cloud and Paris, France

Corresponding author:

Dr. Laura Biganzoli, MD
“Sandro Pitigliani” Department of Medical Oncology
Hospital of Prato
Via Suor Niccolina Infermiera, 20, 59100 Prato PO, Italy
email: laura.biganzoli@uslcentro.toscana.it

Summary

Breast cancer is increasingly prevalent in older adults in the context of ongoing demographic changes and is a significant part of routine oncology practice. Nonetheless, due to its highly heterogeneous nature, management of breast cancer in this population is challenging, with the validity of the available evidence very limited for older adults. Decision-making should not be driven by age alone but involve geriatric assessments plus careful consideration of life expectancy, competing risks of mortality, and patient preferences.

A multidisciplinary task force including members of the International Society of Geriatric Oncology (SIOG) and the European Society of Breast Cancer Specialists (EUSOMA) gathered to expand and update the previous 2012 evidence-based recommendations for the management of breast cancer in older individuals with the endorsement of the European Cancer Organisation. These were expanded to include chemotherapy toxicity prediction calculators, cultural and social considerations, surveillance imaging, genetic screening, genomic tools, neoadjuvant systemic treatment options, bone-modifying agents, targeted therapies and supportive care. Recommendations on geriatric assessment, ductal carcinoma in situ, screening, primary endocrine therapy, surgery, radiotherapy, adjuvant systemic therapy and secondary breast cancer were updated.

Introduction

Aging is the leading risk factor for cancer.(2) The prevalence of breast cancer (BC) in older adults is increasing and the higher cancer mortality in older adults compared with younger women establishes a major health disparity which may be explained by more advanced presentation, delayed diagnosis, organ function decline and multimorbidities.(3) Nonetheless, functional age (and not chronological age) and the potential underlying frailty should drive decision-making. Older patients are underrepresented in clinical trials which do not always enrol individuals more frequently seen in routine practice. Therefore, the risks and benefits of anticancer therapy should be carefully weighed.(4)

A multidisciplinary task force including specialists in medical oncology, radiation oncology, surgery, geriatrics, radiology and epidemiology and patient advocates affiliated with the International Society of Geriatric Oncology (SIOG) was created in 2007 to prepare recommendations for the management of BC in older individuals.(5) These were subsequently updated in 2012 in collaboration with the European Society of Breast Cancer Specialists (EUSOMA).(6) Here we present an update of the task force recommendations based on the new evidence which has become available since 2012 (Table 1). These recommendations are a consensus by an expert task force on available evidence and expert opinion.

Search strategy, selection criteria and grading of the evidence

Each task force expert performed a scoping literature review on Pubmed/Medline on individual topics pertaining to breast oncology (MeSH: "older" or "elderly" and "breast cancer" and "surgery", "radiotherapy" or "systemic therapy") and any updates available since the previous recommendations were published in April 2012. The list of topics included epidemiology, geriatric assessment, cultural and social considerations, genetic screening, ductal carcinoma in situ, screening, surveillance imaging, primary endocrine therapy, surgery, radiotherapy, adjuvant and neoadjuvant systemic therapy, genomic tools, treatment of secondary breast cancer, chemotherapy toxicity prediction, bone-modifying agents, targeted therapies and supportive care. The experts presented the results of each individual scoping review to the task force during various meetings held between February 2019 and August 2020. During these meetings, the need to update the previous recommendations was discussed and consensus reached by unanimity; the level of evidence was graded according to the four-classes classification proposed by the US Agency for Healthcare Research and Quality (AHRQ) and recently adopted by EUSOMA.(1)

General and worldwide concepts on ageing

Frailty involves decreased physiological and functional reserve leading to vulnerability to stressors and adverse outcomes. Strayifying patients as fit, vulnerable and frail may identify those at risk of complications.(7) Collaboration between cancer specialists and geriatricians and geriatric assessment (GA) are recommended. Frail individuals require tailored approaches based on a GA and focusing on supportive care. Fit individuals may tolerate standard treatment similarly to younger patients. Vulnerable individuals may require treatment adjustments and geriatric interventions. Competing mortality risks may justify less aggressive approaches. The National Comprehensive Cancer Network (NCCN) and American Society of Clinical Oncology (ASCO) guidelines recommend evaluating life expectancy and calculators such as *ePrognosis* may aid in assessing whether cancer is likely to shorten it.(8, 9) Since competing mortality risks are more prevalent in older adults even without multimorbidities, treatment decisions should consider not only the risk of BC recurrence, but also the risk of dying of other causes, which is strongly influenced by frailty.

GA is a multidimensional evaluation aiming to determine physiologic age and guide diagnostic and therapeutic interventions targeting reversible deficits and devisising treatment strategies to eliminate or mitigate them.(10) Increasing evidence supports the role of GA in the care of older patients with BC. The implementation of GA may improve tolerance, health-related quality of life (QoL) and satisfaction.(11-15) ASCO recommends GA for patients aged 65 years and older considered for chemotherapy.(8) GA can be time-consuming and may not be necessary for all older patients. Several screening tools (some self-reported) can identify patients requiring GA, and should be considered as the gateway to any cancer treatment decision-making in patients aged 70 and older.(16, 17)

The Cancer and Aging Research Group (CARG) and the Chemotherapy Risk Assessment Scale for High-age patients (CRASH) scores estimate the risk of grade 3-5 chemotherapy toxicity in older patients (Table 2) and were validated in cohorts including 20% of BC patients.(18, 19) A BC-specific risk score (CARG-Breast) has been developed and validated but is not yet available.(20) Chemotherapy toxicity calculators should be used as an adjunct in the decision-making process.(21) Multimorbidity and toxicity may influence treatment efficacy (especially endocrine therapy) as nonadherence increases with age.(22)

Cultural and social aspects, including religious myths and taboos, and patient values must be considered during diagnosis and treatment, especially in the context of the current migration flows. Older adults from immigrant populations may have more disabilities, worse self-rated health and poorer outcomes. Literacy and education are also heterogeneous and some assessment tools may not be universally applicable.

Mammography screening and surveillance

Screening

Most screening programs extend until 69-70 years and a minority until 74-75 years. The European Commission Initiative on Breast Cancer and the US Preventive Services Task Force recommend screening mammography for women aged 70–74 years despite the risk of over-diagnosis.(23, 24) A meta-analysis found a relative risk reduction for BC mortality of 0.80 for women aged 70–74 years,(25) although there is controversy also in younger patients. Screening every 2-3 years is deemed to provide the best balance between benefits and harms. The American Cancer Society recommends mammography in older women,(26) particularly in the

context of a life expectancy ≥10 years. However, screening is unlikely to be beneficial after age 75(24) and decisions should consider overall health and life expectancy.

Surveillance

No evidence supports the benefit of mammographic surveillance on disease-specific mortality for older BC survivors in the context of multimorbidities and competing mortality risks. The risk for ipsilateral recurrence and contralateral BCs over the age of 75 years is not defined and is influenced by tumour biology and adjuvant therapy.(27) International guidelines recommend indefinite annual mammography regardless of age.(9, 28) Annual or biennial mammography is recommended for women aged 70–80 years although multimorbidities, life expectancy and frailty should be considered.(27) It should be avoided in patients over 80 years with multimorbidities or life expectancy ≤5 years.(29)

Genetic screening and its implications

The prevalence of pathogenic variants associated with a germline BC predisposition is almost 3 times less over age 65 (5.6% vs 14.2%).(30) BRCA2 and CHEK2 have been found to be relatively prevalent in women aged over 65 with BC.(30) Nonetheless, they are less likely to undergo genetic testing, as guidelines often focus on younger populations. For older patients, genetic testing based on simple, cancer-based criteria may potentially deliver consistent, cost-effective and patient-centred outcomes. Selection of candidates appropriate for screening should be considered in line with current local and/or national guidelines.

In the curative setting, germline pathologic variant carriers may benefit from high-risk surveillance or risk-reducing interventions in the context of an adequate life expectancy.(9) Also, carriers should be offered cascade testing and evaluation of their relatives. For advanced disease, poly ADP-ribose polymerase (PARP) inhibition is a potential alternative to chemotherapy for older BRCA carriers, especially regarding QoL.(31)

Neoadjuvant systemic therapy

Fit older patients should be considered for neoadjuvant strategies similarly to their younger counterparts based on the clinical subtypes of the primary tumour.(32) Due to the higher risk of adverse outcomes,(33-35) vulnerable patients may be better served by upfront surgery,

particularly if BC is already operable. The likelihood of breast conservation should also be considered based on disease characteristics, expected response and patient preference. In fit older persons with high-grade triple negative BC (TNBC), optimal chemotherapy is still debated. Similarly to the adjuvant setting, sequential regimens with anthracyclines and taxanes may be considered although evidence is very limited and shorter regimens remain reasonable. Adding platinum compounds remains debated and may be challenging for most older adults.

Pathological response after neoadjuvant chemotherapy may guide adjuvant treatment decisions for TNBC and human epidermal growth factor receptor 2 (HER2)-positive BC.(36, 37) The CREATE-X and KATHERINE trials enrolled few older individuals but did not show any new safety concerns. Therefore, fit older patients should be considered for such approaches in case of residual disease.

Neoadjuvant endocrine therapy (ET) is associated with lower toxicity, reasonable response rates, and similar breast-conservation rates as neoadjuvant chemotherapy, but survival data are not available. This approach may be useful in older patients not deemed suitable for upfront surgery pending preoperative assessments. Aromatase inhibitors (AI) are recommended over tamoxifen due to improved clinical and radiological response and breast conservation rates.(38) A course of 4-6 months should be considered.

Surgery

While surgery remains the standard treatment in most older patients with early disease, there is a risk of over-treatment with competing mortality risks warranting the use of GA and survival estimates before proceeding with it.(39) However, BC surgery is generally safe, whereas endocrine therapy may cause side effects potentially impacting QoL.(22)

Surgery or not

Two systematic reviews demonstrate a local control and survival benefit with surgery over primary endocrine therapy (PET) in patients with a life expectancy ≥5 years.(40, 41) However, in a large cohort study, no BC-specific survival differences were seen between surgery and PET in strong hormone receptor (HR)-positive disease.(42) When PET involves aromatase inhibitors (AIs), the median time to progression is approximately five years.(42) The benefit of PET versus upfront surgery is expected to be more pronounced with a life expectancy of less than 5 years.

Ductal carcinoma in-situ (DCIS)

Opportunistic screening exposes older patients to potential over-diagnosis and over-treatment of DCIS. Ongoing non-intervention trials will define the role of 'watch and wait' approaches. Meanwhile, fit patients with high-grade DCIS and no multimorbidities should undergo surgery. In low- and intermediate-grade DCIS, surgery and/or postoperative radiotherapy may be spared based on life expectancy and competing risks.(43)

Surgery to the axilla

Less invasive approaches to the axilla in case of cN0 disease are particularly relevant for older adults. Axillary clearance does not produce any survival benefit, and in older patients regional recurrences without axillary surgery remains rare.(44) Therefore, in older adults, sentinel node biopsy (SNB) should be 'standard' for clinically/radiologically node-negative axillae. In most cases further axillary surgery can be avoided if only 1-2 sentinel nodes are involved(45) or replaced by radiotherapy.(46) As even SNB is associated with side effects and likely does not improve prognosis by itself, omission of axillary staging by SNB may be appropriate for frail individuals with low-volume, luminal A-like tumours.

Oncoplastic and reconstructive surgery

Oncoplastic and reconstructive surgery are offered less frequently to older patients.(47) Some older patients may decline such approaches more frequently compared with their younger counterparts, but their personal preferences should be balanced with risks. Oncoplastic and reconstructive procedures may be reasonable alternatives to simple mastectomy or breast conservation.(47) The pros and cons of complex versus simpler procedures should be carefully assessed and discussed with patients.

Radiotherapy

Radiotherapy after breast conserving surgery

Postoperative whole breast radiotherapy (WBRT) halves the risk of first recurrence and remains standard-of-care for most older patients following breast conserving surgery (BCS).(48) However, the absolute benefit in older patients with low-grade, HR-positive disease is modest. Omission of radiation therapy (RT) remains controversial. The CALGB 9343 trial

showed a loco-regional recurrence rate without RT of 10%, versus 2% with RT after 12 years of follow-up in women aged over 70, with no detrimental impact on OS, and these relapses could be corrected successfully by second and deferred surgery.(49) The PRIME II trial showed a lower risk of ipsilateral breast tumour recurrence (IBTR) at 5 years for those receiving WBRT.(50) Both studies suggest omitting radiotherapy in low-risk patients may be reasonable and the results of the PRIMETIME study are awaited. Recommendations regarding radiotherapy omission in low-risk patients from the 2017 NCCN and National Institute for Care and Clinical Excellence guidelines are presented in Table 3.

Tumour bed boost

In the EORTC boost/no boost trial,(51) the relative risk reduction was not statistically significant for patients aged over 60 years. Therefore, a boost is advised in this age group only in case of a higher risk of recurrence.

Partial breast irradiation

No trials of partial breast irradiation (PBI) focused specifically on older patients. The GEC-ESTRO trial of multicatheter brachytherapy versus WBRT suggested that PBI is not inferior to WBRT.(52) The UK IMPORT-LOW trial showed that partial breast and reduced dose EBRT is non-inferior to standard WBRT, with equivalent or fewer side effects.(53) The UK consensus recommends PBI to women aged ≥50 years or with grade 1-2, pN0, HR-positive, HER2-negative, tumours ≤30mm and with radial margins ≥1mm.(54)

Regional nodal irradiation

Three randomised controlled trials show the benefit of regional nodal irradiation (RNI) in high-risk early BC,(46, 55, 56) however none specifically focused on older patients. RNI is indicated in patients with 4 or more positive nodes, but it is unclear which group of patients with 1-3 positive nodes benefit from it.(57)

Postmastectomy radiotherapy

Evidence supporting the role of postmastectomy radiotherapy (PMRT) in older women is lacking and recommendations are extrapolated from analyses conducted in younger patients. PMRT is standard of care in patients with ≥4 positive nodes, whilst the role of PMRT in patients with 1-3 positive nodes remains controversial. An EBCTCG meta-analysis showed PMRT reduced 20-year BC-mortality by 7.9% for patients with 1-3 positive lymph nodes and

by 9.3% for patients with ≥4 positive lymph nodes.(48) Therefore, some argue that PMRT should be standard for all node-positive patients, while others question its role in the context of current treatment approaches. Specific guidelines are available.(9, 58, 59) The BIG 2-04 MRC SUPREMO trial evaluating PMRT in patients with 1-3 positive nodes or pN0 with LVI/grade 3 with no upper age limit remains in follow-up phase.(60) While NICE and NCCN guidelines suggest that decision-making should be driven by nodal disease burden, (58, 61) the ASCO-ASTRO-SSO recommendations highlight the relevance of age, life expectancy, multimorbidities, tumour burden and biology.(59)

Dose fractionation schedules after breast conserving surgery or mastectomy

Hypofractionated schedules are recommended for older as in younger patients as per the FAST FORWARD study results.(62)

Adjuvant systemic therapy

Adjuvant chemotherapy in older adults with HER2-negative disease

BC subtype and stage are key in informing adjuvant chemotherapy decisions. Prospective trials(63) and large retrospective cohorts(64, 65) confirm the potential large benefit of adjuvant chemotherapy on BC-specific survival or overall survival mostly in ER-negative disease, irrespective of nodal status. A recent retrospective study showed OS benefit in patients aged ≥70 years with node-positive, ER-positive, HER2-negative BC, also with comorbidities,(66) despite selection bias remains a significant limitation. For luminal disease, genomic tools may identify those who might benefit from chemotherapy. However, most gene expression assay validation studies excluded older patients and do not address competing risks. OncotypeDx® remains the most frequently studied tool in this age group. Its prognostic accuracy is not influenced by age, but disappointingly a high RS does not predict adjuvant chemotherapy benefit in older patients.(67) Therefore, integrating general health status with gene prognostic models is essential. Nonetheless, although results should be interpreted cautiously, this should not disqualify older patients from such tests. The ASTER 70s study will clarify the role of tumour genomic data in older BC patients.

Online prediction tools are affordable but have substantial limitations in older patients.(68) NHS PREDICT is accurate in older patients only when predicting outcomes at 5 years (but not

at 10 years) and is not reliable in the presence of multimorbidities and over 80 years.(69) Additionally, it estimates survival but not the risk of recurrence. The Age Gap Decision Tool is promising in comparing local treatment with or without chemotherapy but requires prospective validation (https://agegap.shef.ac.uk/).

