

# Management of breast cancer in elderly patients

Elisa Vicini<sup>1</sup>, Vikram Swaminathan<sup>2</sup> & Riccardo Alberto Audisio<sup>\*3</sup>



## Practice Points

- Breast cancer mortality rates have decreased in recent years for younger women but not for elderly patients.
- Upper age limit extension for mammographic screening benefits should be balanced with costs.
- Older women usually show less aggressive tumors with hormonal receptors.
- Frailty is an essential part of geriatric assessment, which is crucial to choose the appropriate treatment for elderly women.
- Primary systemic treatment should be considered to obtain tumor shrinkage and improve the surgical options, to test the treatment response and to improve long-term disease-free survival; close monitoring of efficacy and toxicity should be mandatory.
- Age should not represent a contraindication for breast-conservative surgery and breast reconstruction. The real advantage of axillary surgery in older breast cancer patients is still controversial.
- There is still no subgroup of older patients in whom radiotherapy after breast-conservative surgery can be systematically omitted and the choice should be balanced depending on hormonal receptor status, quality of life and the possible need of a second surgery at relapse.
- Endocrine therapy remains the most widely used form of adjuvant treatment for breast cancer in older women. Aromatase inhibitors have shown a longer disease-free survival rate, alone or in a switch strategy after 2–3 years on tamoxifen to balance and optimize side-effect management.

<sup>1</sup>University of Pavia, Department of General Surgery, IRCCS Policlinico San Matteo, Pavia, Italy

<sup>2</sup>FY2 Surgery, Southport District General Hospital, Town Lane, Southport, PR8 6PN, UK

<sup>3</sup>University of Liverpool, St Helens Teaching Hospital, Marshalls Cross Road, St Helens, WA9 3DA, UK

\*Author for correspondence: Tel.: +44 1744 646 783; Fax: +44 1744 646 331; raudisio@doctors.org.uk

- Age by itself does not represent an absolute exclusion criteria for chemotherapy; however, little chemotherapy data is available on elderly patients; even less is present on the association of two or more drugs due to the consequence of increased toxicity.
- More research is needed to examine in depth and to provide more information about breast cancer in elderly women, with dedicated trials or alternative study designs, in order to optimize management and to avoid undertreatment.

**SUMMARY:** Despite 40% of breast cancers being diagnosed in women older than 65 years of age in developed countries, we are far from fully understanding the biology and optimizing treatment for this rapidly expanding age group. According to recent statistics, breast cancer mortality rates have decreased in recent years for younger women, while elderly patients have not enjoyed such an improvement. Older patients have peculiar characteristics, due to the presence of comorbidities, competitive causes of death, frailty, polypharmacy, deranged cognitive and nutritional status, and psychosocial problems; for these reasons older women need tailored treatment planning, which poses a barrier to their recruitment into clinical trials. Targeted research is urgently needed for these patients, either through prospective investigations or large and good quality epidemiological studies.

### Epidemiology

The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use guidelines for industries conventionally identify the geriatric population as the age-group composed of individuals who are  $\geq 65$  years of age, recommending, however, the inclusion of a good number of very old individuals with multiple comorbidities, in order to obtain a realistic representation of the old population [1].

A study by Emilio Zagheni from the Max Planck Institute of Rostock, Germany, demonstrated how average CO<sub>2</sub> emission per capita tails off from 65 years of age, due to lifestyle changes caused by age and by retirement from work [2].

Lacking a universally accepted definition of old age, conventionally, elderly starts at 65 years of age, which is the retirement age in most developed countries. Also according to comorbidities and performance status, the age of 65 years is the time when an individual becomes unable to actively contribute to society [3].

According to the 2005 European Commission Green Paper “Confronting demographic change: a new solidarity between the generations”, in the period between 2005 and 2050, the number of individuals in the age group between 65 and

79 years (old people) will reach 44% of the population, and the number of very old people ( $\geq 80$  years old) will increase by 180%.

We can estimate that in Europe by 2007 cancer prevalence was 3% in the general population, while in the old population this prevalence increases to 15% [4]. Six sites are most frequently affected in older women, representing just over 50% of all cancer cases: breast (18%), colon-rectum (13%), lung (11%), stomach (6%) and uterus (6%) [5].

A distinguishing aspect of cancer is a strong and steady increase in prevalence, rapidly expanding with increasing age. The increased incidence of cancer with age is constant in both men and women, and this trend is observed in the great majority of tumors of epithelial origin, such as breast or lung cancer, and in non-Hodgkin lymphomas as well, up to the ninth decade of life [6].

Increased cancer risk requires years of prolonged exposure to certain lifestyles (smoking, reproductive choices, hormonal treatments, occupational exposures), that mount in parallel with the increase of age. Aging by itself should not be considered an independent risk-factor of developing a tumor, but an indirect indicator of risk, pointing out the exposure time to relevant carcinogens during life [7–9].

This results in alarming epidemiological data: in the USA more than 40% of new breast cancer cases occur in women aged over 65 years (Surveillance Epidemiology and End Results database).

In 2007 the International Society of Geriatric Oncology created a task force with the aim to develop guidelines for the management of breast cancer in elderly women; this document was consequently updated, jointly with European Society of Mastology, in 2012. This working group has been emphasizing critical issues concerning undertreatment, erroneous 'ageist' therapeutic choices and lack of controlled clinical studies focused on older women [10].

### Diagnosis

The introduction of mammographic screening programs in the last 20 years has dramatically decreased breast cancer mortality, promoting early diagnosis and resulting in life expectancy similar to the general population for breast cancer patients [11].

During the early years of screening an increased incidence was recorded due to the increase in detection rate. More recently incidence rates began to decrease as a consequence of the saturation of screening programs and the reduction in hormonal manipulation [12–14]. Conversely, the incidence has not decreased among older women [15,16]. The mammographic screening upper age limit has been extended to 75 years of age in most European countries and in the USA. For patients with a good performance status and a life expectancy longer than 5 years, screening mammography programs have been proven to improve overall survival up to 85 years of age, even if the number of breast cancer deaths has been demonstrated to be smaller in this age group [17–22].

Invasive breast cancer is often detected with a larger average diameter in elderly women than in younger females, partly as consequence of the lack of a screening program. However, a lot of palpable and treatable lesions not yet locally advanced and ulcerated can be detected with a simple breast examination.