Chemotherapy regimen choice

Although no evidence supports differential use of adjuvant chemotherapy, older adults may experience more frequent adverse events including death.(70) Benefits of adjuvant combination chemotherapy are maintained at least up until age 70, although biased by chemotherapy duration(71) and limited to HR-negative and/or node-positive disease.(65)

Modified regimens should not be utilised in older patients (Table 4). The CALGB 49907 trial showed significantly worse survival with capecitabine versus standard regimens (four cycles of doxorubicin/cyclophosphamide [AC] or six cycles of cyclophosphamide/methotrexate/fluorouracil [CMF]) in older women, with a high interaction of ER status and competing risks diluting overall survival benefits with longer follow-up.(63) The ELDA trial demonstrated worse QoL with docetaxel versus CMF and no survival benefit.(72)

Older adults were excluded or highly selected in trials of sequential anthracycline and taxane-based regimens, which should be considered only in fit patients with large, node-positive, triple-negative tumours. Dose-dense regimens should not be utilised based on the increased toxicity risk and the lack of efficacy data in older persons. In many older patients, four cycles of docetaxel/cyclophosphamide (TC) may be appropriate, which is superior to AC and more tolerable.(73) Weekly paclitaxel may be considered for high-risk patients unfit for polychemotherapy. Table 4 illustrates common chemotherapy regimens that may be considered.

Safety of adjuvant chemotherapy in older adults

Older patients have higher risk of chemotherapy toxicity and mortality.(74) Risks include haematological toxicity, anthracycline-associated cardiotoxicity (occurring in up to 38%), taxane-related neurotoxicity, falls, decreased QoL, and hospitalisations. However, functional

decline and impaired QoL may be temporary.(75) Long-term consequences include musculoskeletal events, acute myeloid leukaemia/myelodysplastic syndrome, cognitive decline, and impaired function. Chemotherapy duration (double for sequential versus single-agent regimens) should be limited, with a 3-month threshold for increased serious side effects.(20)

Anti-HER2 treatment in adjuvant setting

Although adjuvant trastuzumab is beneficial regardless of age,(76, 77) anti-HER2 (neo)adjuvant strategies remain poorly investigated in patients ≥65 years. Pertuzumab may be considered for high-risk individuals,(37) but diarrhoea may be debilitating in older adults, as with adjuvant neratinib (Table 4).

SIOG recommends adjuvant chemotherapy along with one year of trastuzumab as a standard approach in older patients with normal cardiac function and early-stage HER2-positive BC larger than 0.5 cm, and consideration of pertuzumab only in selected high-risk and fit patients (Table 4).(78) The preferred chemotherapy backbone includes four cycles of TC or weekly paclitaxel. Although evidence is scarce, omission of chemotherapy and utilisation of single-agent trastuzumab (plus endocrine therapy if indicated),(79) may be appropriate in vulnerable and frail patients.(78) A shorter course of adjuvant anti-HER2 therapy may also be considered for older patients with small, node-negative disease or cardiac problems.

Safety of anti-HER2 therapy in older persons

Age correlates with higher cardiac toxicity rates on trastuzumab,(80) with 15-40% of patients requiring early discontinuation especially ≥80 years of age and with multimorbidities,(81) likely predominantly due to chemotherapy-related adverse events. However, up to one third of cardiac events occur within two years of treatment completion, which may be more specifically related to trastuzumab.

Role of adjuvant endocrine treatment

All postmenopausal women suitable for ET should be offered endocrine therapy regardless of age. However, ET may be omitted in the absence of any documented impact on mortality in patients with very low-risk disease and/or short life expectancy.(82)

Choice of agent

Selection of agents should take into account multimorbidities and recurrence risk. AIs result in slightly better reduction in recurrence and BC-specific mortality compared to tamoxifen, and are preferable upfront especially in high-risk patients.(83) Following a few years of AIs, switching to tamoxifen is similarly effective to their continuation. Musculoskeletal side effects may impair adherence to AIs Long-term problems may include osteoporosis, cardiovascular risk, diabetes, hypercholesterolemia and cognitive impairment. Conversely, AIs are associated with a lower risk of venous thrombosis, endometrial cancer and fatty liver disease compared to tamoxifen. Good compliance should drive treatment decisions.

Duration of therapy

Letrozole improves survival outcomes versus placebo among patients who receive an initial five-year course of tamoxifen. After five intial years of AIs, data are less clear: a recurrence-free survival (RFS) benefit is not confirmed in all studies although bone-related adverse events are more frequent. The more modest impact on RFS and the impact on bone health is confirmed by large meta-analyses. Therefore, the current standard of care should include five years of ET, and extended therapy may be offered to fit, healthy older women with high-risk disease who tolerated the first five years.(84) In frail patients, recommendations should be guided by the individual circumstances.

Role of adjuvant bone modifying agents

Adjuvant systemic therapies for BC are associated with an increased risk of bone loss. Therefore, a baseline assessment of bone mineral density (BMD) in older patients suitable for adjuvant endocrine therapy is mandatory, followed by calcium and vitamin D supplementation and use of bisphosphonates to preserve bone mass while on AIs. Also, adjuvant bisphosphonates also improve survival outcomes in patients with early-stage disease.(85) An

EBCTCG meta-analysis documented a 2-3% benefit in BC-mortality limited to postmenopausal women receiving bisphosphonates.(86)

Zoledronate or clodronate should be offered regardless of age to postmenopausal women with moderate- to high-risk BC according to international consensus. Evidence is insufficient for alendronate and risedronate. Bisphosponate use should take into account the minor improvement in long-term survival and their potential side effects, including electrolyte disturbances (mostly hypocalcemia), atypical fractures and osteonecrosis of the jaw,(87, 88) multimorbidities, renal function, fitness and patient preferences. The role of denosumab is controversial and should not be considered in the adjuvant setting for older patients to reduce mortality. The ABCSG-18 study showed improved DFS and bone fracture rate in patients on adjuvant denosumab(89) but the subsequent D-CARE study failed to detect any benefit in bone metastasis-free survival or DFS.(90) Additionally, a rebound effect with more vertebral fractures occurring upon its discontinuation has been demonstrated.

Systemic treatment for metastatic disease

Different treatment schedules, dose reductions or stepwise dose-escalation before reaching standard recommended dose might be required in older patients(91) and reduce the risk of adverse outcomes.

Chemotherapy

Chemotherapy should be considered in suitable older patients with HR-negative disease, HR-positive disease resistant to ET or with rapidly progressive disease and/or extensive visceral involvement and based on GA and patient preferences. The increased toxicity risk in this age group mandates particular attention to minimising side effects.(8) Single-agent regimens are preferred over polychemotherapy(6) and chemotherapy toxicity prediction tools may also be useful. Preference should be given to agents studied in older populations. Nab-paclitaxel is associated with very few allergic reactions, does not require steroids and is safe and effective in patients over 65.(92) Following anthracyclines or taxanes, eribulin is also appropriate, with similar efficacy and toxicity regardless of age and no impact on GA parameters nor QoL.(93)

HER2-positive metastatic breast cancer

Older patients with HER2-positive metastatic BC and adequate cardiac function should receive HER2-directed therapy based on fitness.(78) Although docetaxel or paclitaxel in combination with trastuzumab and pertuzumab are recommended in fit patients, taxanes may cause severe toxicities. In older patients not suitable for taxanes, capecitabine or vinorelbine may be considered. The EORTC 75111-10114 study(94) enrolling older patients evaluated trastuzumab and pertuzumab with or without metronomic oral cyclophosphamide. Vinorelbine along with dual anti-HER2 blockade may also be considered.

ET with trastuzumab plus pertuzumab or lapatinib is a reasonable alternative for patients with ER-positive disease, despite diarrhoea may be an issue requiring close monitoring. T-DM1 is recommended in later therapy lines in fit older patients, but further research in frail patients is warranted.

Targeted agents in luminal tumours

Efficacy of cyclin-dependent kinases 4/6 (CDK4/6) inhibition is age-independent in the subgroup and pooled analyses of the landmark studies of palbociclib, ribociclib and abemaciclib,(95-98) with no age-related changes in pharmacokinetics. Nevertheless, patients ≥75 years experience higher rates of toxicity and dose modifications.(98) While ET alone is still reasonable in selected cases, CDK4/6 inhibitors are a suitable treatment in older patients.(99)

Everolimus should be used with caution in older patients in view of its safety profile. A subgroup analysis of the BOLERO-2 study revealed a higher rate of discontinuations in patients ≥70 years and more on-treatment deaths.(100) 26% of patients enrolled in the expanded-access BALLET trial were aged ≥70, which similarly reported more frequent AE-related dose discontinuations, reductions and interruptions.

Supportive care

Supportive care is important as cancer and its treatment can seriously harm and lead to various degrees of decompensation of older patients. For detailed guidance, the reader can also consult

the ESMO, MASCC and SIOG websites (https://www.esmo.org/; https://www.mascc.org/; https://www.siog.org/).

Digestive symptoms

Nausea and vomiting can be treatment-related or have alternative aetiologies. In older individuals, diagnosis may be challenging as clinical signs may be absent or atypical. Guidelines for prevention of chemotherapy and radiation therapy-induced nausea and vomiting should be followed. General management guidelines for diarrhoea, constipation and stomatitis are available.

Malnutrition

More than 30% of older patients experience severe malnutrition in the hospital and nursing home settings. Malnutrition can lead to osteopenia/osteoporosis, sarcopenia, immunological deficiencies and iron, vitamin B12 or folate-related anaemia, and predicts outcomes at three years. This may be improved by timely intervention.

Depression

Depression in older cancer patients is often under-recognised and untreated but can be successfully managed with psychological support, and antidepressants when indicated. Drug interactions should be considered, such as those between selective serotonin-reuptake inhibitors and tamoxifen.

Pain control

Pain can be related to or complicated by multimorbidities such as arthritis or osteoporotic fractures. Older patients are generally more susceptible to changes in drug doses, side effects, and drug interactions. Particular attention should be paid to potential side effects of nonsteroidal anti-inflammatory drugs (renal function, gastric ulcers). Guidelines are available, with the above caveats.

Febrile neutropenia prevention and treatment

Guidelines on the primary prophylactic use of white blood cell growth factors acknowledge the increased risk of myelosuppression in individuals aged >65. In the general population, the febrile neutropenia risk threshold of ≥20% is for consideration of primary prophylaxis, but for older persons, a lower threshold may be used, e.g. >10%, which is reached in older persons when using standard myelosuppressive regimens as anthracyclines or TC.

Conclusions

The management of BC in older adults should involve routine use of GA tools and close interaction with members of the multidisciplinary team due to the intrinsic heterogeneity of this population. In the context of the limited applicability of the evidence generated in younger and/or more fit individuals, patient preferences, life expectancy, predicted survival benefits and impact on toxicity and QoL should be carefully considered in decision-making.

Conflict of interest statement

Dr. Biganzoli reports personal fees from AstraZeneca, grants, personal fees and non-financial support from Celgene, personal fees from Daiichi-Sankyo, personal fees from Eisai, grants and personal fees from Genomic Health, personal fees and non-financial support from Ipsen, personal fees from Lilly, grants and personal fees from Novartis, personal fees and non-financial support from Pfizer, personal fees from Pierre Fabre, personal fees and non-financial support from Roche, outside the submitted work. Dr. Battisti reports grants and personal fees from Pfizer, grants from Genomic Health, outside the submitted work. Dr. Wildiers reports that his institution received consulting fees and honoraria from AstraZeneca, Biocartis, Lilly, Novartis, Pfizer, PUMA Biotechnology, Roche, Sirtex, Daiiji. His institution received unrestricted research grants from Roche and Novartis. He received travel support from Roche and Pfizer. Dr. McCartney has nothing to disclose. Dr. Colloca has nothing to disclose. Dr. Kunkler has nothing to disclose. Dr. Cardoso has nothing to disclose. Prof. Cheung has nothing to disclose. Dr. de Glas has nothing to disclose. Dr. Trimboli has nothing to disclose. Dr. Korc-Grodzicki has nothing to disclose. Dr. Soto-Perez-de-Celis has nothing to disclose. Dr. Ponti has nothing to disclose. Dr. Tsang has nothing to disclose. Dr. Marotti has nothing to disclose. Dr. Benn has nothing to disclose. Dr. Aapro reports personal fees and non-financial support from Multinational Association for Supportive Care in Cancer, personal fees and non-financial support from European Society of Medical Oncology, personal fees and non-financial support from European CanCer Organisation, grants and personal fees from Helsinn, personal fees from Tesaro, grants and personal fees from Sandoz, personal fees from Merck USA, personal fees from Vifor, personal fees from Pfizer, personal fees from Taiho, personal fees from Kyowa Kirin, outside the submitted workDr. Brain reports personal fees and other from Pfizer, personal fees and other from Roche, other from Pierre Fabre, grants, personal fees and other from BMS, personal fees from Samsung, other from Novartis, other from AstraZeneca, personal fees from TLC PharmaChem, personal fees from Clinigen, personal fees from Mylan, personal fees from G1 Therapeutics, outside the submitted work.

No authors are employed by NIH.

Contributions

All authors contributed equally to literature search, figures, data interpretation and writing.

Disclosure

This paper has not been submitted to another journal and has not been published in whole or in part elsewhere previously.

References

1. Biganzoli L, Marotti L, Hart CD, Cataliotti L, Cutuli B, Kühn T, et al. Quality indicators in breast cancer care: An update from the EUSOMA working group. Eur J Cancer. 2017;86:59-81.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin. 2019;69(1):7-34.
3. Bagegni NA, Peterson LL. Age-related disparities in older women with breast cancer. Adv Cancer Res. 2020;146:23-56.
4. Hurria A, Levit LA, Dale W, Mohile SG, Muss HB, Fehrenbacher L, et al. Improving the Evidence Base for Treating Older Adults With Cancer: American Society of Clinical Oncology Statement. J Clin Oncol. 2015;33(32):3826-33.
5. Wildiers H, Kunkler I, Biganzoli L, Fracheboud J, Vlastos G, Bernard-Marty C, et al. Management of breast cancer in elderly individuals: recommendations of the International Society of Geriatric Oncology. Lancet Oncol. 2007;8(12):1101-15.
6. Biganzoli L, Wildiers H, Oakman C, Marotti L, Loibl S, Kunkler I, et al. Management of elderly patients with breast cancer: updated recommendations of the International Society of Geriatric Oncology (SIOG) and European Society of Breast Cancer Specialists (EUSOMA). Lancet Oncol. 2012;13(4):e148-60.
7. Guerard EJ, Deal AM, Chang Y, Williams GR, Nyrop KA, Pergolotti M, et al. Frailty Index Developed From a Cancer-Specific Geriatric Assessment and the Association With Mortality Among Older Adults With Cancer. J Natl Compr Canc Netw. 2017;15(7):894-902.
8. Mohile SG, Dale W, Somerfield MR, Schonberg MA, Boyd CM, Burhenn PS, et al. Practical Assessment and Management of Vulnerabilities in Older Patients Receiving Chemotherapy: ASCO Guideline for Geriatric Oncology. J Clin Oncol. 2018;36(22):2326-47.
9. NCCN. NCCN clinical practice guidelines in oncology version 3.2019 genetic/familial high-risk assessment: breast and ovarian.; 2019.
10. Wildiers H, Heeren P, Puts M, Topinkova E, Janssen-Heijnen ML, Extermann M, et al. International Society of Geriatric Oncology consensus on geriatric assessment in older patients with cancer. J Clin Oncol. 2014;32(24):2595-603.
11. Mohile SG, Epstein RM, Hurria A, Heckler CE, Canin B, Culakova E, et al. Communication With Older Patients With Cancer Using Geriatric Assessment: A Cluster-Randomized Clinical Trial From the National Cancer Institute Community Oncology Research Program. JAMA Oncol. 2019;6(2):1-9.
12. Li D, Sun C-L, Kim H, Chung V, Koczywas M, Fakih M, et al. Geriatric assessment-driven intervention (GAIN) on chemotherapy toxicity in older adults with cancer: A randomized controlled trial. Journal of Clinical Oncology. 2020;38(15_suppl):12010-.
13. Mohile SG, Mohamed MR, Culakova E, Xu H, Loh KP, Magnuson A, et al. A geriatric assessment (GA) intervention to reduce treatment toxicity in older patients with advanced cancer: A University of Rochester Cancer Center NCI community oncology research program cluster randomized clinical trial (CRCT). Journal of Clinical Oncology. 2020;38(15_suppl):12009-.
14. Qian CL, Knight HP, Ferrone CR, Kunitake H, Castillo CF-d, Lanuti M, et al. Randomized trial of a perioperative geriatric intervention for older adults with cancer. Journal of Clinical Oncology. 2020;38(15_suppl):12012-.
15. Soo W-K, King M, Pope A, Parente P, Darzins P, Davis ID. Integrated geriatric assessment and treatment (INTEGERATE) in older people with cancer planned for systemic anticancer therapy. Journal of Clinical Oncology. 2020;38(15_suppl):12011-.
16. Decoster L, Van Puyvelde K, Mohile S, Wedding U, Basso U, Colloca G, et al. Screening tools for multidimensional health problems warranting a geriatric assessment in older cancer patients: an update on SIOG recommendations†. Ann Oncol. 2015;26(2):288-300.
17. Hamaker ME, Jonker JM, de Rooij SE, Vos AG, Smorenburg CH, van Munster BC. Frailty screening methods for predicting outcome of a comprehensive geriatric assessment in elderly patients with cancer: a systematic review. Lancet Oncol. 2012;13(10):e437-44.
18. Extermann M, Boler I, Reich RR, Lyman GH, Brown RH, DeFelice J, et al. Predicting the risk of chemotherapy toxicity in older patients: the Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH) score. Cancer. 2012;118(13):3377-86.

19. Hurria A, Togawa K, Mohile SG, Owusu C, Klepin HD, Gross CP, et al. Predicting chemotherapy toxicity in older adults with cancer: a prospective multicenter study. J Clin Oncol. 2011;29(25):3457-65.
20. Hurria A, Magnuson A, Gross CP, Tew WP, Klepin HD, Wildes TM, editors. Development and validation of a chemotherapy toxicity (Chemo Tox) risk score for older patients (pts) with breast cancer (BC) receiving adjuvant/neoadjuvant treatment (Adjuvant Tx): A R01 and BCRF funded prospective multicenter student [abstract]. 2018 San Antonio Breast Cancer Symposium; 2018 2018 Dec 4-8; San Antonio, TX.
21. Soto-Perez-de-Celis E, Li D, Yuan Y, Lau YM, Hurria A. Functional versus chronological age: geriatric assessments to guide decision making in older patients with cancer. Lancet Oncol. 2018;19(6):e305-e16.
22. van de Water W, Bastiaannet E, Hille ET, Meershoek-Klein Kranenbarg EM, Putter H, Seynaeve CM, et al. Age-specific nonpersistence of endocrine therapy in postmenopausal patients diagnosed with hormone receptor-positive breast cancer: a TEAM study analysis. Oncologist. 2012;17(1):55-63.
23. de Glas NA, de Craen AJ, Bastiaannet E, Op 't Land EG, Kiderlen M, van de Water W, et al. Effect of implementation of the mass breast cancer screening programme in older women in the Netherlands: population based study. Bmj. 2014;349:g5410.
24. García-Albéniz X, Hernán MA, Logan RW, Price M, Armstrong K, Hsu J. Continuation of Annual Screening Mammography and Breast Cancer Mortality in Women Older Than 70 Years. Ann Intern Med. 2020;172(6):381-9.
25. Nelson HD, Fu R, Cantor A, Pappas M, Daeges M, Humphrey L. Effectiveness of Breast Cancer Screening: Systematic Review and Meta-analysis to Update the 2009 U.S. Preventive Services Task Force Recommendation. Ann Intern Med. 2016;164(4):244-55.
26. Bredemeyer M. ACS Releases Guideline on Breast Cancer Screening. Am Fam Physician. 2016;93(8):711-2.
27. Freedman RA, Keating NL, Partridge AH, Muss HB, Hurria A, Winer EP. Surveillance Mammography in Older Patients With Breast Cancer-Can We Ever Stop?: A Review. JAMA Oncol. 2017;3(3):402-9.
28. Runowicz CD, Leach CR, Henry NL, Henry KS, Mackey HT, Cowens-Alvarado RL, et al. American Cancer Society/American Society of Clinical Oncology Breast Cancer Survivorship Care Guideline. CA Cancer J Clin. 2016;66(1):43-73.
29. Brownlee S, Chalkidou K, Doust J, Elshaug AG, Glasziou P, Heath I, et al. Evidence for overuse of medical services around the world. Lancet. 2017;390(10090):156-68.
30. Chavarri-Guerra Y, Hendricks CB, Brown S, Marcum C, Hander M, Segota ZE, et al. The Burden of Breast Cancer Predisposition Variants Across The Age Spectrum Among 10 000 Patients. J Am Geriatr Soc. 2019;67(5):884-8.
31. Liposits G, Loh KP, Soto-Perez-de-Celis E, Dumas L, Battisti NML, Kadambi S, et al. PARP inhibitors in older patients with ovarian and breast cancer: Young International Society of Geriatric Oncology review paper. J Geriatr Oncol. 2019;10(2):337-45.
32. Mieog JS, van der Hage JA, van de Velde CJ. Preoperative chemotherapy for women with operable breast cancer. Cochrane Database Syst Rev. 2007(2):Cd005002.
33. Barcenas CH, Niu J, Zhang N, Zhang Y, Buchholz TA, Elting LS, et al. Risk of hospitalization according to chemotherapy regimen in early-stage breast cancer. J Clin Oncol. 2014;32(19):2010-7.
34. Pinder PC, Duan Z, Goodwin JS, Hortobagyi GN, Giordano SH. Congestive Heart Failure in Older Women Treated With Adjuvant Anthracycline Chemotherapy for Breast Cancer. Journal of Clinical Oncology. 2007;25(25):3808-15.
35. Rosenstock AS, Lei X, Tripathy D, Hortobagyi GN, Giordano SH, Chavez-MacGregor M. Short-term mortality in older patients treated with adjuvant chemotherapy for early-stage breast cancer. Breast Cancer Res Treat. 2016;157(2):339-50.
36. Masuda N, Lee SJ, Ohtani S, Im YH, Lee ES, Yokota I, et al. Adjuvant Capecitabine for Breast Cancer after Preoperative Chemotherapy. N Engl J Med. 2017;376(22):2147-59.
37. von Minckwitz G, Huang CS, Mano MS, Loibl S, Mamounas EP, Untch M, et al. Trastuzumab Emtansine for Residual Invasive HER2-Positive Breast Cancer. N Engl J Med. 2019;380(7):617-28.

38. Spring LM, Gupta A, Reynolds KL, Gadd MA, Ellisen LW, Isakoff SJ, et al. Neoadjuvant Endocrine Therapy for Estrogen Receptor-Positive Breast Cancer: A Systematic Review and Meta-analysis. JAMA Oncol. 2016;2(11):1477-86.
39. de Glas NA, Kiderlen M, Bastiaannet E, de Craen AJ, van de Water W, van de Velde CJ, et al. Postoperative complications and survival of elderly breast cancer patients: a FOCUS study analysis. Breast Cancer Res Treat. 2013;138(2):561-9.
40. Hind D, Wyld L, Beverley CB, Reed MW. Surgery versus primary endocrine therapy for operable primary breast cancer in elderly women (70 years plus). Cochrane Database Syst Rev. 2006(1):Cd004272.
41. Morgan JL, Reed MW, Wyld L. Primary endocrine therapy as a treatment for older women with operable breast cancer - a comparison of randomised controlled trial and cohort study findings. Eur J Surg Oncol. 2014;40(6):676-84.
42. Syed BM, Al-Khyatt W, Johnston SJ, Wong DW, Winterbottom L, Kennedy H, et al. Long-term clinical outcome of oestrogen receptor-positive operable primary breast cancer in older women: a large series from a single centre. Br J Cancer. 2011;104(9):1393-400.
43. Ward EP, Weiss A, Blair SL. Incidence and treatments of DCIS in octogenarians: grade matters. Breast Cancer Res Treat. 2017;165(2):403-9.
44. Martelli G, Miceli R, Daidone MG, Vetrella G, Cerrotta AM, Piromalli D, et al. Axillary dissection versus no axillary dissection in elderly patients with breast cancer and no palpable axillary nodes: results after 15 years of follow-up. Ann Surg Oncol. 2011;18(1):125-33.
45. Giuliano AE, Ballman KV, McCall L, Beitsch PD, Brennan MB, Kelemen PR, et al. Effect of Axillary Dissection vs No Axillary Dissection on 10-Year Overall Survival Among Women With Invasive Breast Cancer and Sentinel Node Metastasis: The ACOSOG Z0011 (Alliance) Randomized Clinical Trial. Jama. 2017;318(10):918-26.
46. Donker M, van Tienhoven G, Straver ME, Meijnen P, van de Velde CJ, Mansel RE, et al. Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (EORTC 10981-22023 AMAROS): a randomised, multicentre, open-label, phase 3 non-inferiority trial. Lancet Oncol. 2014;15(12):1303-10.
47. James R, McCulley SJ, Macmillan RD. Oncoplastic and reconstructive breast surgery in the elderly. Br J Surg. 2015;102(5):480-8.
48. McGale P, Taylor C, Correa C, Cutter D, Duane F, Ewertz M, et al. Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. Lancet. 2014;383(9935):2127-35.
49. Hughes KS, Schnaper LA, Bellon JR, Cirrincione CT, Berry DA, McCormick B, et al. Lumpectomy plus tamoxifen with or without irradiation in women age 70 years or older with early breast cancer: long-term follow-up of CALGB 9343. J Clin Oncol. 2013;31(19):2382-7.
50. Kunkler IH, Williams LJ, Jack WJ, Cameron DA, Dixon JM. Breast-conserving surgery with or without irradiation in women aged 65 years or older with early breast cancer (PRIME II): a randomised controlled trial. Lancet Oncol. 2015;16(3):266-73.
51. Bartelink H, Maingon P, Poortmans P, Weltens C, Fourquet A, Jager J, et al. Whole-breast irradiation with or without a boost for patients treated with breast-conserving surgery for early breast cancer: 20-year follow-up of a randomised phase 3 trial. Lancet Oncol. 2015;16(1):47-56.
52. Strnad V, Ott OJ, Hildebrandt G, Kauer-Dorner D, Knauerhase H, Major T, et al. 5-year results of accelerated partial breast irradiation using sole interstitial multicatheter brachytherapy versus whole-breast irradiation with boost after breast-conserving surgery for low-risk invasive and in-situ carcinoma of the female breast: a randomised, phase 3, non-inferiority trial. Lancet. 2016;387(10015):229-38.
53. Coles CE, Griffin CL, Kirby AM, Titley J, Agrawal RK, Alhasso A, et al. Partial-breast radiotherapy after breast conservation surgery for patients with early breast cancer (UK IMPORT LOW trial): 5-year results from a multicentre, randomised, controlled, phase 3, non-inferiority trial. Lancet. 2017;390(10099):1048-60.
54. Bloomfield DJ. Development of Postoperative Radiotherapy for Breast Cancer: UK Consensus Statements - a Model of Patient, Clinical and Commissioner Engagement? Clin Oncol (R Coll Radiol). 2017;29(10):639-41.

55. Poortmans PM, Collette S, Kirkove C, Van Limbergen E, Budach V, Struikmans H, et al. Internal Mammary and Medial Supraclavicular Irradiation in Breast Cancer. N Engl J Med. 2015;373(4):317-27.
56. Whelan TJ, Olivotto IA, Parulekar WR, Ackerman I, Chua BH, Nabid A, et al. Regional Nodal Irradiation in Early-Stage Breast Cancer. N Engl J Med. 2015;373(4):307-16.
57. Bartelink H. Regional nodal irradiation for early breast cancer; clinical benefit according to risk stratification. Breast. 2019;48 Suppl 1:S65-s8.
58. (NICE) NIfHaCE. Early and locally advanced breast cancer: diagnosis and management. 2018.
59. Recht A, Comen EA, Fine RE, Fleming GF, Hardenbergh PH, Ho AY, et al. Postmastectomy Radiotherapy: An American Society of Clinical Oncology, American Society for Radiation Oncology, and Society of Surgical Oncology Focused Guideline Update. Pract Radiat Oncol. 2016;6(6):e219-e34.
60. Kunkler IH, Canney P, van Tienhoven G, Russell NS. Elucidating the role of chest wall irradiation in 'intermediate-risk' breast cancer: the MRC/EORTC SUPREMO trial. Clin Oncol (R Coll Radiol). 2008;20(1):31-4.
61. Gradishar WJ, Anderson BO, Balassanian R, Blair SL, Burstein HJ, Cyr A, et al. NCCN Guidelines Insights: Breast Cancer, Version 1.2017. J Natl Compr Canc Netw. 2017;15(4):433-51.
62. Murray Brunt A, Haviland JS, Wheatley DA, Sydenham MA, Alhasso A, Bloomfield DJ, et al. Hypofractionated breast radiotherapy for 1 week versus 3 weeks (FAST-Forward): 5-year efficacy and late normal tissue effects results from a multicentre, non-inferiority, randomised, phase 3 trial. The Lancet. 2020;395(10237):1613-26.
63. Muss HB, Polley MC, Berry DA, Liu H, Cirrincione CT, Theodoulou M, et al. Randomized Trial of Standard Adjuvant Chemotherapy Regimens Versus Capecitabine in Older Women With Early Breast Cancer: 10-Year Update of the CALGB 49907 Trial. J Clin Oncol. 2019;37(26):2338-48.
64. Elkin EB, Hurria A, Mitra N, Schrag D, Panageas KS. Adjuvant chemotherapy and survival in older women with hormone receptor-negative breast cancer: assessing outcome in a population-based, observational cohort. J Clin Oncol. 2006;24(18):2757-64.
65. Giordano SH, Duan Z, Kuo YF, Hortobagyi GN, Goodwin JS. Use and outcomes of adjuvant chemotherapy in older women with breast cancer. J Clin Oncol. 2006;24(18):2750-6.
66. Tamirisa N, Lin H, Shen Y, Shaitelman SF, Sri Karuturi M, Giordano SH, et al. Association of Chemotherapy With Survival in Elderly Patients With Multiple Comorbidities and Estrogen Receptor-Positive, Node-Positive Breast Cancer. JAMA Oncol. 2020.
67. Kizy S, Altman AM, Marmor S, Denbo JW, Jensen EH, Tuttle TM, et al. 21-gene recurrence score testing in the older population with estrogen receptor-positive breast cancer. J Geriatr Oncol. 2019;10(2):322-9.
68. de Glas NA, van de Water W, Engelhardt EG, Bastiaannet E, de Craen AJ, Kroep JR, et al. Validity of Adjuvant! Online program in older patients with breast cancer: a population-based study. Lancet Oncol. 2014;15(7):722-9.
69. de Glas NA, Bastiaannet E, Engels CC, de Craen AJ, Putter H, van de Velde CJ, et al. Validity of the online PREDICT tool in older patients with breast cancer: a population-based study. Br J Cancer. 2016;114(4):395-400.
70. Muss HB, Woolf S, Berry D, Cirrincione C, Weiss RB, Budman D, et al. Adjuvant chemotherapy in older and younger women with lymph node-positive breast cancer. Jama. 2005;293(9):1073-81.
71. Peto R, Davies C, Godwin J, Gray R, Pan HC, Clarke M, et al. Comparisons between different polychemotherapy regimens for early breast cancer: meta-analyses of long-term outcome among 100,000 women in 123 randomised trials. Lancet. 2012;379(9814):432-44.
72. Perrone F, Nuzzo F, Di Rella F, Gravina A, Iodice G, Labonia V, et al. Weekly docetaxel versus CMF as adjuvant chemotherapy for older women with early breast cancer: final results of the randomized phase III ELDA trial. Ann Oncol. 2015;26(4):675-82.
73. Caparica R, Bruzzone M, Poggio F, Ceppi M, de Azambuja E, Lambertini M. Anthracycline and taxane-based chemotherapy versus docetaxel and cyclophosphamide in the adjuvant treatment of HER2-negative breast cancer patients: a systematic review and meta-analysis of randomized controlled trials. Breast Cancer Res Treat. 2019;174(1):27-37.