### Biological characteristics

Well-known biological features in elderly women breast cancer are: lower aneuploidy, low expression of HER-2, proliferative index Ki67 levels, p53 and EGF receptor [23,24] and a

higher estrogen receptor (ER) and progesterone receptor expression (over 80%) [25].

There are still no strong specific data available about the biology and the clinical management of older women with ductal carcinoma *in situ* and studies are often based on screen-detected nonpalpable lesions in cohorts of younger patients [26–28]. The guidelines suggest that treatment should be reserved for older women with good health status [10].

### Assessment of frailty

Assessment of suitability for more aggressive management is crucial within the elderly age group. Geriatric syndromes are closely related to the management of cancer in elderly patients. The increased number of comorbidities within this population complicates management. Often patients are declared unfit for more aggressive interventions due to these comorbidities or perceived functional status. Frailty is an essential part of this geriatric assessment. The Comprehensive Geriatric Assessment (CGA) along with other tools (Groeningen Frailty Index, Vulnerable Elders' Survey-13, Timed Up and Go test) exist for this purpose, providing quantitative assessment by determining the patient's medical, psychological and functional capability. They can include assessment of comorbidities, medications, nutritional status, functional status (activities of daily living) and psychosocial appraisal. Practitioners should use the information obtained from the CGA to produce and develop treatment plans, determine patients suitable for short- or long-term therapy, as well as the nature of appropriate treatment. The geriatric assessment tools also help guide practitioners with organizing potential long-term management, such as rehabilitative services, thus optimizing the utility of healthcare services within this group of patients. This leads to an unbiased assessment of patient status, aiding to avoid undertreatment of these elderly breast cancer patients, making sure treatment options are not overlooked owing to age or comorbidities.

Geriatric assessment tools differ from the standard approach to medical evaluation; standard medical evaluation works well within the general population, however, it often overlooks the most common problems faced by the older patient, such as intellectual decline or impairment, lack of mobility and iatrogenic disorders. Evidence from literature suggests that

geriatric assessment tools (such as the CGA) do provide valuable information of significance to the management of illness the elderly. Authors have reported a subsequent change to the treatment plan for elderly patients, including a switch to surgical management in patients previously declared unfit [29,30]. A published systematic review analyzed 20 randomized controlled trials (including a total of 10,427 participants) investigating inpatient CGA for a mixed elderly population. Data confirmed the benefit of inpatient CGA against not performing an assessment. An increase was identified with the chance of patients living at home in the long-term; for every 100 patients undergoing CGA, three more will be alive and in their own homes [31]. A recently published meta-analysis by Ellis *et al.* found several statistically significant benefits for patients who had CGA performed, including a significant reduction in death or deterioration ( $p = 0.001$ ) and an overall benefit on cognitive measures ( $p = 0.02$ ) as well as showing that significantly more elderly patients were likely to survive hospital admission and return home if they undergo CGA while they are inpatients [32]. These advantageous factors are most likely due to the improved initial assessment of a patient's current status (psychological and physical), thus allowing for more suitable interventions/treatments to be performed as well as more appropriate long-term management plans to be implemented. Geriatric assessment principles and findings show significant benefit with the management of older patients; tailored studies specifically performed on elderly cancer populations need to be pursued in order to validate the CGA in a cancer setting. Age alone should not be a factor to influence management of these patients in modern society and the assessment of frailty could potentially represent the key to the appropriate selection of management for these older cancer patients [33].

#### Primary & neoadjuvant treatment

Endocrine treatment is usually effective because of an increased hormonal receptor status in older women [25].

Several randomized trials were performed to compare hormonal therapy with tamoxifen alone versus surgery alone or plus tamoxifen in hormonal receptor-positive cancers. Patients who underwent surgery presented with a delayed local progression, longer disease-free survival time

and good locoregional disease control, avoiding rescue surgery, although this did not translate into a cancer-related survival benefit [34–36]. A Cochrane meta-analysis failed to prove that overall survival at 5 years is poorer in cases treated with tamoxifen alone than those who received either surgery alone or surgery and adjuvant therapy [37,38]; research on primary endocrine therapy is still ongoing. Aromatase inhibitors (letrozole/anastrozole/exemestane) seem to achieve slightly higher response rates compared with tamoxifen, particularly letrozole even in patients with low estrogen receptor expression. However, tamoxifen is not to be ruled out given the significant bone loss which is frequently induced by aromatase inhibitors [39–44].

Owing to the high rate of local progressions with primary endocrine treatment alone, at present, this treatment should be reserved to those few patients who have not been sufficiently reassured about the safety of surgical excision or those who cannot be treated even under local anesthesia, or with a very short life expectancy and in metastatic hormonal receptor-positive disease [42].

Neoadjuvant systemic therapy can be considered by a multidisciplinary team of specialists in order to obtain tumor shrinkage and improve the surgical options, to test the treatment response and improve long-term disease-free survival [45]. The choice of treatment should be made considering tumor features including some main parameters (hormonal-receptor status, HER-2 expression and Ki67 levels), comorbidities and patients status; some newly proposed markers need to be tested [23,46]. The use of pathological complete remission as one of the main prognostic factors for overall and disease-free survival, especially if chemotherapy is used, is still widely accepted [47].

An unquestionable advantage of neoadjuvant endocrine treatment rests on the fact that it allows a 3–6-month window to optimize the performance of unfit patients and correct those domains which are deemed deranged. At the same time, a significant reduction in cancer size is most likely to take place and several patients who would have been candidates for a mastectomy can often be rescued by breast-sparing surgery, if they so wish [48]. The value of neoadjuvant hormonal treatment as a valid 'bridge to surgery' should not be underestimated [49–51]. A close monitoring of efficacy and effects

should be performed after 3 months and further investigations are needed to compare local recurrence and survival rates compared with the adjuvant administration.

Neoadjuvant chemotherapy can be proposed in elderly women with good health status and hormone receptor-negative tumors [52]. However, a retrospective study suggested that patients with hormone receptor-positive disease could also benefit from neoadjuvant chemotherapy due to the higher pathologic complete response rate compared with neoadjuvant hormonal treatment, with better progression-free survival and overall survival [53].

In the metastatic setting, chemotherapy is indicated similarly as in younger women, following careful assessment of costs and benefits for each individual patient.