74. Muss HB, Berry DA, Cirrincione C, Budman DR, Henderson IC, Citron ML, et al. Toxicity of Older and Younger Patients Treated With Adjuvant Chemotherapy for Node-Positive Breast Cancer: The Cancer and Leukemia Group B Experience. Journal of Clinical Oncology. 2007;25(24):3699-704.
75. Brouwers B, Hatse S, Dal Lago L, Neven P, Vuylsteke P, Dalmasso B, et al. The impact of adjuvant chemotherapy in older breast cancer patients on clinical and biological aging parameters. Oncotarget. 2016;7(21):29977-88.
76. Cameron D, Piccart-Gebhart MJ, Gelber RD, Procter M, Goldhirsch A, de Azambuja E, et al. 11 years' follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive early breast cancer: final analysis of the HERceptin Adjuvant (HERA) trial. Lancet. 2017;389(10075):1195-205.
77. Perez EA, Romond EH, Suman VJ, Jeong JH, Sledge G, Geyer CE, Jr., et al. Trastuzumab plus adjuvant chemotherapy for human epidermal growth factor receptor 2-positive breast cancer: planned joint analysis of overall survival from NSABP B-31 and NCCTG N9831. J Clin Oncol. 2014;32(33):3744-52.
78. Brain E, Caillet P, de Glas N, Biganzoli L, Cheng K, Lago LD, et al. HER2-targeted treatment for older patients with breast cancer: An expert position paper from the International Society of Geriatric Oncology. J Geriatr Oncol. 2019;10(6):1003-13.
79. Sawaki M, Taira N, Uemura Y, Saito T, Baba S, Kobayashi K, et al. Randomized Controlled Trial of Trastuzumab With or Without Chemotherapy for HER2-Positive Early Breast Cancer in Older Patients. J Clin Oncol. 2020:Jco2000184.
80. Reeder-Hayes KE, Meyer AM, Hinton SP, Meng K, Carey LA, Dusetzina SB. Comparative Toxicity and Effectiveness of Trastuzumab-Based Chemotherapy Regimens in Older Women With Early-Stage Breast Cancer. J Clin Oncol. 2017;35(29):3298-305.
81. Vaz-Luis I, Keating NL, Lin NU, Lii H, Winer EP, Freedman RA. Duration and toxicity of adjuvant trastuzumab in older patients with early-stage breast cancer: a population-based study. J Clin Oncol. 2014;32(9):927-34.
82. Christiansen P, Bjerre K, Ejlertsen B, Jensen MB, Rasmussen BB, Laenkholm AV, et al. Mortality rates among early-stage hormone receptor-positive breast cancer patients: a population-based cohort study in Denmark. Journal of the National Cancer Institute. 2011;103(18):1363-72.
83. Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials. Lancet. 2015;386(10001):1341-52.
84. Rossi L, McCartney A, De Santo I, Risi E, Moretti E, Malorni L, et al. The optimal duration of adjuvant endocrine therapy in early luminal breast cancer: A concise review. Cancer Treat Rev. 2019;74:29-34.
85. O'Carrigan B, Wong MH, Willson ML, Stockler MR, Pavlakis N, Goodwin A. Bisphosphonates and other bone agents for breast cancer. Cochrane Database Syst Rev. 2017;10(10):Cd003474.
86. Adjuvant bisphosphonate treatment in early breast cancer: meta-analyses of individual patient data from randomised trials. Lancet. 2015;386(10001):1353-61.
87. Coleman R, Woodward E, Brown J, Cameron D, Bell R, Dodwell D, et al. Safety of zoledronic acid and incidence of osteonecrosis of the jaw (ONJ) during adjuvant therapy in a randomised phase III trial (AZURE: BIG 01-04) for women with stage II/III breast cancer. Breast Cancer Res Treat. 2011;127(2):429-38.
88. Mauri D, Valachis A, Polyzos IP, Polyzos NP, Kamposioras K, Pesce LL. Osteonecrosis of the jaw and use of bisphosphonates in adjuvant breast cancer treatment: a meta-analysis. Breast Cancer Res Treat. 2009;116(3):433-9.
89. Gnant M, Pfeiler G, Steger GG, Egle D, Greil R, Fitzal F, et al. Adjuvant denosumab in postmenopausal patients with hormone receptor-positive breast cancer (ABCSG-18): disease-free survival results from a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 2019;20(3):339-51.
90. Coleman RE, Finkelstein D, Barrios CH, Martin M, Iwata H, Glaspy JA, et al. Adjuvant denosumab in early breast cancer: First results from the international multicenter randomized phase III placebo controlled D-CARE study. Journal of Clinical Oncology. 2018;36(15_suppl):501-.
91. Lichtman SM, Wildiers H, Chatelut E, Steer C, Budman D, Morrison VA, et al. International Society of Geriatric Oncology Chemotherapy Taskforce: evaluation of chemotherapy in older patients--an analysis of the medical literature. J Clin Oncol. 2007;25(14):1832-43.

92. Biganzoli L, Cinieri S, Berardi R, Pedersini R, McCartney A, Minisini AM, et al. EFFECT: a randomized phase II study of efficacy and impact on function of two doses of nab-paclitaxel as first-line treatment in older women with advanced breast cancer. Breast Cancer Res. 2020;22(1):83.
93. Leo S, Arnoldi E, Repetto L, Coccorullo Z, Cinieri S, Fedele P, et al. Eribulin Mesylate as Third or Subsequent Line Chemotherapy for Elderly Patients with Locally Recurrent or Metastatic Breast Cancer: A Multicentric Observational Study of GIOGer (Italian Group of Geriatric Oncology)-ERIBE. Oncologist. 2019;24(6):e232-e40.
94. Wildiers H, Tryfonidis K, Dal Lago L, Vuylsteke P, Curigliano G, Waters S, et al. Pertuzumab and trastuzumab with or without metronomic chemotherapy for older patients with HER2-positive metastatic breast cancer (EORTC 75111-10114): an open-label, randomised, phase 2 trial from the Elderly Task Force/Breast Cancer Group. Lancet Oncol. 2018;19(3):323-36.
95. Rugo HS, Turner NC, Finn RS, Joy AA, Verma S, Harbeck N, et al. Palbociclib plus endocrine therapy in older women with HR+/HER2- advanced breast cancer: a pooled analysis of randomised PALOMA clinical studies. Eur J Cancer. 2018;101:123-33.
96. Sonke GS, Hart LL, Campone M, Erdkamp F, Janni W, Verma S, et al. Ribociclib with letrozole vs letrozole alone in elderly patients with hormone receptor-positive, HER2-negative breast cancer in the randomized MONALEESA-2 trial. Breast Cancer Res Treat. 2018;167(3):659-69.
97. Goetz MP, Okera M, Wildiers H, editors. Safety and Efficacy of Abemaciclib plus endocrine therapy in Elderly patients with HR+, HER2- advanced breast cancer: an age-specific subgroup analysis of MONARCH2 and 3 trials. San Antonio Breast Cancer Symposium; 2019; San Antonio, TX.
98. Howie LJ, Singh H, Bloomquist E, Wedam S, Amiri-Kordestani L, Tang S, et al. Outcomes of Older Women With Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor-Negative Metastatic Breast Cancer Treated With a CDK4/6 Inhibitor and an Aromatase Inhibitor: An FDA Pooled Analysis. J Clin Oncol. 2019;37(36):3475-83.
99. Battisti NML, De Glas N, Sedrak MS, Loh KP, Liposits G, Soto-Perez-de-Celis E, et al. Use of cyclin-dependent kinase 4/6 (CDK4/6) inhibitors in older patients with ER-positive HER2-negative breast cancer: Young International Society of Geriatric Oncology review paper. Ther Adv Med Oncol. 2018;10:1758835918809610.
100. Pritchard KI, Burris HA, 3rd, Ito Y, Rugo HS, Dakhil S, Hortobagyi GN, et al. Safety and efficacy of everolimus with exemestane vs. exemestane alone in elderly patients with HER2-negative, hormone receptor-positive breast cancer in BOLERO-2. Clin Breast Cancer. 2013;13(6):421-32.e8.

Table 1: Summary of the EUSOMA/SIOG recommendations.

Domain	2012 recommendation	Current recommendations	Level of evidence

General recommendations for all aspects of management	• All management decisions for an older individual with breast cancer should consider:
	  • physiological age
	  • life expectancy
	  • potential risks versus absolute benefits
	  • treatment tolerance
	  • patient preferences
	  • potential barriers to treatment
		• Screening for frailty is recommended for patients aged 70 and older to identify those at increased vulnerability to stressors and adverse outcome
		• Treatment can be tailored based on patients grouping as fit, vulnerable/pre-frail, and frail
			I
			
			IV

Competing causes of mortality	• Relative breast cancer survival is the preferred way to describe the outcome of older breast cancer pts. • Assessment of co-morbidity and function may predict likelihood of dying from non-breast cancer causes.	• Even in the absence of multimorbidities, competing causes of mortality are more prevalent in older adults compared to their younger counterparts. • Treatment decisions for anti-cancer treatment should be based not only on risk of recurrence or breast cancer mortality, but should also weigh the risk of dying of other causes as an equally important factor.	III IV
Geriatric evaluation	• Collaborative geriatric and oncology management may optimise care. • General health and functional status may be captured in a multidomain geriatric assessment; however, it is unclear which older pts are most likely to benefit and which tool is optimal. • A screening assessment is a reasonable first step in identifying pts that may benefit from an extended CGA. • Active intervention for CGA-identified reversible geriatric domains may reduce morbidity and mortality and improve quality of life. • Serial geriatric assessment may identify incident deterioration, for which intervention may improve outcomes.	• A screening tool (ST) should be considered as the gateway or minimum starting point to any cancer treatment decision-making in older patients	III

Chemotherapy toxicity calculators		• Toxicity calculators such as CARG and CRASH can be used to estimate the risk of grade 3-5 chemotherapy toxicity in older patients. • They have not to be used as the sole factor to determine whether an older patient should receive chemotherapy, but rather as an adjunct in the decision-making process	III IV
Cultural and social considerations		• Due to widespread immigration, society is becoming increasingly multi-cultural and diverse, and this should be considered in the clinical approach to patient care • Older immigrants are at risk of poorer outcomes due to numerous barriers to accessing care • Engagement with a patient's social and cultural community is an important factor in improving outcomes for patients and caregivers	Not applicable
Screening mammography	• There is no strong data for screening mammography in women > 70y. • Screening in women aged 70-75y could be appropriate with the ultimate decision for an individual based on risks and benefits of screening, pt preference, physiological age and life expectancy.	• Biennial screening mammography in women age 70-75y of age may benefit part of this group, but optimal criteria to define those who really benefit are lacking • Screening in women 75 years or older could be appropriate with the individual decision based on risks and benefits, patient preference, physiological age, and life expectancy, but may lead to more over-diagnosis.	III IV
Surveillance mammography		• Annual or biennial surveillance mammography for breast cancer survivors ≥70 years could be appropriate, with the individual decision based on risks and benefits, tumor biology, patient preference, physiological age and life expectancy. • Overuse of medical services in patients over 80 years, with advanced multimorbidities or life expectancy less than 5 years, should be avoided.	IV IV
Genetic screening		• Genetic testing may have relevant implications for families and on therapeutic decisions regardless of patient age. • Selection of candidates appropriate for screening should be consistent with local practice and/or guidelines.	IV IV
Genomic tools		• Integration of information regarding the general health status in multi-gene prognostic models is essential to ensure accuracy of these prediction tools in older patients	IV
Neoadjuvant systemic therapy		• Carefully selected, fit, older patients should be considered for neoadjuvant systemic therapy similarly to younger women.	IV

		• Less fit older patients are best served by surgery upfront that may enable systemic treatment de-escalation based on pathological findings and physical recovery after surgery. • In fit older persons with high-grade triple negative BC (TNBC), optimal chemotherapy is still debated. With very limited evidence, sequential regimens with anthracyclines and taxanes may be considered in principle because of the aggressive phenotype and frequent chemosensitivity, or shorter ones with either alone. But the addition of platinum compounds remains poorly consensual in practice, even for younger patients, and is unlikely feasible in the large majority of older persons. • Fit, older patients should be considered for capecitabine in case of residual triple-negative disease following neoadjuvant chemotherapy • Fit, older patients should be considered for T-DM1 in case of residual HER2-positive disease following neoadjuvant systemic therapy • Neoadjuvant endocrine therapy for at least 4-6 months is useful for older patients who are not immediately suitable for surgery and aromatase inhibitors are favoured over tamoxifen in view of better response rates	IV IV IV IV III
Surgery	• Pts ≥70y should be offered the same surgery as younger pts • Standard of care is BCS plus WBRT, or mastectomy ± postoperative radiotherapy • Mastectomy is indicated for large or multifocal tumours not amenable to conservative excision, pts who are not fit for WBRT and pts who prefer mastectomy to BCS plus WBRT. • ALND is indicated for clinically positive or highly suspected nodes • In clinically node negative disease, axillary staging by SLNB with completion ALND for tumour positive SLNB remains the standard of care. Omission of SLNB and completion ALND might be reasonable in some older pts – see full text	• Surgery remains the choice of primary treatment in the majority of older patients with early breast cancer • SLNB remains the standard of care for staging the axilla in patients with clinically/radiologically negative axilla. • For patients with a positive SN, completion axillary therapy (surgery or radiotherapy) is not always needed, and if needed, radiotherapy should be preferred to axillary clearance, especially in the cases of low axillary nodal burden and ER-positive disease requiring adjuvant endocrine therapy. • Axillary surgery may be omitted in patients with cT1N0 luminal A-like tumours and/or short life expectancy. • Primary endocrine therapy may be considered as an alternative in selected patients with a strongly ER-positive tumour and short life expectancy (no more than 5 years). Adverse events of ET should be taken into account in this decision.	I III IV IV IV

		• Oncoplastic and reconstructive surgery may be offered, taking into account patient preferences and co-morbidities.	IV
Primary endocrine therapy	• Primary endocrine therapy should only be offered to older individuals with ER-positive tumours who have a short estimated life expectancy (<2-3y), who are considered unfit for surgery after optimisation of medical conditions or who refuse surgery. • The involvement of a geriatrician is strongly recommended to estimate life expectancy and guide management of reversible comorbidities • It is reasonable to choose tamoxifen, or an AI based on potential side effects.	• When primary endocrine therapy involves AIs, the median time to progression is approximately five years • The benefit of PET versus upfront surgery is expected to be most pronounced with a life expectancy of <5 years	III IV
Ductal carcinoma insitu	• There is no strong data available in older women with DCIS. • Healthy older women with localised DCIS should be considered for BCS and postoperative radiotherapy.	• Surgery for DCIS should take into account grade and life expectancy. • Fit patients with high-grade DCIS should undergo surgery. • In low/intermediate grade DCIS, withholding surgery or avoiding radiotherapy can be considered.	IV III IV
Radiotherapy	• WBRT after BCS – with a boost to the tumour bed - should be considered in all older pts as it decreases risk of local relapse. There is no subgroup of fit older pts in whom post-BCS WBRT may be systematically omitted – see full text • Post-mastectomy chest wall radiation should be considered for older pts with ≥4 nodes or a pT3/4 tumour • Hypofractionated radiation schedules offer similar local-regional control and adverse effects as standard WBRT • The evidence for PBI in older pts is not sufficiently robust to recommend it as standard therapy	• WBRT remains the standard of care for most older patients following BCS; omission of radiotherapy in low-risk patients may be safe and reasonable. • In patients over 60 years, the use of a boost is advised only for those at higher risk of recurrence. • PBI is recommended to women ≥50 years and grade 1-2, pN0, HR-positive, HER2-negative, tumours ≤30mm and with radial margins ≥1mm The role of PMRT in patients with 1-3 positive nodes remains controversial. • Hypofractionated schedules (40 Gy in 15 fractions over 3 weeks, 42.5 Gy in 16 fractions over 3.5 weeks or 26 Gy in five fractions over 1 week) are recommended for older as in younger patients	I I IV IV
Adjuvant chemotherapy in HER2 negative disease	• The decision to treat with adjuvant chemotherapy should not be age-based. Older pts with node-positive, hormone-negative disease potentially derive the largest benefit. • 4 cycles of an anthracycline-containing regimen are usually preferred over CMF	• The use of chemotherapy should not be guided by chronological age alone. • Older adults with hormone receptor-negative disease may derive most benefit from adjuvant chemotherapy irrespective of nodal status. • A duration of chemotherapy beyond 3 months is an important risk factor for the occurrence of serious side effects.	IV III

	• Standard AC and CMF chemotherapy are superior to single agent capecitabine • Taxanes are associated with increased toxicity compared with younger women, but can be added to anthracyclines in high-risk healthy older pts, or replace anthracyclines to reduce the cardiac risk. • Pts with HER2-positive breast cancer, without cardiac disease, should be offered trastuzumab in combination with chemotherapy – see full text	• Standard regimens include 4 cycles of docetaxel/cyclophosphamide (TC) or 4 cycles of AC. • Weekly paclitaxel x 12 may be an option in patients unfit for polychemotherapy • Only carefully selected, fit, older patients with high-risk disease (large, node-positive, triple-negative) may be considered for a sequential combination of anthracyclines and taxanes. • Dose-dense regimens should not be utilised in general based on the increased toxicity risk and the lack of efficacy data in older persons	III II IV IV IV
Multigene-expression assays		• There is limited evidence about the use of multi-gene expression assays in older patients, whether for prognosis or treatment benefit prediction. • Integration of information regarding the general health status in multi-gene prognostic models is essential to ensure accuracy of these prediction tools in older patients	IV IV
Adjuvant anti-HER2 therapy		• Adjuvant chemotherapy along with one year of trastuzumab is recommended as a standard approach in older patients with no cardiac dysfunction and early-stage HER2+ BC ≥ 0.5 cm. • Preferred chemotherapy options include the use of taxanes without anthracyclines, for example in the form of four cycles of docetaxel/cyclophosphamide (TC) or 12 consecutive weeks of weekly paclitaxel, avoiding cardiac toxicity of anthracyclines and duration of chemotherapy beyond the 3-month threshold at risk of grade 3-5 adverse events. • A sequential regimen of anthracyclines and taxanes with trastuzumab is appropriate only in a very selected group of fit, healthy older patients. • Pertuzumab may be added only in high risk and fit patients, but diarrhea can be a debilitating side effect in older invididuals. • Extended adjuvant therapy with neratinib is probably not an appropriate option for older patients due to potential risk of grade ≥3 diarrhea • Although evidence is scarce, the utilization of single-agent trastuzumab without chemotherapy, but with endocrine therapy if hormone sensitive, may be appropriate in vulnerable and frail patients.	II IV IV IV IV IV

		• Shorter courses of anti-HER2 therapy may be considered for older patients with small, node-negative tumours or in the context of cardiac problems	II
Adjuvant endocrine therapy	• There is no age-dependent efficacy of tamoxifen or AIs • Efficacy is slightly greater with AIs, however, older patients are more vulnerable to toxicity and safety is important in choice of agent • Initial treatment should be tamoxifen or an AI. Pts treated with tamoxifen should be considered for a switch to an AI after 2-3 years. Extension of adjuvant treatment with an AI after 5 years of tamoxifen could be considered for healthy older pts. • Omission of endocrine therapy is an option for pts with a very low-risk tumour (pT1aN0) or life-threatening comorbidities	• The efficacy of adjuvant endocrine therapy is independent of age. • Good compliance should be the driving factor for treatment choice and adjust it according to side effects. • The choice of agent and decisions on its duration should be made in the context of multimorbidities and estimated risk of breast cancer recurrence as side effects may limit compliance and impact substantially on health domains relevant to older patients (myalgia, arthralgia, osteoporosis, cardiovascular risk, cognition) • Aromatase inhibitors are slightly more beneficial than tamoxifen with regards to risk of recurrence and breast cancer mortality and should be considered the standard of care in older women • The extended use of an aromatase inhibitor after 5 years of tamoxifen is beneficial, while data are less clear if they are already use upfront	I IV IV IV I
Adjuvant bone modifying agents		• Bone health is influenced by systemic treatments for early breast cancer and its baseline assessment and monitoring are recommended in older patients • Adjuvant bone modifying agents improve bone health and may also reduce cancer recurrence risk and survival • Adjuvant bisphosphonates (either zoledronic acid 4mg every 6 months or clodronate 1600mg daily) should be offered to patients with moderate- to high-risk disease, regardless of age • Denosumab also improves bone health but provides no improvement in relapse risk and therefore should not be considered in this setting	IV I IV II
Metastatic breast cancer	<u>Chemotherapy</u> • Hormone treatment is the treatment of choice for older women with ER-positive metastatic breast cancer • Chemotherapy is indicated for ER-negative, hormone refractory, or rapidly progressing disease	<u>Chemotherapy</u> • Particular care should be paid to avoiding treatment-related toxicities; this may include adjustments to treatment schedules based on pharmacological or empirical data • Monotherapy is preferred over polychemotherapy regimens when possible	IV IV

	• Single agent chemotherapy and combination oral chemotherapy are feasible options in older pts • Dose reductions and schedule modifications are controversial, but should be considered based on pharmacology and toxicity <u>HER2-positive disease</u> • Pts with HER2-positive disease should receive HER2-targeted therapy and chemotherapy. In pts with HER2-positive ER-positive disease with a contraindication to chemotherapy or without life threatening disease, anti-HER2 therapy plus endocrine therapy is an option. In pts with HER2-positive ER-negative disease, trastuzumab monotherapy could be reasonable. • Bevacizumab is active in older pts in terms of increased PFS, however, toxicity and cost-efficacy are important issues that need to be further elaborated.	• All available chemotherapeutics can be used in principle like in younger persons. Recent data provides evidence for the use of single agent nab-paclitaxel and eribulin in older patients <u>HER2-positive disease</u> • Anti-HER2 therapy should be given unless contraindicated by impaired left ventricular ejection fraction, with treatment adjusted according to patient fitness. • A taxane, preferably paclitaxel, in combination with trastuzumab and pertuzumab is recommended as first-line therapy only in fit patients. It may cause unacceptable toxicity in non-fit patients • Endocrine therapy may be suitable in lieu of chemotherapy in patients with HR-positive disease • In unfit patients, taxanes-free chemotherapy backbones include metronomic cyclophosphamide, vinorelbine or capecitabine • Appropriate monitoring for diarrhoea caused by lapatinib and pertuzumab is required • T-DM1 may be used in second- or later lines of therapy in fit patients, with careful monitoring in frail patients	II I IV II II I IV
Targeted therapies		• CDK4/6 inhibitors in combination with endocrine therapy represent a suitable treatment in older patients, with frequent adjustments needed. • Endocrine therapy alone is still a reasonable first-line option in selected cases • Use of everolimus should be approached with caution and on a case-by-case basis due to its worse safety profile in older patients	III III II
Supportive care		• Due to increased physiological vulnerability and decreased functional reserve, older patients are at risk of decompensation whilst receiving cancer treatment • Guidelines exist for the supportive care of patients with cancer and should be followed in this cohort • For older persons, a threshold for the risk of occurrence of febrile neutropenia risk lower than 20% may be used.	IV IV IV

		• Particular care should be paid to digestive symptoms, malnutrition, pain control and depression. All these issues may be masked by concurrent issues or present in atypical fashion. • Older patients are more susceptible to changes in medications, side effects and drug interactions and as such diligent review and monitoring of all existing medications is vital.	IV IV
Drug safety and compliance	• Careful drug prescription is warranted because of physiological age-related pharmacokinetic alteration, comorbidities and polypharmacy • Renal function evaluation is mandatory for treatment with renally excreted or nephrotoxic drugs • A thorough medication review is advised, ideally involving a clinical pharmacist • Drug compliance should be actively promoted • Close adverse event monitoring to allow prompt intervention is recommended, since older pts have lower physiological reserve, side effects may present in an atypical fashion, and unaddressed toxicity may compromise compliance	• Older patients are more susceptible to changes in medications, side effects and drug interactions and as such diligent review and monitoring of all existing medications is vital. • The risk of treatment toxicity increases with age and multimorbidity, which may affect adherence to treatment and ultimately its efficacy • Patients with multimorbidities are at increased risk of non-adherence • Non-adherence to adjuvant endocrine is associated to reduced efficacy; close monitoring is recommended • Issues relating to language barriers, cultural differences, and a lack of literacy and numeracy should be considered in the context of poor compliance or adherence	Not applicable
Barriers to treatment	• Barriers to therapy should be identified and addressed • Special attention should be paid to comorbidity (particularly cognitive status, anxiety and depression) and social setting (particularly transport) that can influence pt decisions • Physician bias should not influence management • Family and/or caregivers cannot reliably predict pt preferences, and caregiver bias should not unduly influence management		Not applicable

Abbreviations: AIs: aromatase inhibitors; ALND: axillary lymph node dissection; BCS: breast conserving surgery; CGA: comprehensive geriatric assessment; CMF: cyclophosphamide, methotrexate, and fluorouracil; DCIS: ductal carcinoma insitu ER: oestrogen receptor; OS: overall survival; PBI: PFS: progression free survival; Pt/s: pt/s; SLNB: sentinel lymph node biopsy; TC: docetaxel and cyclophosphamide; WBRT: whole breast radiotherapy; y: years.

Table 2: Variables included in the Cancer and Aging Research Group (CARG) and Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH) risk scores.

Cancer and Aging Research Group (CARG) Chemotherapy Toxicity Calculator	Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH) tool
http://www.mycarg.org/Chemo_Toxicity_Calculator	https://www.moffitt.org/eforms/crashscoreform/
Patient-related factors • Age **Tumor-related factors** • Cancer type **Treatment-related factors** • Planned chemotherapy dose • Planned number of chemotherapy drugs **Laboratory values** • Hemoglobin level • Creatinine clearance **Geriatric assessment variables** • Hearing impairment • Number of falls in the past 6 months • Ability to take own medications • Limitations in walking one block • Limitations in social activities	**Patient-related factors** • Diastolic blood pressure • Eastern Cooperative Oncology Group Performance Status **Treatment-related factors** • Type of chemotherapy **Laboratory values** • Lactate dehydrogenase levels **Geriatric assessment variables** • Instrumental activities of daily living • Cognitive impairment • Malnutrition

Table 3: Published recommendations regarding the omission of radiotherapy post breast-conserving surgery (BCS) in low-risk patients.

Recommendations regarding omission of radiotherapy after breast conserving surgery in low-risk patients: National Institute for Care and Clinical Excellence (NICE) versus National Comprehensive Cancer Network (NCCN)	
NICE guidelines (2018)	**NCCN guidelines (2017)**
• A very low absolute risk of local recurrence, defined as women aged ≥65 years, T1N0, oestrogen receptor (ER)-positive, HER2-negative and grade 1-2 • Receipt of BCS for invasive breast cancer with clear margins • Commitment to take adjuvant endocrine therapy for ≥5 years	• Women aged ≥70 years with invasive breast cancer, clinically node negative, who will receive adjuvant endocrine therapy (aromatase inhibitor or tamoxifen)

Table 4: Chemotherapy in HER2-negative and HER2-positive disease in the adjuvant setting.

Chemotherapy in HER2-negative disease	
Regimens	**Comments**
AC x 4 (CMF x6) or TC x4	Validated in older patients
Weekly paclitaxel x 12	Option in HER2-negative unfit high-risk patients
Sequential anthracyclines taxanes	No data in the general older population, only to be considered for very high risk and fit patients
Capecitabine or weekly docetaxel	No indication
Primary prophylaxis of febrile neutropenia with G-CSF	Recommended in case of polychemotherapy, even with threshold for risk of febrile neutropenia occurrence lower than 20%
Chemotherapy and anti-HER2 therapy in HER2-positive disease	
Regimens	**Comments**
TC x 4 + trastuzumab	Validated without trastuzumab in a subgroup analysis of a randomized trial, but only one single arm combination phase II study available; not specific for older adults
Weekly paclitaxel x 12 + trastuzumab	Can be considered also in high-risk patients unsuitable for polychemotherapy
TCH x 6	Not tested in older patients and probably not suitable because of high dose carboplatin
Trastuzumab without chemotherapy	Can be considered only in patients unfit for chemotherapy (+ endocrine therapy if ER-positive)
Pertuzumab	Consider adding to trastuzumab only in high risk, node positive and fit patients if available despite scarce data on older adults are available

Primary prophylaxis of febrile neutropenia with G-CSF	Recommended in case of polychemotherapy administered every 3 weeks, even with threshold for risk of febrile neutropenia occurrence lower than 20%
Duration	One year of anti-HER2 therapy Shorter duration possible for small pN0 tumours or if cardiac issues

Abbreviations: ER, endocrine receptor; AC, adriamycin/cyclophosphamide; CMF, cyclophosphamide/methotrexate/5FU; TC, docetaxel/cyclophosphamide; G-CSF, granulocyte colony-stimulating factor; TCH, docetaxel/carboplatin/trastuzumab, AUC, area under the curve

Appendix: Further list of reference articles

Introduction

1. Biganzoli L, Marotti L, Hart CD, Cataliotti L, Cutuli B, Kühn T, et al. Quality indicators in breast cancer care: An update from the EUSOMA working group. Eur J Cancer. 2017;86:59-81.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin. 2019;69(1):7-34.
3. DeSantis CE, Ma J, Gaudet MM, Newman LA, Miller KD, Goding Sauer A, et al. Breast cancer statistics, 2019. CA Cancer J Clin. 2019;69(6):438-51.
4. Bagegni NA, Peterson LL. Age-related disparities in older women with breast cancer. Adv Cancer Res. 2020;146:23-56.
5. Cesari M, Marzetti E, Thiem U, Pérez-Zepeda MU, Abellan Van Kan G, Landi F, et al. The geriatric management of frailty as paradigm of "The end of the disease era". Eur J Intern Med. 2016;31:11-4.
6. Colloca G, Corsonello A, Marzetti E, Balducci L, Landi F, Extermann M, et al. Treating cancer in older and oldest old patients. Curr Pharm Des. 2015;21(13):1699-705.
7. Lichtman SM. Call for changes in clinical trial reporting of older patients with cancer. J Clin Oncol. 2012;30(8):893-4.
8. Hurria A, Levit LA, Dale W, Mohile SG, Muss HB, Fehrenbacher L, et al. Improving the Evidence Base for Treating Older Adults With Cancer: American Society of Clinical Oncology Statement. J Clin Oncol. 2015;33(32):3826-33.
9. Wildiers H, Kunkler I, Biganzoli L, Fracheboud J, Vlastos G, Bernard-Marty C, et al. Management of breast cancer in elderly individuals: recommendations of the International Society of Geriatric Oncology. Lancet Oncol. 2007;8(12):1101-15.
10. Biganzoli L, Wildiers H, Oakman C, Marotti L, Loibl S, Kunkler I, et al. Management of elderly patients with breast cancer: updated recommendations of the International Society of Geriatric Oncology (SIOG) and European Society of Breast Cancer Specialists (EUSOMA). Lancet Oncol. 2012;13(4):e148-60.
11. West S, King V, Carey T, Lohr KN, \McKoy N, Sutton SF, et al. Systems to Rate the Strength of Scientific Evidence. US Agency for Healthcare Research and Quality; 2002. Contract No.: AHRQ Publication No. 02-E016.
12. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci. 2001;56(3):M146-56.

General and worldwide concepts on ageing

13. Cohen HJ, Smith D, Sun CL, Tew W, Mohile SG, Owusu C, et al. Frailty as determined by a comprehensive geriatric assessment-derived deficit-accumulation index in older patients with cancer who receive chemotherapy. Cancer. 2016;122(24):3865-72.
14. Guerard EJ, Deal AM, Chang Y, Williams GR, Nyrop KA, Pergolotti M, et al. Frailty Index Developed From a Cancer-Specific Geriatric Assessment and the Association With Mortality Among Older Adults With Cancer. J Natl Compr Canc Netw. 2017;15(7):894-902.
15. Morley JE, Vellas B, van Kan GA, Anker SD, Bauer JM, Bernabei R, et al. Frailty consensus: a call to action. J Am Med Dir Assoc. 2013;14(6):392-7.
16. Mohile SG, Dale W, Somerfield MR, Schonberg MA, Boyd CM, Burhenn PS, et al. Practical Assessment and Management of Vulnerabilities in Older Patients Receiving Chemotherapy: ASCO Guideline for Geriatric Oncology. J Clin Oncol. 2018;36(22):2326-47.
17. NCCN. NCCN clinical practice guidelines in oncology version 3.2019 genetic/familial

high-risk assessment: breast and ovarian.; 2019.
18. Wasif N, Neville M, Gray R, Cronin P, Pockaj BA. Competing Risk of Death in Elderly Patients with Newly Diagnosed Stage I Breast Cancer. J Am Coll Surg. 2019;229(1):30-6.e1.