### Surgical treatment

The surgical approach should always have radical oncological intent no matter the patient's age. We have mounting evidence of an increasing interest of older women in having their breast preserved and even reconstructed, if there are not contraindications [54,55]; conservative surgery even after neoadjuvant treatment in order to avoid mastectomy should be considered, when available and safe. When mastectomy is performed, breast implants can be poorly tolerated and might provide cosmetic outcomes which are quite different from the physiological breast of an older woman; an autologous flap could also be an option, even if the surgical procedure in this case might be more demanding [56]. On the other hand the compliance with adjuvant radiation treatment should also be taken into account when designing a tailored treatment plan.

Some authors have proved that increasing age is associated with increased risk of node involvement, mainly in small tumors, probably due to decreased immune defense mechanisms in older people [57]. Sentinel node biopsy and axillary clearance can be performed under the very same guidelines as for younger patients [58]. Intraoperative pathological examination of the sentinel node avoids a second operation under general anesthesia but extends the operating time [59].

Although it is associated with minimal morbidity, the real advantage of axillary surgery in older breast cancer patients is still controversial: an elegant investigation from Martelli *et al.* and its associated long term follow-up studies seem

to deny any substantial advantage in clinical negative axilla patients [60–62].

### Radiotherapy

The benefits of radiation therapy (RT) seem to decrease with increasing age. Postoperative RT on the mammary gland after conservative surgery reduces the risk of local recurrence but has been proven not to affect overall survival in women >70 years old, with node-negative and hormonal receptor-positive cancers treated with adjuvant hormonal therapy; on the other hand a historical series suggests it may cause local side effects [63,64].

Most importantly, the compliance to the 4–5 (or at least 3) weeks in hypofractionated scheme treatment plans should be taken into account. In some areas, geographical barriers and distance from the radiation unit might affect completion of treatment.

Clinical trials have been proposed to avoid breast irradiation after conservative surgery in elderly patients [65,66], but there are still no defined indications about systematic omission of RT after breast-conservative surgery for particular subgroups and the choice should be balanced, taking into account hormonal receptors status, quality of life and the possible need of a second surgery at relapse [67–69].

Intraoperative RT is thus looked at with great interest, where a short increase in the operative time is likely to result in similar outcomes [70]. More investigations in the field are still needed. Possible alternatives could be hypofractionated radiotherapy schemes or partial breast irradiation [71–75].

The same indications as in younger women call for the need of chest wall and lymphatic irradiation in women with T3–T4 tumors or N2–N3 tumors [76].

### Hormonal therapy

Endocrine therapy remains the most widely used form of adjuvant treatment for breast cancer in older women, due to the majority of cases with ER expression [77]. For women with tumors that have been reliably shown to be ER-negative, adjuvant tamoxifen remains a matter for research [78,79].

Aromatase inhibitors have shown a longer disease-free survival rate, alone or in a switch strategy after 2–3 years on tamoxifen to balance and optimize side-effect management [80].



Aromatase inhibitors are frequently preferred in patients lacking mobility due to a thromboembolic risk associated with tamoxifen; however several senior patients are on warfarin or aspirin. This subsequently minimizes the risk of developing clots, however the association between tamoxifen and warfarin may increase the level of anticoagulation and the risk of bleeding complications and should be considered under close monitoring [81].

Tamoxifen should be considered if the patient is already suffering from arthritis or severe bone loss, due to its protective effect on bone loss [82,83]. In any case, a switch to tamoxifen should be considered when relevant side effects occur (i.e., major muscular pain, cramps and aches). Concomitant administration of calcium and vitamin D is recommended to contrast bone mass loss; bisphosphonates should be considered if bone loss occurs during monitoring [84–88].

Aromatase inhibitors seem to less consistently negatively influence cognitive function in breast cancer survivors compared with tamoxifen, but long-term trials are needed. Another critical issue is that sometimes cognitive impairment is due to concomitant chemotherapy [89].

### Chemotherapy

The indication for adjuvant chemotherapy in elderly women should be balanced between the likelihood of recurrence and the estimated competitive causes of death [90].

Retrospective analysis demonstrated a significant reduction in mortality after chemotherapy in women younger than 70 years of age affected by hormonal receptor-negative and node-positive tumors; a similar significant benefit of chemotherapy also occurs among older women [91–95].

The Early Breast Cancer Trialists' Collaborative Group provided an overview of the running randomized trials investigating the effects of chemotherapy and hormonal therapy on recurrence and 15-year survival, but few women of age 70 years or older entered those trials despite evidence that the magnitude of benefit was possibly similar to the 60–69 years of age group [96].

Age by itself does not represent an absolute exclusion criteria for chemotherapy, however adjuvant chemotherapy is not indicated for the vast majority of patients older than 70 years, particularly if affected by node-negative disease and ER-positive tumors.

Very little chemotherapy data are available on elderly patients; even less are present on the association of two or more drugs due to the consequence of increased toxicity. Renal function should be closely monitored during chemotherapeutic treatment in elderly patients [97].

Adjuvant chemotherapy is usually administered before endocrine therapy in ER-positive patients and positive lymph nodal involvement, provided the patient is deemed fit enough. Even more is the case of ER- and positive lymph nodes [98,99].

Trastuzumab for HER-2-positive tumors should be considered after chemotherapy in women without cardiac conditions [100].

Regimens containing anthracyclines and taxanes are considered more effective than cyclophosphamide methotrexate and fluorouracil 5FU in prolonging overall survival, but this is extrapolated from younger cohorts [101–104].

Employing schemes containing anthracyclines in elderly patients remains extremely controversial and this choice should be carefully considered only for fit women <80 years old with good mental status and family support affected by tumors showing high risk of recurrence or metastatic spreading and under close monitoring of hematological and cardiological toxicity [105]. The association with taxanes could increase overall survival even in older patients, however this is often unfeasible because it increases toxicity.

A US survey for insurance reimbursement proved significant toxicity caused by chemotherapy in older women, with a 6-month hospitalization rate of 20.1% in comparison with an 8.6% rate for patients who did not receive chemotherapy. A 5% mortality rate occurred after hospitalization; previous comorbidities and anthracycline-based cocktails were predictive factors associated to increased hospitalization mortality [106].