19. Dottorini L, Catena L, Sarno I, Di Menna G, Marte A, Novelli E, et al. The role of Geriatric screening tool (G8) in predicting side effect in older patients during therapy with aromatase inhibitor. J Geriatr Oncol. 2019;10(2):356-8.
20. Hamaker ME, Te Molder M, Thielen N, van Munster BC, Schiphorst AH, van Huis LH. The effect of a geriatric evaluation on treatment decisions and outcome for older cancer patients - A systematic review. J Geriatr Oncol. 2018;9(5):430-40.
21. Kenis C, Baitar A, Decoster L, De Grève J, Lobelle JP, Flamaing J, et al. The added value of geriatric screening and assessment for predicting overall survival in older patients with cancer. Cancer. 2018;124(18):3753-63.
22. Li D, Soto-Perez-de-Celis E, Hurria A. Geriatric Assessment and Tools for Predicting Treatment Toxicity in Older Adults With Cancer. Cancer J. 2017;23(4):206-10.
23. Puts MT, Santos B, Hardt J, Monette J, Girre V, Atenafu EG, et al. An update on a systematic review of the use of geriatric assessment for older adults in oncology. Ann Oncol. 2014;25(2):307-15.
24. Wildiers H, Heeren P, Puts M, Topinkova E, Janssen-Heijnen ML, Extermann M, et al. International Society of Geriatric Oncology consensus on geriatric assessment in older patients with cancer. J Clin Oncol. 2014;32(24):2595-603.
25. Honecker F, Harbeck N, Schnabel C, Wedding U, Waldenmaier D, Saupe S, et al. Geriatric assessment and biomarkers in patients with metastatic breast cancer receiving first-line mono-chemotherapy: Results from the randomized phase III PELICAN trial. J Geriatr Oncol. 2018;9(2):163-9.
26. Parks RM, Lakshmanan R, Winterbottom L, Al Morgan D, Cox K, Cheung KL. Comprehensive geriatric assessment for older women with early breast cancer - a systematic review of literature. World J Surg Oncol. 2012;10:88.
27. Mohile SG, Epstein RM, Hurria A, Heckler CE, Canin B, Culakova E, et al. Communication With Older Patients With Cancer Using Geriatric Assessment: A Cluster-Randomized Clinical Trial From the National Cancer Institute Community Oncology Research Program. JAMA Oncol. 2019;6(2):1-9.
28. Li D, Sun C-L, Kim H, Chung V, Koczywas M, Fakih M, et al. Geriatric assessment-driven intervention (GAIN) on chemotherapy toxicity in older adults with cancer: A randomized controlled trial. Journal of Clinical Oncology. 2020;38(15_suppl):12010-.
29. Mohile SG, Mohamed MR, Culakova E, Xu H, Loh KP, Magnuson A, et al. A geriatric assessment (GA) intervention to reduce treatment toxicity in older patients with advanced cancer: A University of Rochester Cancer Center NCI community oncology research program cluster randomized clinical trial (CRCT). Journal of Clinical Oncology. 2020;38(15_suppl):12009-.
30. Qian CL, Knight HP, Ferrone CR, Kunitake H, Castillo CF-d, Lanuti M, et al. Randomized trial of a perioperative geriatric intervention for older adults with cancer. Journal of Clinical Oncology. 2020;38(15_suppl):12012-.
31. Soo W-K, King M, Pope A, Parente P, Darzins P, Davis ID. Integrated geriatric assessment and treatment (INTEGERATE) in older people with cancer planned for systemic anticancer therapy. Journal of Clinical Oncology. 2020;38(15_suppl):12011-.
32. Decoster L, Van Puyvelde K, Mohile S, Wedding U, Basso U, Colloca G, et al. Screening tools for multidimensional health problems warranting a geriatric assessment in older cancer patients: an update on SIOG recommendations†. Ann Oncol. 2015;26(2):288-300.
33. Hamaker ME, Jonker JM, de Rooij SE, Vos AG, Smorenburg CH, van Munster BC. Frailty screening methods for predicting outcome of a comprehensive geriatric assessment in elderly patients with cancer: a systematic review. Lancet Oncol. 2012;13(10):e437-44.
34. Extermann M, Boler I, Reich RR, Lyman GH, Brown RH, DeFelice J, et al. Predicting the risk of chemotherapy toxicity in older patients: the Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH) score. Cancer. 2012;118(13):3377-86.
35. Hurria A, Togawa K, Mohile SG, Owusu C, Klepin HD, Gross CP, et al. Predicting chemotherapy toxicity in older adults with cancer: a prospective multicenter study. J Clin Oncol. 2011;29(25):3457-65.
36. Hurria A, Magnuson A, Gross CP, Tew WP, Klepin HD, Wildes TM, editors. Development and validation of a chemotherapy toxicity (Chemo Tox) risk score for older patients (pts) with breast cancer (BC) receiving adjuvant/neoadjuvant treatment (Adjuvant Tx): A R01 and BCRF funded

prospective multicenter student [abstract]. 2018 San Antonio Breast Cancer Symposium; 2018 2018 Dec 4-8; San Antonio, TX.
37. Soto-Perez-de-Celis E, Li D, Yuan Y, Lau YM, Hurria A. Functional versus chronological age: geriatric assessments to guide decision making in older patients with cancer. Lancet Oncol. 2018;19(6):e305-e16.
38. van de Water W, Bastiaannet E, Hille ET, Meershoek-Klein Kranenbarg EM, Putter H, Seynaeve CM, et al. Age-specific nonpersistence of endocrine therapy in postmenopausal patients diagnosed with hormone receptor-positive breast cancer: a TEAM study analysis. Oncologist. 2012;17(1):55-63.
39. Wulaningsih W, Garmo H, Ahlgren J, Holmberg L, Folkvaljon Y, Wigertz A, et al. Determinants of non-adherence to adjuvant endocrine treatment in women with breast cancer: the role of comorbidity. Breast Cancer Res Treat. 2018;172(1):167-77.
40. Daher M. Cultural beliefs and values in cancer patients. Ann Oncol. 2012;23 Suppl 3:66-9.
41. Solé-Auró A, Crimmins EM. Health of Immigrants in European countries. Int Migr Rev. 2008;42(4):861-76.
42. Kristiansen M, Razum O, Tezcan-Güntekin H, Krasnik A. Aging and health among migrants in a European perspective. Public Health Rev. 2016;37:20.
43. Soto-Perez-de-Celis E. Global geriatric oncology: One size does not fit all. J Geriatr Oncol. 2019;10(2):199-201.

Mammography screening and surveillance

44. Basu P, Ponti A, Anttila A, Ronco G, Senore C, Vale DB, et al. Status of implementation and organization of cancer screening in The European Union Member States-Summary results from the second European screening report. Int J Cancer. 2018;142(1):44-56.
45. European guidelines on breast cancer screening and diagnosis 2019 [Available from: https://ecibc.jrc.ec.europa.eu/recommendations/details/Professional/screeningage/70-74
46. Siu AL. Screening for Breast Cancer: U.S. Preventive Services Task Force Recommendation Statement. Ann Intern Med. 2016;164(4):279-96.
47. de Glas NA, de Craen AJ, Bastiaannet E, Op 't Land EG, Kiderlen M, van de Water W, et al. Effect of implementation of the mass breast cancer screening programme in older women in the Netherlands: population based study. Bmj. 2014;349:g5410.
48. García-Albéniz X, Hernán MA, Logan RW, Price M, Armstrong K, Hsu J. Continuation of Annual Screening Mammography and Breast Cancer Mortality in Women Older Than 70 Years. Ann Intern Med. 2020;172(6):381-9.
49. Nelson HD, Fu R, Cantor A, Pappas M, Daeges M, Humphrey L. Effectiveness of Breast Cancer Screening: Systematic Review and Meta-analysis to Update the 2009 U.S. Preventive Services Task Force Recommendation. Ann Intern Med. 2016;164(4):244-55.
50. Bredemeyer M. ACS Releases Guideline on Breast Cancer Screening. Am Fam Physician. 2016;93(8):711-2.
51. Freedman RA, Keating NL, Partridge AH, Muss HB, Hurria A, Winer EP. Surveillance Mammography in Older Patients With Breast Cancer-Can We Ever Stop?: A Review. JAMA Oncol. 2017;3(3):402-9.
52. Runowicz CD, Leach CR, Henry NL, Henry KS, Mackey HT, Cowens-Alvarado RL, et al. American Cancer Society/American Society of Clinical Oncology Breast Cancer Survivorship Care Guideline. CA Cancer J Clin. 2016;66(1):43-73.
53. Brownlee S, Chalkidou K, Doust J, Elshaug AG, Glasziou P, Heath I, et al. Evidence for overuse of medical services around the world. Lancet. 2017;390(10090):156-68.

Genetic screening and its implications

54. Chavarri-Guerra Y, Hendricks CB, Brown S, Marcum C, Hander M, Segota ZE, et al. The Burden of Breast Cancer Predisposition Variants Across The Age Spectrum Among 10 000 Patients. J Am Geriatr Soc. 2019;67(5):884-8.

55. Tung N, Lin NU, Kidd J, Allen BA, Singh N, Wenstrup RJ, et al. Frequency of Germline Mutations in 25 Cancer Susceptibility Genes in a Sequential Series of Patients With Breast Cancer. J Clin Oncol. 2016;34(13):1460-8.
56. Manahan ER, Kuerer HM, Sebastian M, Hughes KS, Boughey JC, Euhus DM, et al. Consensus Guidelines on Genetic` Testing for Hereditary Breast Cancer from the American Society of Breast Surgeons. Ann Surg Oncol. 2019;26(10):3025-31.
57. Kemp Z, Turnbull A, Yost S, Seal S, Mahamdallie S, Poyastro-Pearson E, et al. Evaluation of Cancer-Based Criteria for Use in Mainstream BRCA1 and BRCA2 Genetic Testing in Patients With Breast Cancer. JAMA Netw Open. 2019;2(5):e194428.
58. Robson M, Im SA, Senkus E, Xu B, Domchek SM, Masuda N, et al. Olaparib for Metastatic Breast Cancer in Patients with a Germline BRCA Mutation. N Engl J Med. 2017;377(6):523-33.
59. Liposits G, Loh KP, Soto-Perez-de-Celis E, Dumas L, Battisti NML, Kadambi S, et al. PARP inhibitors in older patients with ovarian and breast cancer: Young International Society of Geriatric Oncology review paper. J Geriatr Oncol. 2019;10(2):337-45.

Neoadjuvant systemic therapy

60. Mieog JS, van der Hage JA, van de Velde CJ. Preoperative chemotherapy for women with operable breast cancer. Cochrane Database Syst Rev. 2007(2):Cd005002.
61. Barcenas CH, Niu J, Zhang N, Zhang Y, Buchholz TA, Elting LS, et al. Risk of hospitalization according to chemotherapy regimen in early-stage breast cancer. J Clin Oncol. 2014;32(19):2010-7.
62. Pinder PC, Duan Z, Goodwin JS, Hortobagyi GN, Giordano SH. Congestive Heart Failure in Older Women Treated With Adjuvant Anthracycline Chemotherapy for Breast Cancer. Journal of Clinical Oncology. 2007;25(25):3808-15.
63. Rosenstock AS, Lei X, Tripathy D, Hortobagyi GN, Giordano SH, Chavez-MacGregor M. Short-term mortality in older patients treated with adjuvant chemotherapy for early-stage breast cancer. Breast Cancer Res Treat. 2016;157(2):339-50.
64. Masuda N, Lee SJ, Ohtani S, Im YH, Lee ES, Yokota I, et al. Adjuvant Capecitabine for Breast Cancer after Preoperative Chemotherapy. N Engl J Med. 2017;376(22):2147-59.
65. von Minckwitz G, Huang CS, Mano MS, Loibl S, Mamounas EP, Untch M, et al. Trastuzumab Emtansine for Residual Invasive HER2-Positive Breast Cancer. N Engl J Med. 2019;380(7):617-28.
66. Alba E, Calvo L, Albanell J, De la Haba JR, Arcusa Lanza A, Chacon JI, et al. Chemotherapy (CT) and hormonotherapy (HT) as neoadjuvant treatment in luminal breast cancer patients: results from the GEICAM/2006-03, a multicenter, randomized, phase-II study. Ann Oncol. 2012;23(12):3069-74.
67. Semiglazov VF, Semiglazov VV, Dashyan GA, Ziltsova EK, Ivanov VG, Bozhok AA, et al. Phase 2 randomized trial of primary endocrine therapy versus chemotherapy in postmenopausal patients with estrogen receptor-positive breast cancer. Cancer. 2007;110(2):244-54.
68. Spring LM, Gupta A, Reynolds KL, Gadd MA, Ellisen LW, Isakoff SJ, et al. Neoadjuvant Endocrine Therapy for Estrogen Receptor-Positive Breast Cancer: A Systematic Review and Meta-analysis. JAMA Oncol. 2016;2(11):1477-86.

Surgery

69. de Glas NA, Kiderlen M, Bastiaannet E, de Craen AJ, van de Water W, van de Velde CJ, et al. Postoperative complications and survival of elderly breast cancer patients: a FOCUS study analysis. Breast Cancer Res Treat. 2013;138(2):561-9.
70. Burstein HJ, Curigliano G, Loibl S, Dubsky P, Gnant M, Poortmans P, et al. Estimating the benefits of therapy for early-stage breast cancer: the St. Gallen International Consensus Guidelines for the primary therapy of early breast cancer 2019. Ann Oncol. 2019;30(10):1541-57.
71. Hind D, Wyld L, Beverley CB, Reed MW. Surgery versus primary endocrine therapy for operable primary breast cancer in elderly women (70 years plus). Cochrane Database Syst Rev. 2006(1):Cd004272.

72. Morgan JL, Reed MW, Wyld L. Primary endocrine therapy as a treatment for older women with operable breast cancer - a comparison of randomised controlled trial and cohort study findings. Eur J Surg Oncol. 2014;40(6):676-84.
73. Syed BM, Al-Khyatt W, Johnston SJ, Wong DW, Winterbottom L, Kennedy H, et al. Long-term clinical outcome of oestrogen receptor-positive operable primary breast cancer in older women: a large series from a single centre. Br J Cancer. 2011;104(9):1393-400.
74. Sagara Y, Mallory MA, Wong S, Aydogan F, DeSantis S, Barry WT, et al. Survival Benefit of Breast Surgery for Low-Grade Ductal Carcinoma In Situ: A Population-Based Cohort Study. JAMA Surg. 2015;150(8):739-45.
75. Ward EP, Weiss A, Blair SL. Incidence and treatments of DCIS in octogenarians: grade matters. Breast Cancer Res Treat. 2017;165(2):403-9.
76. Martelli G, Miceli R, Daidone MG, Vetrella G, Cerrotta AM, Piromalli D, et al. Axillary dissection versus no axillary dissection in elderly patients with breast cancer and no palpable axillary nodes: results after 15 years of follow-up. Ann Surg Oncol. 2011;18(1):125-33.
77. Giuliano AE, Ballman KV, McCall L, Beitsch PD, Brennan MB, Kelemen PR, et al. Effect of Axillary Dissection vs No Axillary Dissection on 10-Year Overall Survival Among Women With Invasive Breast Cancer and Sentinel Node Metastasis: The ACOSOG Z0011 (Alliance) Randomized Clinical Trial. Jama. 2017;318(10):918-26.
78. Donker M, van Tienhoven G, Straver ME, Meijnen P, van de Velde CJ, Mansel RE, et al. Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (EORTC 10981-22023 AMAROS): a randomised, multicentre, open-label, phase 3 non-inferiority trial. Lancet Oncol. 2014;15(12):1303-10.
79. Association of Breast Surgery Multidisciplinary Consensus Meeting on the further management of the malignant axillary node. London, UK; 2015.
80. Coates AS, Winer EP, Goldhirsch A, Gelber RD, Gnant M, Piccart-Gebhart M, et al. Tailoring therapies--improving the management of early breast cancer: St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2015. Ann Oncol. 2015;26(8):1533-46.
81. James R, McCulley SJ, Macmillan RD. Oncoplastic and reconstructive breast surgery in the elderly. Br J Surg. 2015;102(5):480-8.
82. Walton L, Ommen K, Audisio RA. Breast reconstruction in elderly women breast cancer: a review. Cancer Treat Rev. 2011;37(5):353-7.

Radiotherapy

83. McGale P, Taylor C, Correa C, Cutter D, Duane F, Ewertz M, et al. Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. Lancet. 2014;383(9935):2127-35.
84. Hughes KS, Schnaper LA, Bellon JR, Cirrincione CT, Berry DA, McCormick B, et al. Lumpectomy plus tamoxifen with or without irradiation in women age 70 years or older with early breast cancer: long-term follow-up of CALGB 9343. J Clin Oncol. 2013;31(19):2382-7.
85. Kunkler IH, Williams LJ, Jack WJ, Cameron DA, Dixon JM. Breast-conserving surgery with or without irradiation in women aged 65 years or older with early breast cancer (PRIME II): a randomised controlled trial. Lancet Oncol. 2015;16(3):266-73.
86. Shumway DA, Griffith KA, Sabel MS, Jones RD, Forstner JM, Bott-Kothari TL, et al. Surgeon and Radiation Oncologist Views on Omission of Adjuvant Radiotherapy for Older Women with Early-Stage Breast Cancer. Ann Surg Oncol. 2017;24(12):3518-26.
87. Gradishar WJ, Anderson BO, Balassanian R, Blair SL, Burstein HJ, Cyr A, et al. NCCN Guidelines Insights: Breast Cancer, Version 1.2017. J Natl Compr Canc Netw. 2017;15(4):433-51.
88. (NICE) NIfHaCE. Early and locally advanced breast cancer: diagnosis and management. 2018.
89. Bartelink H, Maingon P, Poortmans P, Weltens C, Fourquet A, Jager J, et al. Whole-breast irradiation with or without a boost for patients treated with breast-conserving surgery for early breast cancer: 20-year follow-up of a randomised phase 3 trial. Lancet Oncol. 2015;16(1):47-56.

90. Strnad V, Ott OJ, Hildebrandt G, Kauer-Dorner D, Knauerhase H, Major T, et al. 5-year results of accelerated partial breast irradiation using sole interstitial multicatheter brachytherapy versus whole-breast irradiation with boost after breast-conserving surgery for low-risk invasive and in-situ carcinoma of the female breast: a randomised, phase 3, non-inferiority trial. Lancet. 2016;387(10015):229-38.
91. Coles CE, Griffin CL, Kirby AM, Titley J, Agrawal RK, Alhasso A, et al. Partial-breast radiotherapy after breast conservation surgery for patients with early breast cancer (UK IMPORT LOW trial): 5-year results from a multicentre, randomised, controlled, phase 3, non-inferiority trial. Lancet. 2017;390(10099):1048-60.
92. Bloomfield DJ. Development of Postoperative Radiotherapy for Breast Cancer: UK Consensus Statements - a Model of Patient, Clinical and Commissioner Engagement? Clin Oncol (R Coll Radiol). 2017;29(10):639-41.
93. Poortmans PM, Collette S, Kirkove C, Van Limbergen E, Budach V, Struikmans H, et al. Internal Mammary and Medial Supraclavicular Irradiation in Breast Cancer. N Engl J Med. 2015;373(4):317-27.
94. Whelan TJ, Olivotto IA, Parulekar WR, Ackerman I, Chua BH, Nabid A, et al. Regional Nodal Irradiation in Early-Stage Breast Cancer. N Engl J Med. 2015;373(4):307-16.
95. Bartelink H. Regional nodal irradiation for early breast cancer; clinical benefit according to risk stratification. Breast. 2019;48 Suppl 1:S65-s8.
96. Poortmans P. Postmastectomy radiation in breast cancer with one to three involved lymph nodes: ending the debate. Lancet. 2014;383(9935):2104-6.
97. Oliai C, Hurvitz SA. Breast cancer: The debate over post-mastectomy radiotherapy should continue. Nat Rev Clin Oncol. 2015;12(10):567-8.
98. Recht A, Comen EA, Fine RE, Fleming GF, Hardenbergh PH, Ho AY, et al. Postmastectomy Radiotherapy: An American Society of Clinical Oncology, American Society for Radiation Oncology, and Society of Surgical Oncology Focused Guideline Update. Pract Radiat Oncol. 2016;6(6):e219-e34.
99. Kunkler IH, Canney P, van Tienhoven G, Russell NS. Elucidating the role of chest wall irradiation in 'intermediate-risk' breast cancer: the MRC/EORTC SUPREMO trial. Clin Oncol (R Coll Radiol). 2008;20(1):31-4.
100. Agrawal RK, Alhasso A, Barrett-Lee PJ, Bliss JM, Bliss P, Bloomfield D, et al. First results of the randomised UK FAST Trial of radiotherapy hypofractionation for treatment of early breast cancer (CRUKE/04/015). Radiother Oncol. 2011;100(1):93-100.
101. Goldhirsch A, Winer EP, Coates AS, Gelber RD, Piccart-Gebhart M, Thürlimann B, et al. Personalizing the treatment of women with early breast cancer: highlights of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2013. Ann Oncol. 2013;24(9):2206-23.
102. Kirova YM, Campana F, Savignoni A, Laki F, Muresan M, Dendale R, et al. Breast-conserving treatment in the elderly: long-term results of adjuvant hypofractionated and normofractionated radiotherapy. Int J Radiat Oncol Biol Phys. 2009;75(1):76-81.
103. Kunkler IH, Audisio R, Belkacemi Y, Betz M, Gore E, Hoffe S, et al. Review of current best practice and priorities for research in radiation oncology for elderly patients with cancer: the International Society of Geriatric Oncology (SIOG) task force. Ann Oncol. 2014;25(11):2134-46.
104. Murray Brunt A, Haviland JS, Wheatley DA, Sydenham MA, Alhasso A, Bloomfield DJ, et al. Hypofractionated breast radiotherapy for 1 week versus 3 weeks (FAST-Forward): 5-year efficacy and late normal tissue effects results from a multicentre, non-inferiority, randomised, phase 3 trial. The Lancet. 2020;395(10237):1613-26.

Adjuvant systemic therapy

Adjuvant chemotherapy for HER2-negative disease

105. Muss HB, Polley MC, Berry DA, Liu H, Cirrincione CT, Theodoulou M, et al. Randomized Trial of Standard Adjuvant Chemotherapy Regimens Versus Capecitabine in Older Women With Early Breast Cancer: 10-Year Update of the CALGB 49907 Trial. J Clin Oncol. 2019;37(26):2338-48.

106. Elkin EB, Hurria A, Mitra N, Schrag D, Panageas KS. Adjuvant chemotherapy and survival in older women with hormone receptor-negative breast cancer: assessing outcome in a population-based, observational cohort. J Clin Oncol. 2006;24(18):2757-64.
107. Giordano SH, Duan Z, Kuo YF, Hortobagyi GN, Goodwin JS. Use and outcomes of adjuvant chemotherapy in older women with breast cancer. J Clin Oncol. 2006;24(18):2750-6.
108. Tamirisa N, Lin H, Shen Y, Shaitelman SF, Sri Karuturi M, Giordano SH, et al. Association of Chemotherapy With Survival in Elderly Patients With Multiple Comorbidities and Estrogen Receptor-Positive, Node-Positive Breast Cancer. JAMA Oncol. 2020.
109. Battisti NML, McCartney A, Biganzoli L. The Conundrum of the Association of Chemotherapy With Survival Outcomes Among Elderly Patients With Curable Luminal Breast Cancer. JAMA Oncol. 2020.
110. Shak S, Miller DP, Howlader N, Gliner N, Howe W, Schussler N, et al., editors. Outcome disparities by age and 21-gene recurrence score results in hormone receptor positive (HR+) breast cancer. European Society for Medical Oncology (ESMO); 2016; Copenhagen, Denmark.
111. Kizy S, Altman AM, Marmor S, Denbo JW, Jensen EH, Tuttle TM, et al. 21-gene recurrence score testing in the older population with estrogen receptor-positive breast cancer. J Geriatr Oncol. 2019;10(2):322-9.
112. Coussy F, Mir O, Bourbouloux E, editors. ASTER 70S or optimal adjuvant treatment for women over 70 with luminal breast cancer: a GERICO/UNICANCER phase III trial (abstract 1362). International Society of Geriatric Oncology (SIOG); 2016; Milan, Italy.
113. de Glas NA, van de Water W, Engelhardt EG, Bastiaannet E, de Craen AJ, Kroep JR, et al. Validity of Adjuvant! Online program in older patients with breast cancer: a population-based study. Lancet Oncol. 2014;15(7):722-9.
114. de Glas NA, Bastiaannet E, Engels CC, de Craen AJ, Putter H, van de Velde CJ, et al. Validity of the online PREDICT tool in older patients with breast cancer: a population-based study. Br J Cancer. 2016;114(4):395-400.
115. Muss HB, Woolf S, Berry D, Cirrincione C, Weiss RB, Budman D, et al. Adjuvant chemotherapy in older and younger women with lymph node-positive breast cancer. Jama. 2005;293(9):1073-81.
116. Peto R, Davies C, Godwin J, Gray R, Pan HC, Clarke M, et al. Comparisons between different polychemotherapy regimens for early breast cancer: meta-analyses of long-term outcome among 100,000 women in 123 randomised trials. Lancet. 2012;379(9814):432-44.
117. Wildiers H, Brain E. Different adjuvant chemotherapy regimens in older breast cancer patients? Ann Oncol. 2015;26(4):613-5.
118. Perrone F, Nuzzo F, Di Rella F, Gravina A, Iodice G, Labonia V, et al. Weekly docetaxel versus CMF as adjuvant chemotherapy for older women with early breast cancer: final results of the randomized phase III ELDA trial. Ann Oncol. 2015;26(4):675-82.
119. Increasing the dose intensity of chemotherapy by more frequent administration or sequential scheduling: a patient-level meta-analysis of 37 298 women with early breast cancer in 26 randomised trials. Lancet. 2019;393(10179):1440-52.
120. Caparica R, Bruzzone M, Poggio F, Ceppi M, de Azambuja E, Lambertini M. Anthracycline and taxane-based chemotherapy versus docetaxel and cyclophosphamide in the adjuvant treatment of HER2-negative breast cancer patients: a systematic review and meta-analysis of randomized controlled trials. Breast Cancer Res Treat. 2019;174(1):27-37.
121. Jones S, Holmes FA, O'Shaughnessy J, Blum JL, Vukelja SJ, McIntyre KJ, et al. Docetaxel With Cyclophosphamide Is Associated With an Overall Survival Benefit Compared With Doxorubicin and Cyclophosphamide: 7-Year Follow-Up of US Oncology Research Trial 9735. J Clin Oncol. 2009;27(8):1177-83.
122. Colleoni M, Price KN, Castiglione-Gertsch M, Gelber RD, Coates AS, Goldhirsch A. Mortality during adjuvant treatment of early breast cancer with cyclophosphamide, methotrexate, and fluorouracil. International Breast Cancer Study Group. Lancet. 1999;354(9173):130-1.
123. Muss HB, Berry DA, Cirrincione C, Budman DR, Henderson IC, Citron ML, et al. Toxicity of Older and Younger Patients Treated With Adjuvant Chemotherapy for Node-Positive Breast Cancer: The Cancer and Leukemia Group B Experience. Journal of Clinical Oncology. 2007;25(24):3699-704.

124. Crivellari D, Bonetti M, Castiglione-Gertsch M, Gelber RD, Rudenstam CM, Thurlimann B, et al. Burdens and benefits of adjuvant cyclophosphamide, methotrexate, and fluorouracil and tamoxifen for elderly patients with breast cancer: the International Breast Cancer Study Group Trial VII. J Clin Oncol. 2000;18(7):1412-22.
125. Bandos H, Melnikow J, Rivera DR, Swain SM, Sturtz K, Fehrenbacher L, et al. Long-term Peripheral Neuropathy in Breast Cancer Patients Treated With Adjuvant Chemotherapy: NRG Oncology/NSABP B-30. Journal of the National Cancer Institute. 2018;110(2).
126. Hershman DL, Till C, Wright JD, Awad D, Ramsey SD, Barlow WE, et al. Comorbidities and Risk of Chemotherapy-Induced Peripheral Neuropathy Among Participants 65 Years or Older in Southwest Oncology Group Clinical Trials. J Clin Oncol. 2016;34(25):3014-22.
127. Brouwers B, Hatse S, Dal Lago L, Neven P, Vuylsteke P, Dalmasso B, et al. The impact of adjuvant chemotherapy in older breast cancer patients on clinical and biological aging parameters. Oncotarget. 2016;7(21):29977-88.
128. Hopkins JO, Allred J, Hurria A, Jatoi A, Lafky JM, Cohen H, et al. Lymphedema, musculoskeletal events and arm function in older patients receiving adjuvant chemotherapy for breast cancer (Alliance A171302). Breast Cancer Res Treat. 2017;166(3):793-808.
129. Lange M, Heutte N, Rigal O, Noal S, Kurtz JE, Levy C, et al. Decline in Cognitive Function in Older Adults With Early-Stage Breast Cancer After Adjuvant Treatment. Oncologist. 2016.
130. Hurria A, Soto-Perez-de-Celis E, Allred JB, Cohen HJ, Arsenyan A, Ballman K, et al. Functional Decline and Resilience in Older Women Receiving Adjuvant Chemotherapy for Breast Cancer. Journal of the American Geriatrics Society. 2019;67(5):920-7.
131. Sanoff HK, Deal AM, Krishnamurthy J, Torrice C, Dillon P, Sorrentino J, et al. Effect of cytotoxic chemotherapy on markers of molecular age in patients with breast cancer. Journal of the National Cancer Institute. 2014;106(4):dju057.

Adjuvant anti-HER2 therapy

132. Cameron D, Piccart-Gebhart MJ, Gelber RD, Procter M, Goldhirsch A, de Azambuja E, et al. 11 years' follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive early breast cancer: final analysis of the HERceptin Adjuvant (HERA) trial. Lancet. 2017;389(10075):1195-205.
133. Perez EA, Romond EH, Suman VJ, Jeong JH, Sledge G, Geyer CE, Jr., et al. Trastuzumab plus adjuvant chemotherapy for human epidermal growth factor receptor 2-positive breast cancer: planned joint analysis of overall survival from NSABP B-31 and NCCTG N9831. J Clin Oncol. 2014;32(33):3744-52.
134. Chan A, Delaloge S, Holmes FA, Moy B, Iwata H, Harvey VJ, et al. Neratinib after trastuzumab-based adjuvant therapy in patients with HER2-positive breast cancer (ExteNET): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 2016;17(3):367-77.
135. Brain E, Caillet P, de Glas N, Biganzoli L, Cheng K, Lago LD, et al. HER2-targeted treatment for older patients with breast cancer: An expert position paper from the International Society of Geriatric Oncology. J Geriatr Oncol. 2019;10(6):1003-13.
136. Tolaney SM, Guo H, Pernas S, Barry WT, Dillon DA, Ritterhouse L, et al. Seven-Year Follow-Up Analysis of Adjuvant Paclitaxel and Trastuzumab Trial for Node-Negative, Human Epidermal Growth Factor Receptor 2-Positive Breast Cancer. J Clin Oncol. 2019;37(22):1868-75.
137. Sawaki M, Taira N, Uemura Y, Saito T, Baba S, Kobayashi K, et al. Randomized Controlled Trial of Trastuzumab With or Without Chemotherapy for HER2-Positive Early Breast Cancer in Older Patients. J Clin Oncol. 2020:Jco2000184.
138. Kramar A, Bachelot T, Madrange N, Pierga JY, Kerbrat P, Espié M, et al. Trastuzumab duration effects within patient prognostic subgroups in the PHARE trial. Ann Oncol. 2014;25(8):1563-70.
139. Reeder-Hayes KE, Meyer AM, Hinton SP, Meng K, Carey LA, Dusetzina SB. Comparative Toxicity and Effectiveness of Trastuzumab-Based Chemotherapy Regimens in Older Women With Early-Stage Breast Cancer. J Clin Oncol. 2017;35(29):3298-305.
140. Romond EH, Jeong JH, Rastogi P, Swain SM, Geyer CE, Jr., Ewer MS, et al. Seven-year follow-up assessment of cardiac function in NSABP B-31, a randomized trial comparing doxorubicin

and cyclophosphamide followed by paclitaxel (ACP) with ACP plus trastuzumab as adjuvant therapy for patients with node-positive, human epidermal growth factor receptor 2-positive breast cancer. J Clin Oncol. 2012;30(31):3792-9.
141. Thavendiranathan P, Abdel-Qadir H, Fischer HD, Camacho X, Amir E, Austin PC, et al. Breast Cancer Therapy-Related Cardiac Dysfunction in Adult Women Treated in Routine Clinical Practice: A Population-Based Cohort Study. J Clin Oncol. 2016;34(19):2239-46.
142. Vaz-Luis I, Keating NL, Lin NU, Lii H, Winer EP, Freedman RA. Duration and toxicity of adjuvant trastuzumab in older patients with early-stage breast cancer: a population-based study. J Clin Oncol. 2014;32(9):927-34.
143. Wang SY, Long JB, Hurria A, Owusu C, Steingart RM, Gross CP, et al. Cardiovascular events, early discontinuation of trastuzumab, and their impact on survival. Breast Cancer Res Treat. 2014;146(2):411-9.