In cyclophosphamide methotrexate and fluorouracil 5FU schemes, cyclophosphamide intravenous infusion seems to improve persistence and adherence when compared with the usual oral administration, but further investigations are needed to prove efficacy [107].

In conclusion, chemotherapy is advisable in older women when indicated, with an accurate drug selection considering comorbidities, tumor features, patient expectations and

tailored schemes; close monitoring of possible lack of compliance, toxicity and side effects is compulsory [108–111].

### Conclusion & future perspective

Breast cancer treatment has improved and refined in the last 20 years. Still, several retrospective studies demonstrate a trend to undertreatment in older women, even after balancing for race, education, tumor stage and biological characteristics; the local and axillary surgical approach is less aggressive, sometimes RT is omitted and chemotherapy is offered only in limited cases. Comorbidities, logistical and cognitive-relational difficulties subsist and limit treatment options [33]. Age increases the likelihood of death from concomitant conditions and the impact of treatment in prolonging survival decreases. Furthermore tumors in older patients usually prove to be less aggressive and show more favorable biological factors [112–115].

A key recommendation is to create therapies tailored to the needs of elderly patients, balancing the risk of progression and death caused by cancer and the risk of disability and death derived from other comorbidities and side effects of treatment (reversible and irreversible). The oncologists should perform a comprehensive geriatric assessment that considers indexes of frailty, malnutrition and cognitive aspects. This approach is fundamental to plan a treatment for breast cancer in older women, especially if intensive treatment regimens are proposed, because it allows the drop-out rate and the treatment effects on the individuals to be predicted [116,117].

Although International Society of Geriatric Oncology and European Society of Mastology guidelines contain the best updated evidence-based approach to face breast cancer in elderly women, many studies concerning the subject, however, still lack type I evidence levels, and treatment choices are often based on studies carried out on younger patients. The difficulties in organizing clinical controlled trials on elderly

patients depend on comorbidities, cognitive status and communication barriers, quality of family support and travel opportunities for patients to go to the hospital and receive treatments [118]. This hurdle makes medical oncologists reluctant to recruit older people, for fear of toxicity, poor compliance, drop-out rate and logistical, economic and social limits. Unsatisfactory communication with doctors and lack of patient's active participation in treatment choices makes older women hesitant to take part to trials and to receive treatment, perceiving them threatened with 'ageism'. If the patient has good family support they are more likely to tolerate even a heavy regimen of treatment [119].

Elderly patients should deserve a treatment that does not interfere with their quality of life and at the same time is effective, and this makes it important to create a tailored treatment based on their specific needs, rather than on chronological age, and on an analysis of comorbidities [120,121].

Current international guidelines should be adopted by clinicians dealing with breast cancer in older patients, in order to guarantee the adequate updated treatment and to provide data nonconditioned by incorrect statement or approaches. Further clinical research is needed to examine in depth and provide more information about this topic, with dedicated trials for old women promoted by physicians and alternative study designs representative of the real elderly population to investigate issues in which a clinical trial is not feasible [122].

### Financial & competing interests disclosure

*The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.*

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### References

Papers of special note have been highlighted as:

■ of interest

■ of considerable interest

- 1 ICH Studies in Support of Special Populations: Geriatrics. *Federal Register* 58(72), 21082 (1993).
- 2 Zagheni E. The leverage of demographic dynamics on carbon dioxide emissions: does age structure matter? *Demography* 48(1), 371–399 (2011).
- 3 Gorman M. Global ageing – the non-governmental organization role in the developing world. *Int. J. Epidemiol.* 31(4), 782–785 (2002).
- 4 Karim-Kos HE, de Vries E, Soerjomataram I, Lemmens V, Siesling S, Coebergh JW. Recent trends of cancer in Europe: a combined approach of incidence, survival and mortality for 17 cancer sites since the 1990s. *Eur. J. Cancer* 44(10), 1345–1389 (2008).
- 5 Ferlay J, Autier P, Boniol M, Heanue M, Colombet M, Boyle P. Estimates of the cancer

- incidence and mortality in Europe in 2006. *Ann. Oncol.* 18(3), 581–592 (2007).
- 6 Pavlidis N, Stanta G, Audisio RA. Cancer prevalence and mortality in centenarians: a systematic review. *Crit. Rev. Oncol. Hematol.* 83(1), 145–152 (2012).
  - 7 Anisimov VN. Biology of aging and cancer. *Cancer Control* 14(1), 23–31 (2007).
  - 8 Fulop T, Larbi A, Kotb R, de Angelis F, Pawelec G. Aging, immunity, and cancer. *Discov. Med.* 11(61), 537–550 (2011).
  - 9 Kyo S, Takakura M, Kanaya T *et al.* Estrogen activates telomerase. *Cancer Res.* 59(23), 5917–5921 (1999).
  - 10 Biganzoli L, Wildiers H, Oakman C *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.* 13(4), e148–e160 (2012).
  - **Updated guidelines from the International Society of Geriatric Oncology.**
  - 11 DeSantis C, Siegel R, Bandi P, Jemal A. Breast cancer statistics. *CA Cancer J. Clin.* 61(6), 409–418 (2011).
  - 12 Pollán M, Pastor-Barriuso R, Ardanaz E *et al.* Recent changes in breast cancer incidence in Spain, 1980–2004. *J. Natl Cancer Inst.* 101(22), 1584–1591 (2009).
  - 13 Zbuk K, Anand SS. Declining incidence of breast cancer after decreased use of hormone-replacement therapy: magnitude and time lags in different countries. *J. Epidemiol. Community Health* 66(1), 1–7 (2012).
  - 14 Héry C, Ferlay J, Boniol M, Autier P. Quantification of changes in breast cancer incidence and mortality since 1990 in 35 countries with Caucasian-majority populations. *Ann. Oncol.* 19(6), 1187–1194 (2008).
  - 15 Schonberg MA, Marcantonio ER, Li D, Silliman RA, Ngo L, McCarthy EP. Breast cancer among the oldest old: tumor characteristics, treatment choices, and survival. *JCO* 28(12), 2038–2045 (2010).
  - 16 August DA, Rea T, Sondak VK. Age-related differences in breast cancer treatment. *Ann. Surg. Oncol.* 1(1), 45–52 (1994).
  - 17 Galit W, Green MS, Lital KB. Routine screening mammography in women older than 74 years: a review of the available data. *Maturitas* 57(2), 109–119 (2007).
  - 18 Caplan LS. To screen or not to screen: the issue of breast cancer screening in older women. *Public Health Rev.* 29(2–4), 231–240 (2001).
  - 19 Schonberg MA, McCarthy EP, Davis RB, Phillips RS, Hamel MB. Breast cancer screening in women aged 80 and older: results from a national survey. *J. Am. Geriatr. Soc.* 52(10), 1688–1695 (2004).
  - 20 Heflin MT, Pollak KI, Kuchibhatla MN, Branch LG, Oddone EZ. The impact of health status on physicians' intentions to offer cancer screening to older women. *J. Gerontol. A Biol. Sci. Med. Sci.* 61(8), 844–850 (2006).
  - 21 Tabar L, Fagerberg G, Duffy SW, Day NE. The Swedish two county trial of mammographic screening for breast cancer: recent results and calculation of benefit. *J. Epidemiol. Community Health* 43, 107–114 (1989).
  - 22 Ecomard LM, Malingret N, Asad-Syed M *et al.* Breast cancer diagnosis among women aged 75 and over: study on information delivered by organized breast cancer screening agencies to women reaching the limit age. *Bull. Cancer* 100(7–8), 671–678 (2013).
  - 23 Syed BM, Green AR, Paish EC *et al.* Biology of primary breast cancer in older women treated by surgery: with correlation with long-term clinical outcome and comparison with their younger counterparts. *Br. J. Cancer* 108(5), 1042–1051 (2013).
  - 24 Bonnier P, Romain S, Charpin C *et al.* Age as a prognostic factor in breast cancer: relationship to pathologic and biologic features. *Int. J. Cancer* 62(2), 138–144 (1995).
  - 25 Morrison DH, Rahardja D, King E, Peng Y, Sarode VR. Tumour biomarker expression relative to age and molecular subtypes of invasive breast cancer. *Br. J. Cancer* 107(2), 382–387 (2012).
  - 26 Cutuli B, Lemanski C, Fourquet A *et al.* Ductal carcinoma *in situ* of the breast (DCIS). Histopathological features and treatment modalities: analysis of 1,289 cases. *Bull. Cancer* 97(3), 301–310 (2010).
  - 27 Shamliyan T, Wang SY, Virnig BA, Tuttle TM, Kane RL. Association between patient and tumor characteristics with clinical outcomes in women with ductal carcinoma *in situ*. *J. Natl Cancer Inst. Monogr.* 41, 121–129 (2010).
  - 28 Di Saverio S, Catena F, Santini D *et al.* 259 patients with DCIS of the breast applying USC/Van Nuys prognostic index: a retrospective review with long term follow up. *Breast Cancer Res. Treat.* 109(3), 405–416 (2008).
  - 29 Stotter A, Tahir M, Pretorius R, Robinson T. Experiences of a multidisciplinary elderly breast cancer clinic: using the right specialists, in the same place, with time. In: *Management of Breast Cancer in Older Women*. Reed M, Audisio R (Eds). Springer, London, UK (2010).
  - 30 Girre V, Falcou MC, Gisselbrecht M *et al.* Does a geriatric oncology consultation modify the cancer treatment plan for elderly patients? *J. Gerontol. A Biol. Sci. Med. Sci.* 63(7), 724–730 (2008).
  - 31 Ellis G, Langhorne P. Comprehensive geriatric assessment for older hospital patients. *Br. Med. Bull.* 71, 45–49 (2005).
  - 32 Ellis G, Whitehead MA, Robinson D, O'Neill D, Langhorne P. Comprehensive geriatric assessment for older adults admitted to hospital: meta-analysis of randomised controlled trials. *BMJ* 343, d6553 (2011).
  - 33 Swaminathan V, Audisio RA. Cancer in older patients: an analysis of elderly oncology. *Ecancermedicalscience* 6, 243 (2012).
  - 34 Johnston SJ, Kenny FS, Syed BM *et al.* A randomised trial of primary tamoxifen versus mastectomy plus adjuvant tamoxifen in fit elderly women with invasive breast carcinoma of high oestrogen receptor content: long-term results at 20 years of follow-up. *Ann. Oncol.* 23(9), 2296–2300 (2012).
  - 35 Fentiman IS, Christiaens MR, Paridaens R *et al.* Treatment of operable breast cancer in the elderly: a randomised clinical trial EORTC 10851 comparing tamoxifen alone with modified radical mastectomy. *Eur. J. Cancer* 39(3), 309–316 (2003).
  - 36 Mustacchi G, Ceccherini R, Milani S *et al.* Tamoxifen alone versus adjuvant tamoxifen for operable breast cancer of the elderly: long-term results of the Phase III randomized controlled multicenter GRETA trial. *Ann. Oncol.* 14(3), 414–420 (2003).
  - 37 Hind D, Wyld L, Beverley CB, Reed MW. Surgery versus primary endocrine therapy for operable primary breast cancer in elderly women (70 years plus) (review). *Cochrane Database Syst. Rev.* (1), (2006).
  - 38 Hind D, Wyld L, Reed MW. Surgery, with or without tamoxifen, vs tamoxifen alone for older women with operable breast cancer: cochrane review. *Br. J. Cancer* 96(7), 1025–1029 (2007).
  - 39 Gennari R, Audisio RA. Breast cancer in elderly women. Optimizing the treatment. *Breast Cancer Res. Treat.* 110(2), 199–209 (2008).
  - 40 Smith IE. Letrozole versus tamoxifen in the treatment of advanced breast cancer and as neoadjuvant therapy. *J. Steroid Biochem. Mol. Biol.* 86(3–5), 289–293 (2003).
  - 41 Macaskill JE, Renshaw L, Dixon JM. Neoadjuvant use of hormonal therapy in