Adjuvant endocrine therapy

144. Christiansen P, Bjerre K, Ejlertsen B, Jensen MB, Rasmussen BB, Laenkholm AV, et al. Mortality rates among early-stage hormone receptor-positive breast cancer patients: a population-based cohort study in Denmark. Journal of the National Cancer Institute. 2011;103(18):1363-72.
145. Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials. Lancet. 2015;386(10001):1341-52.
146. Ruhstaller T, Giobbie-Hurder A, Colleoni M, Jensen MB, Ejlertsen B, de Azambuja E, et al. Adjuvant Letrozole and Tamoxifen Alone or Sequentially for Postmenopausal Women With Hormone Receptor-Positive Breast Cancer: Long-Term Follow-Up of the BIG 1-98 Trial. J Clin Oncol. 2019;37(2):105-14.
147. Kidwell KM, Harte SE, Hayes DF, Storniolo AM, Carpenter J, Flockhart DA, et al. Patient-reported symptoms and discontinuation of adjuvant aromatase inhibitor therapy. Cancer. 2014;120(16):2403-11.
148. Wagner LI, Zhao F, Goss PE, Chapman JW, Shepherd LE, Whelan TJ, et al. Patient-reported predictors of early treatment discontinuation: treatment-related symptoms and health-related quality of life among postmenopausal women with primary breast cancer randomized to anastrozole or exemestane on NCIC Clinical Trials Group (CCTG) MA.27 (E1Z03). Breast Cancer Res Treat. 2018;169(3):537-48.
149. Amir E, Seruga B, Niraula S, Carlsson L, Ocana A. Toxicity of adjuvant endocrine therapy in postmenopausal breast cancer patients: a systematic review and meta-analysis. Journal of the National Cancer Institute. 2011;103(17):1299-309.
150. Hamood R, Hamood H, Merhasin I, Keinan-Boker L. Diabetes After Hormone Therapy in Breast Cancer Survivors: A Case-Cohort Study. J Clin Oncol. 2018;36(20):2061-9.
151. Matthews A, Stanway S, Farmer RE, Strongman H, Thomas S, Lyon AR, et al. Long term adjuvant endocrine therapy and risk of cardiovascular disease in female breast cancer survivors: systematic review. Bmj. 2018;363:k3845.
152. Ganz PA, Petersen L, Bower JE, Crespi CM. Impact of Adjuvant Endocrine Therapy on Quality of Life and Symptoms: Observational Data Over 12 Months From the Mind-Body Study. J Clin Oncol. 2016;34(8):816-24.
153. Phillips KA, Ribi K, Sun Z, Stephens A, Thompson A, Harvey V, et al. Cognitive function in postmenopausal women receiving adjuvant letrozole or tamoxifen for breast cancer in the BIG 1-98 randomized trial. Breast. 2010;19(5):388-95.
154. Hong N, Yoon HG, Seo DH, Park S, Kim SI, Sohn JH, et al. Different patterns in the risk of newly developed fatty liver and lipid changes with tamoxifen versus aromatase inhibitors in postmenopausal women with early breast cancer: A propensity score-matched cohort study. Eur J Cancer. 2017;82:103-14.
155. Jin H, Tu D, Zhao N, Shepherd LE, Goss PE. Longer-term outcomes of letrozole versus placebo after 5 years of tamoxifen in the NCIC CTG MA.17 trial: analyses adjusting for treatment crossover. J Clin Oncol. 2012;30(7):718-21.

156. Blok EJ, Kroep JR, Meershoek-Klein Kranenbarg E, Duijm-de Carpentier M, Putter H, van den Bosch J, et al. Optimal Duration of Extended Adjuvant Endocrine Therapy for Early Breast Cancer; Results of the IDEAL Trial (BOOG 2006-05). Journal of the National Cancer Institute. 2018;110(1).
157. Goss PE, Ingle JN, Pritchard KI, Robert NJ, Muss H, Gralow J, et al. Extending Aromatase-Inhibitor Adjuvant Therapy to 10 Years. N Engl J Med. 2016;375(3):209-19.
158. Mamounas EP, Bandos H, Lembersky BC, Jeong JH, Geyer CE, Jr., Rastogi P, et al. Use of letrozole after aromatase inhibitor-based therapy in postmenopausal breast cancer (NRG Oncology/NSABP B-42): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 2019;20(1):88-99.
159. Tjan-Heijnen VCG, van Hellemond IEG, Peer PGM, Swinkels ACP, Smorenburg CH, van der Sangen MJC, et al. Extended adjuvant aromatase inhibition after sequential endocrine therapy (DATA): a randomised, phase 3 trial. Lancet Oncol. 2017;18(11):1502-11.
160. Goldvaser H, Barnes TA, Seruga B, Cescon DW, Ocana A, Ribnikar D, et al. Toxicity of Extended Adjuvant Therapy With Aromatase Inhibitors in Early Breast Cancer: A Systematic Review and Meta-analysis. Journal of the National Cancer Institute. 2018;110(1).
161. Rossi L, McCartney A, De Santo I, Risi E, Moretti E, Malorni L, et al. The optimal duration of adjuvant endocrine therapy in early luminal breast cancer: A concise review. Cancer Treat Rev. 2019;74:29-34.

Adjuvant bone modifying agents

162. Gralow JR, Biermann JS, Farooki A, Fornier MN, Gagel RF, Kumar R, et al. NCCN Task Force Report: Bone Health In Cancer Care. J Natl Compr Canc Netw. 2013;11 Suppl 3:S1-50; quiz S1.
163. O'Carrigan B, Wong MH, Willson ML, Stockler MR, Pavlakis N, Goodwin A. Bisphosphonates and other bone agents for breast cancer. Cochrane Database Syst Rev. 2017;10(10):Cd003474.
164. Adjuvant bisphosphonate treatment in early breast cancer: meta-analyses of individual patient data from randomised trials. Lancet. 2015;386(10001):1353-61.
165. Dhesy-Thind S, Fletcher GG, Blanchette PS, Clemons MJ, Dillmon MS, Frank ES, et al. Use of Adjuvant Bisphosphonates and Other Bone-Modifying Agents in Breast Cancer: A Cancer Care Ontario and American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol. 2017;35(18):2062-81.
166. Hadji P, Coleman RE, Wilson C, Powles TJ, Clezardin P, Aapro M, et al. Adjuvant bisphosphonates in early breast cancer: consensus guidance for clinical practice from a European Panel. Ann Oncol. 2016;27(3):379-90.
167. Coleman R, Woodward E, Brown J, Cameron D, Bell R, Dodwell D, et al. Safety of zoledronic acid and incidence of osteonecrosis of the jaw (ONJ) during adjuvant therapy in a randomised phase III trial (AZURE: BIG 01-04) for women with stage II/III breast cancer. Breast Cancer Res Treat. 2011;127(2):429-38.
168. Mauri D, Valachis A, Polyzos IP, Polyzos NP, Kamposioras K, Pesce LL. Osteonecrosis of the jaw and use of bisphosphonates in adjuvant breast cancer treatment: a meta-analysis. Breast Cancer Res Treat. 2009;116(3):433-9.
169. Gnant M, Pfeiler G, Steger GG, Egle D, Greil R, Fitzal F, et al. Adjuvant denosumab in postmenopausal patients with hormone receptor-positive breast cancer (ABCSG-18): disease-free survival results from a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 2019;20(3):339-51.
170. Coleman RE, Finkelstein D, Barrios CH, Martin M, Iwata H, Glaspy JA, et al. Adjuvant denosumab in early breast cancer: First results from the international multicenter randomized phase III placebo controlled D-CARE study. Journal of Clinical Oncology. 2018;36(15_suppl):501-.
171. Cummings SR, Ferrari S, Eastell R, Gilchrist N, Jensen JB, McClung M, et al. Vertebral Fractures After Discontinuation of Denosumab: A Post Hoc Analysis of the Randomized Placebo-Controlled FREEDOM Trial and Its Extension. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research. 2018;33(2):190-8.

Systemic treatment for metastatic disease

172. Lichtman SM, Wildiers H, Chatelut E, Steer C, Budman D, Morrison VA, et al. International Society of Geriatric Oncology Chemotherapy Taskforce: evaluation of chemotherapy in older patients--an analysis of the medical literature. J Clin Oncol. 2007;25(14):1832-43.
173. Barginear M, Dueck AC, Allred JB, Bunnell C, Cohen HJ, Freedman RA, et al. Age and the Risk of Paclitaxel-Induced Neuropathy in Women with Early-Stage Breast Cancer (Alliance A151411): Results from 1,881 Patients from Cancer and Leukemia Group B (CALGB) 40101. Oncologist. 2019;24(5):617-23.
174. Biganzoli L, Aapro M, Loibl S, Wildiers H, Brain E. Taxanes in the treatment of breast cancer: Have we better defined their role in older patients? A position paper from a SIOG Task Force. Cancer Treat Rev. 2016;43:19-26.
175. Hurria A, Soto-Perez-de-Celis E, Blanchard S, Burhenn P, Yeon CH, Yuan Y, et al. A Phase II Trial of Older Adults With Metastatic Breast Cancer Receiving nab-Paclitaxel: Melding the Fields of Geriatrics and Oncology. Clin Breast Cancer. 2019;19(2):89-96.
176. Aapro M, Tjulandin S, Bhar P, Gradishar W. Weekly nab-paclitaxel is safe and effective in ≥65 years old patients with metastatic breast cancer: a post-hoc analysis. Breast. 2011;20(5):468-74.
177. Biganzoli L, Cinieri S, Berardi R, Pedersini R, McCartney A, Minisini AM, et al. EFFECT: a randomized phase II study of efficacy and impact on function of two doses of nab-paclitaxel as first-line treatment in older women with advanced breast cancer. Breast Cancer Res. 2020;22(1):83.
178. Muss H, Cortes J, Vahdat LT, Cardoso F, Twelves C, Wanders J, et al. Eribulin monotherapy in patients aged 70 years and older with metastatic breast cancer. Oncologist. 2014;19(4):318-27.
179. Leo S, Arnoldi E, Repetto L, Coccorullo Z, Cinieri S, Fedele P, et al. Eribulin Mesylate as Third or Subsequent Line Chemotherapy for Elderly Patients with Locally Recurrent or Metastatic Breast Cancer: A Multicentric Observational Study of GIOGer (Italian Group of Geriatric Oncology)-ERIBE. Oncologist. 2019;24(6):e232-e40.
180. Wildiers H, Tryfonidis K, Dal Lago L, Vuylsteke P, Curigliano G, Waters S, et al. Pertuzumab and trastuzumab with or without metronomic chemotherapy for older patients with HER2-positive metastatic breast cancer (EORTC 75111-10114): an open-label, randomised, phase 2 trial from the Elderly Task Force/Breast Cancer Group. Lancet Oncol. 2018;19(3):323-36.
181. Huober J, Weder P, Veyret C, Thürlimann B, Xyrafas A, Vanlemmens L, et al. PERNETTA: A non-comparative randomized open label phase II trial of pertuzumab (P) + trastuzumab (T) with or without chemotherapy both followed by T-DM1 in case of progression, in patients with HER2-positive metastatic breast cancer (MBC): (SAKK 22/10 / UNICANCER UC-0140/1207). Annals of Oncology. 2018;29:viii93.
182. Perez EA, López-Vega JM, Petit T, Zamagni C, Easton V, Kamber J, et al. Safety and efficacy of vinorelbine in combination with pertuzumab and trastuzumab for first-line treatment of patients with HER2-positive locally advanced or metastatic breast cancer: VELVET Cohort 1 final results. Breast Cancer Res. 2016;18(1):126.
183. Rimawi M, Ferrero JM, de la Haba-Rodriguez J, Poole C, De Placido S, Osborne CK, et al. First-Line Trastuzumab Plus an Aromatase Inhibitor, With or Without Pertuzumab, in Human Epidermal Growth Factor Receptor 2-Positive and Hormone Receptor-Positive Metastatic or Locally Advanced Breast Cancer (PERTAIN): A Randomized, Open-Label Phase II Trial. J Clin Oncol. 2018;36(28):2826-35.
184. Johnston SRD, Hegg R, Im SA, Park IH, Burdaeva O, Kurteva G, et al. Phase III, Randomized Study of Dual Human Epidermal Growth Factor Receptor 2 (HER2) Blockade With Lapatinib Plus Trastuzumab in Combination With an Aromatase Inhibitor in Postmenopausal Women With HER2-Positive, Hormone Receptor-Positive Metastatic Breast Cancer: ALTERNATIVE. J Clin Oncol. 2018;36(8):741-8.
185. Rugo HS, Turner NC, Finn RS, Joy AA, Verma S, Harbeck N, et al. Palbociclib plus endocrine therapy in older women with HR+/HER2- advanced breast cancer: a pooled analysis of randomised PALOMA clinical studies. Eur J Cancer. 2018;101:123-33.

186. Sonke GS, Hart LL, Campone M, Erdkamp F, Janni W, Verma S, et al. Ribociclib with letrozole vs letrozole alone in elderly patients with hormone receptor-positive, HER2-negative breast cancer in the randomized MONALEESA-2 trial. Breast Cancer Res Treat. 2018;167(3):659-69.
187. Goetz MP, Okera M, Wildiers H, editors. Safety and Efficacy of Abemaciclib plus endocrine therapy in Elderly patients with HR+, HER2- advanced breast cancer: an age-specific subgroup analysis of MONARCH2 and 3 trials. San Antonio Breast Cancer Symposium; 2019; San Antonio, TX.
188. Howie LJ, Singh H, Bloomquist E, Wedam S, Amiri-Kordestani L, Tang S, et al. Outcomes of Older Women With Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor-Negative Metastatic Breast Cancer Treated With a CDK4/6 Inhibitor and an Aromatase Inhibitor: An FDA Pooled Analysis. J Clin Oncol. 2019;37(36):3475-83.
189. Battisti NML, De Glas N, Sedrak MS, Loh KP, Liposits G, Soto-Perez-de-Celis E, et al. Use of cyclin-dependent kinase 4/6 (CDK4/6) inhibitors in older patients with ER-positive HER2-negative breast cancer: Young International Society of Geriatric Oncology review paper. Ther Adv Med Oncol. 2018;10:1758835918809610.
190. Pritchard KI, Burris HA, 3rd, Ito Y, Rugo HS, Dakhil S, Hortobagyi GN, et al. Safety and efficacy of everolimus with exemestane vs. exemestane alone in elderly patients with HER2-negative, hormone receptor-positive breast cancer in BOLERO-2. Clin Breast Cancer. 2013;13(6):421-32.e8.
191. Jerusalem G, Mariani G, Ciruelos EM, Martin M, Tjan-Heijnen VC, Neven P, et al. Safety of everolimus plus exemestane in patients with hormone-receptor-positive, HER2-negative locally advanced or metastatic breast cancer progressing on prior non-steroidal aromatase inhibitors: primary results of a phase IIIb, open-label, single-arm, expanded-access multicenter trial (BALLET). Ann Oncol. 2016;27(9):1719-25.

Supportive care

192. Roila F, Molassiotis A, Herrstedt J, Aapro M, Gralla RJ, Bruera E, et al. 2016 MASCC and ESMO guideline update for the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting and of nausea and vomiting in advanced cancer patients. Ann Oncol. 2016;27(suppl 5):v119-v33.
193. Bossi P, Antonuzzo A, Cherny NI, Rosengarten O, Pernot S, Trippa F, et al. Diarrhoea in adult cancer patients: ESMO Clinical Practice Guidelines. Ann Oncol. 2018;29(Suppl 4):iv126-iv42.
194. Larkin PJ, Cherny NI, La Carpia D, Guglielmo M, Ostgathe C, Scotté F, et al. Diagnosis, assessment and management of constipation in advanced cancer: ESMO Clinical Practice Guidelines. Ann Oncol. 2018;29 Suppl 4:iv111-iv25.
195. Peterson DE, Boers-Doets CB, Bensadoun RJ, Herrstedt J. Management of oral and gastrointestinal mucosal injury: ESMO Clinical Practice Guidelines for diagnosis, treatment, and follow-up. Ann Oncol. 2015;26 Suppl 5:v139-51.
196. Leij-Halfwerk S, Verwijs MH, van Houdt S, Borkent JW, Guaitoli PR, Pelgrim T, et al. Prevalence of protein-energy malnutrition risk in European older adults in community, residential and hospital settings, according to 22 malnutrition screening tools validated for use in adults ≥65 years: A systematic review and meta-analysis. Maturitas. 2019;126:80-9.
197. Bellera CA, Rainfray M, Mathoulin-Pélissier S, Mertens C, Delva F, Fonck M, et al. Screening older cancer patients: first evaluation of the G-8 geriatric screening tool. Ann Oncol. 2012;23(8):2166-72.
198. Muscaritoli M, Arends J, Aapro M. From guidelines to clinical practice: a roadmap for oncologists for nutrition therapy for cancer patients. Ther Adv Med Oncol. 2019;11:1758835919880084.
199. Williams S, Dale J. The effectiveness of treatment for depression/depressive symptoms in adults with cancer: a systematic review. Br J Cancer. 2006;94(3):372-90.
200. Henry NL, Stearns V, Flockhart DA, Hayes DF, Riba M. Drug interactions and pharmacogenomics in the treatment of breast cancer and depression. Am J Psychiatry. 2008;165(10):1251-5.
201. Urban D, Cherny N, Catane R. The management of cancer pain in the elderly. Crit Rev Oncol Hematol. 2010;73(2):176-83.

202. Fallon M, Giusti R, Aielli F, Hoskin P, Rolke R, Sharma M, et al. Management of cancer pain in adult patients: ESMO Clinical Practice Guidelines. Ann Oncol. 2018;29(Suppl 4):iv166-iv91.
203. Klastersky J, de Naurois J, Rolston K, Rapoport B, Maschmeyer G, Aapro M, et al. Management of febrile neutropaenia: ESMO Clinical Practice Guidelines. Ann Oncol. 2016;27(suppl 5):v111-v8.