- elderly patients with early or locally advanced hormone receptor-positive breast cancer. *Oncologist* 11(10), 1081–1088 (2006).
- 42 Mouridsen H, Gershonovich M, Sun Y *et al.* Superior efficacy of letrozole versus tamoxifen as first-line therapy for postmenopausal women with advanced breast cancer: results of a Phase III study of the International Letrozole Breast Cancer Group. *J. Clin. Oncol.* 19(10), 2596–2606 (2001).
- 43 Ellis MJ, Ma C. Letrozole in the neoadjuvant setting: the P024 trial. *Breast Cancer Res Treat.* 105(Suppl. 1), S33–S43 (2007).
- 44 Ellis MJ, Suman VJ, Hoog J *et al.* Randomized Phase II neoadjuvant comparison between letrozole, anastrozole, and exemestane for postmenopausal women with estrogen receptor-rich stage 2 to 3 breast cancer: clinical and biomarker outcomes and predictive value of the baseline PAM50-based intrinsic subtype – ACOSOG Z1031. *J. Clin. Oncol.* 29(17), 2342–2349 (2011).
- 45 Kaufmann M, Hortobagyi GN, Goldhirsch A *et al.* Recommendations from an international expert panel on the use of neoadjuvant (primary) systemic treatment of operable breast cancer: an update. *J. Clin. Oncol.* 24(12), 1940–1949 (2006).
- 46 Wang L, Jiang Z, Sui M, Shen J, Xu C, Fan W. The potential biomarkers in predicting pathologic response of breast cancer to three different chemotherapy regimens: a case control study. *BMC Cancer* 9, 226–235 (2009).
- 47 Berruti A, Generali D, Kaufmann M *et al.* International expert consensus on primary systemic therapy in the management of early breast cancer: highlights of the Fourth Symposium on Primary Systemic Therapy in the Management of Operable Breast Cancer, Cremona, Italy (2010). *J. Natl Cancer Inst. Monogr.* 43, 147–151 (2011).
- 48 Ellis MJ. Preoperative endocrine therapy for older women with breast cancer: renewed interest in an old idea. *Cancer Control* 7(6), 557–562 (2000).
- 49 Tondini C, Fenaroli P, Labianca R. Pre-operative endocrine therapy for postmenopausal women: when and why? *Ann. Oncol.* 12(11), 1505–1506 (2001).
- 50 Alba E, Calvo L, Albanell J *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.* 23(12), 3069–3074 (2012).
- 51 Semiglazov VF, Semiglazov VV, Dashyan GA *et al.* Phase 2 randomized trial of primary endocrine therapy versus chemotherapy in postmenopausal patients with estrogen receptor-positive breast cancer. *Cancer* 110(2), 244–254 (2007).
- 52 Gajdos C, Tartter PI, Bleiweiss IJ, Lopchinsky RA, Bernstein JL. The consequence of undertreating breast cancer in the elderly. *J. Am. Coll. Surg.* 192(6), 698–707 (2001).
- 53 Guarneri V, Broglio K, Kau SW *et al.* Prognostic value of pathologic complete response after primary chemotherapy in relation to hormone receptor status and other factors. *J. Clin. Oncol.* 24(7), 1037–1044 (2006).
- 54 Morrow M, Bucci C, Rademaker A. Medical contraindications are not a major factor in the underutilization of breast conserving therapy. *J. Am. Coll. Surg.* 186(3), 269–274 (1998).
- 55 Alderman AK, Bynum J, Sutherland J, Birkmeyer N, Collins ED, Birkmeyer J. Surgical treatment of breast cancer among the elderly in the United States. *Cancer* 117(4), 698–704 (2011).
- 56 Walton L, Ommen K, Audisio RA. Breast reconstruction in elderly women breast cancer: a review. *Cancer Treat. Rev.* 37(5), 353–357 (2011).
- 57 Wildiers H, Van Calster B, van de Poll-Franse LV *et al.* Relationship between age and axillary lymph node involvement in women with breast cancer. *J. Clin. Oncol.* 27(18), 2931–2937 (2009).
- 58 Barry JM, Weber WP, Sacchini V. The evolving role of axillary lymph node dissection in the modern era of breast cancer management. *Surg. Oncol.* 21(2), 143–145 (2012).
- 59 Gennari R, Curigliano G, Rotmensz N *et al.* Breast carcinoma in elderly women: features of disease presentation, choice of local and systemic treatments compared with younger postmenopausal patients. *Cancer* 101(6), 1302–1310 (2004).
- 60 Martelli G, DePalo G, Rossi N *et al.* Long-term follow-up of elderly patients with operable breast cancer treated with surgery without axillary dissection plus adjuvant tamoxifen. *Br. J. Cancer* 72(5), 1251–1255 (1995).
- 61 Martelli G, Boracchi P, DePalo M *et al.* A randomized trial comparing axillary dissection to no axillary dissection in older patients with T1N0 breast cancer: results after 5 years of follow-up. *Ann. Surg.* 242(1), 1–6 (2005).
- 62 Martelli G, Boracchi P, Ardoino I *et al.* Axillary dissection versus no axillary dissection in older patients with T1N0 breast cancer: 15-year results of a randomized controlled trial. *Ann. Surg.* 256(6), 920–924 (2012).
- 63 Hughes KS, Schnaper LA, Bellon JR *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.* 31(19), 2382–2387 (2013).
- 64 Williams LJ, Kunkler IH, King CC, Jack W, van der Pol M. A randomised controlled trial of post-operative radiotherapy following breast-conserving surgery in a minimum-risk population. Quality of life at 5 years in the PRIME trial. *Health Technol. Assess.* 15(12), i–xi (2011).
- 65 Tinterri C, Gatzemeier W, Zanini V *et al.* Conservative surgery with and without radiotherapy in elderly patients with early-stage breast cancer: a prospective randomised multicentre trial. *Breast* 18(6), 373–377 (2009).
- 66 Vrana D, Gatek J, Lukesova L *et al.* Omission of adjuvant radiation therapy in elderly patients with low risk breast cancer undergoing breast-conserving surgery – two center experience. *Biomed. Pap. Med. Fac. Univ. Palacky Olomouc Czech. Repub.* doi:10.5507/bp.2013.032 (2013) (Epub ahead of print).
- 67 Sautter-Bihl ML, Sedlmayer F, Budach W *et al.* When are breast cancer patients old enough for the quitclaim of local control? *Strahlenther. Onkol.* 188(12), 1069–1073 (2012).
- 68 Truong PT, Bernstein V, Lesperance M, Speers CH, Olivotto IA. Radiotherapy omission after breast-conserving surgery is associated with reduced breast cancer-specific survival in elderly women with breast cancer. *Am. J. Surg.* 191(6), 749–755 (2006).
- 69 Sautter-Bihl ML, Budach W, Dunst J *et al.* DEGRO practical guidelines for radiotherapy of breast cancer I: breast-conserving therapy. *Strahlenther. Onkol.* 183(12), 661–666 (2007).
- 70 Barry M, Sacchini V. Evaluating the role of intra-operative radiation therapy in the modern management of breast cancer. *Surg. Oncol.* 21(4), 159–163 (2012).
- 71 Schoenfeld JD, Harris JR. Abbreviated course of radiotherapy (RT) for breast cancer. *Breast* 20(Suppl. 3), S116–S127 (2011).
- 72 Smith BD, Bentzen SM, Correa CR *et al.* Fractionation for whole breast irradiation: an American Society for Radiation Oncology (ASTRO) evidence-based guideline. *Int. J. Radiat. Oncol. Biol. Phys.* 81(1), 59–68 (2011).

- 73 MacLeod N, McIntyre A, Canney PA. What are the minimal standards of radiotherapy planning and dosimetry for 'hypofractionated' radiotherapy in breast cancer? *Breast* 19(3), 172–175 (2010).
- 74 Smith BD, Arthur DW, Buchholz TA *et al.* Accelerated partial breast irradiation consensus statement from the American Society for Radiation Oncology (ASTRO). *J. Am. Coll. Surg.* 209(2), 269–277 (2009).
- 75 Leonardi MC, Maisonneuve P, Mastropasqua MG *et al.* How do the ASTRO consensus statement guidelines for the application of accelerated partial breast irradiation fit intraoperative radiotherapy? A retrospective analysis of patients treated at the European Institute of Oncology. *Int. J. Radiat. Oncol. Biol. Phys.* 83(3), 806–813 (2012).
- 76 Sautter-Bihl ML, Souchon R, Budach W *et al.* DEGRO practical guidelines for radiotherapy of breast cancer II. Postmastectomy radiotherapy, irradiation of regional lymphatics, and treatment of locally advanced disease. *Strahlenther. Onkol.* 184(7), 347–353 (2008).
- 77 Pennery E. The role of endocrine therapies in reducing risk of recurrence in postmenopausal women with hormone receptor-positive breast cancer. *Eur. J. Oncol. Nurs.* 12(3), 233–243 (2008).
- 78 Clarke MJ. Tamoxifen for early breast cancer. *Cochrane Database Syst. Rev.* (4), (2008).
- 79 Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Davies C, Godwin J *et al.* Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. *Lancet* 378(9793), 771–84 (2011).
- **Relates breast cancer hormone receptors and efficacy of adjuvant tamoxifen.**
- 80 Regan MM, Neven P, Giobbie-Hurder A *et al.* Assessment of letrozole and tamoxifen alone and in sequence for postmenopausal women with steroid hormone receptor-positive breast cancer: the BIG 1–98 randomised clinical trial at 8.1 years median follow-up. *Lancet Oncol.* 12(12), 1101–1108 (2011).
- 81 Givens CB, Bullock LN, Franks AS. Safety of concomitant tamoxifen and warfarin. *Ann. Pharmacother.* 43(11), 1867–1871 (2009).
- 82 Coleman RE, Banks LM, Girgis SI *et al.* Skeletal effects of exemestane on bone-mineral density, bone biomarkers, and fracture incidence in postmenopausal women with early breast cancer participating in the Intergroup Exemestane Study (IES): a randomised controlled study. *Lancet Oncol.* 8(2), 119–127 (2007).
- 83 Eastell R, Adams JE, Coleman RE *et al.* Effect of anastrozole on bone mineral density: 5-year results from the anastrozole, tamoxifen, alone or in combination trial 18233230. *J. Clin. Oncol.* 26(7), 1051–1057 (2008).
- 84 Gralow JR, Biermann JS, Farooki A *et al.* NCCN task force report: bone health in cancer care. *J. Natl Compr. Canc. Netw.* 7(Suppl. 3), S1–S32, quiz S33–S35 (2009).
- 85 Michaud LB. Managing cancer treatment-induced bone loss and osteoporosis in patients with breast or prostate cancer. *Am. J. Health Syst. Pharm.* 67(7 Suppl. 3), S20–S30, quiz S31–S31 (2010).
- 86 Brufsky A, Bundred N, Coleman R *et al.* Integrated analysis of zoledronic acid for prevention of aromatase inhibitor-associated bone loss in postmenopausal women with early breast cancer receiving adjuvant letrozole. *Oncologist* 13(5), 503–514 (2008).
- 87 Aapro M. Improving bone health in patients with early breast cancer by adding bisphosphonates to letrozole: the Z-ZO-E-ZO-FAST program. *Breast* 15(Suppl. 1), S30–S40 (2006).
- 88 Van Poznak C, Hannon RA, Mackey JR *et al.* Prevention of aromatase inhibitor-induced bone loss using risidronate: the SABRE trial. *J. Clin. Oncol.* 28(6), 967–975 (2010).
- 89 Buwalda B, Schagen SB. Is basic research providing answers if adjuvant anti-estrogen treatment of breast cancer can induce cognitive impairment? *Life Sci.* 93(17), 581–588 (2013).
- 90 Bernardi D, Errante D, Galligioni E *et al.* Treatment of breast cancer in older women. *Acta Oncol.* 47(2), 187–198 (2008).
- 91 Muss HB, Woolf S, Berry D *et al.* Adjuvant chemotherapy in older and younger women with lymph node-positive breast cancer. *JAMA* 293(9), 1073–1081 (2005).
- 92 Muss HB, Berry DA, Cirincione CT *et al.* Adjuvant chemotherapy in older women with early-stage breast cancer. *N. Engl. J. Med.* 360(20), 2055–2065 (2009).
- 93 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.* 24(18), 2750–2756 (2006).
- 94 Pierga JY, Girre V, Laurence V *et al.* Characteristics and outcome of 1755 operable breast cancers in women over 70 years of age. *Breast* 13(5), 369–375 (2004).
- 95 Fargeot P, Bonnetterre J, Roché H *et al.* Disease-free survival advantage of weekly epirubicin plus tamoxifen versus tamoxifen alone as adjuvant treatment of operable, node-positive, elderly breast cancer patients: 6-year follow-up results of the French adjuvant study group 08 trial. *J. Clin. Oncol.* 22(23), 4622–4630 (2004).
- 96 Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *Lancet* 365(9472), 1687–1717 (2005).
- **Overview of the running randomized trials concerning the effects of chemotherapy and hormonal therapy that proves that elderly women are under-represented.**
- 97 Lichtman SM, Wildiers H, Launay-Vacher V, Steer C, Chatelut E, Aapro M. International Society of Geriatric Oncology (SIOG) recommendations for the adjustment of dosing in elderly cancer patients with renal insufficiency. *Eur. J. Cancer* 43(1), 14–34 (2007).
- 98 Weiss A, Noorbaksh A, Tokin C, Chang D, Blair SL. Hormone receptor-negative breast cancer: undertreatment of patients over 80. *Ann. Surg. Oncol.* 20(10), 3274–3278 (2013).
- 99 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.* 24(18), 2757–2764 (2006).
- **Observational study about chemotherapy in old women.**
- 100 Carli P, Turchet E, Quitadamo D *et al.* Target therapy in elderly breast cancer patients. *Crit. Rev. Oncol. Hematol.* 83(3), 422–431 (2012).
- 101 Wilcken NR, Stockler MR. ACP Journal Club. Individual patient meta-analysis: taxane plus anthracycline reduces mortality from early breast cancer. *Ann. Intern. Med.* 156(12), JC6–4 (2012).
- 102 Qin YY, Li H, Guo XJ *et al.* Adjuvant chemotherapy, with or without taxanes, in early or operable breast cancer: a meta-analysis of 19 randomized trials with 30698 patients. *PLoS ONE* 6(11), e26946 (2011).
- 103 Mansi JL, Yellowlees A, Lipscombe J *et al.* Five-year outcome for women randomised in a Phase III trial comparing doxorubicin and cyclophosphamide with doxorubicin and docetaxel as primary medical therapy in early breast cancer: an Anglo-Celtic Cooperative Oncology Group study. *Breast Cancer Res. Treat.* 122(3), 787–794 (2010).

- 104 Lagha A, Chraiet N, Labidi S *et al.* Impact of taxanes in the adjuvant setting of node-negative breast cancers. *Bull. Cancer* 100(5), 465–471 (2013).
- 105 Aapro M. SIOG (International Society of Geriatric Oncology) recommendations for anthracycline use in the elderly. *Hematol. Rep.* 3(3s), e6 (2011).
- 106 Du XL, Osborne C, Goodwin JS. Population-based assessment of hospitalizations for toxicity from chemotherapy in older women with breast cancer. *J. Clin. Oncol.* 20(24), 4636–4642 (2002).
- 107 Ruddy KJ, Pitcher BN, Archer LE *et al.* Persistence, adherence, and toxicity with oral in older women with early-stage breast cancer (Adherence Companion Study 60104 for CALGB 49907). *Ann. Oncol.* 23(12), 3075–3081 (2012).
- 108 Bowles EJ, Wellman R, Feigelson HS *et al.* Risk of heart failure in breast cancer patients after anthracycline and trastuzumab treatment: a retrospective cohort study. *J. Natl Cancer Inst.* 104(17), 1293–1305 (2012).
- 109 Du XL, Xia R, Burau K, Liu CC. Cardiac risk associated with the receipt of anthracycline and trastuzumab in a large nationwide cohort of older women with breast cancer, 1998–2005. *Med. Oncol.* 28(Suppl. 1), S80–S90 (2011).
- 110 Muss HB, Berry DA, Cirincione C *et al.* Toxicity of older and younger patients treated with adjuvant chemotherapy for node-positive breast cancer: the Cancer and Leukemia Group B Experience. *J. Clin. Oncol.* 25(24), 3699–3704 (2007).
- 111 Patt DA, Duan Z, Fang S, Hortobagyi GN, Giordano SH. Acute myeloid leukemia after adjuvant breast cancer therapy in older women: understanding risk. *J. Clin. Oncol.* 25(25), 3871–3876 (2007).
- 112 Kuzan TY, Koca E, Dizdar O *et al.* Breast cancer in octogenarian women: clinical characteristics and outcome. *J. BUON* 18(2), 328–334 (2013).
- 113 van de Water W, Bastiaannet E, Dekkers OM *et al.* Adherence to treatment guidelines and survival in patients with early-stage breast cancer by age at diagnosis. *Br. J. Surg.* 99(6), 813–820 (2012).
- 114 Bastiaannet E, Portielje JE, van de Velde CJ *et al.* Lack of survival gain for elderly women with breast cancer. *Oncologist* 16(4), 415–423 (2011).
- **Evaluation of survival among elderly women affected by breast cancer.**
- 115 Malik MK, Tarttter PI, Belfer R. Undertreated breast cancer in the elderly. *J. Cancer Epidemiol.* 893104 (2013).
- 116 Puts MT, Hardt J, Monette J, Girre V, Springall E, Alibhai SM. Use of geriatric assessment for older adults in the oncology setting: a systematic review. *J. Natl Cancer Inst.* 104(15), 1133–1163 (2012).
- 117 Puts MT, Monette J, Girre V *et al.* Are frailty markers useful for predicting treatment toxicity and mortality in older newly diagnosed cancer patients? Results from a prospective pilot study. *Crit. Rev. Oncol. Hematol.* 78(2), 138–149 (2011).
- 118 Townsley CA, Selby R, Siu LL. Systematic review of barriers to the recruitment of older patients with cancer onto clinical trials. *J. Clin. Oncol.* 23(13), 3112–3124 (2005).
- **Important for a future perspective.**
- 119 Mandelblatt JS, Sheppard VB, Hurria A *et al.* Breast cancer adjuvant chemotherapy decisions in older women: the role of patient preference and interactions with physicians. *J. Clin. Oncol.* 28(19), 3146–3153 (2010).
- 120 Wyld L, Reed MW. The need for targeted research into breast cancer in the elderly. *Br. J. Surg.* 90(4), 388–399 (2003).
- 121 Husain LS, Collins K, Reed M, Wyld L. Choices in cancer treatment: a qualitative study of the older women's (>70 years) perspective. *Psychooncology* 17(4), 410–416 (2008).
- 122 Vandembroucke JP. Why do the results of randomised and observational studies differ? *BMJ* 343, d7020 (2011).