Conservative Surgery

23

Umberto Veronesi

23.1 Premises

Surgical oncology showed a great evolution over the past century. The increased incidence of malignancies leads to an increased interest in discovering new diagnostic and therapeutic techniques. Since the end of the nineteenth century, the objective of the surgeons was to offer the "maximal tolerable treatment," as the effort was concentrated on delivering as extensive surgery as could be tolerated, in order to improve disease control. This approach resulted in devastating interventions with a negative effect on the quality of life. At the end of the sixties, when it was made clear that the prognosis was mainly linked to the presence or absence of distant metastases and not to the extent of local treatment, the opposite trend was developed with the objective to identify the "minimal effective treatment," aiming at preservation of the affected organ, that would improve the patients quality of life.

The advances in the field of systemic treatments led to an improved control of the disseminated disease. Adjuvant chemotherapy and endocrine therapy became therefore component of the treatment. More recently the progress in the knowledge on cell genetic is leading to targeted treatments increasing the therapeutic efficiency and sparing the patient the side effects of chemotherapy.

Radiotherapy is often essential for obtaining a good local control. The progression of informatics technology changed the radiation treatment from two-dimensional radiotherapy to three-D conformal radiotherapy and recently to intensity-modulated radiation therapy.

Since the publication of the paper on a study conducted from January 1988 to December 1989 [1], neoadjuvant treatments are being used for several oncologic patients for downstaging. Chemotherapy, as well as hormone therapy for hormone-dependent tumors, in the preoperative setting is shown often to decrease the extent of the solid tumors, rendering them operable, often with the conservation of the organ.

23.2 Value of Randomized Trials

Randomized trials have contributed significantly to the changes in surgical oncology in breast cancer that were fundamental for all the revolutionary changes performed. An attempt to improve the prognosis through a more extended treatment was the aim of the trial on internal mammary node dissection. A large international randomized trial was published in 1976 comparing radical mastectomy with or without internal mammary dissection [2]. From 1963 to 1968, 1,453 patients in five centers were randomized. The 5-year survival was similar in the two groups. The Cancer Institute of Milan participated in this study and published the 10-year follow-up of 716 patients in 1981 [3], without differences in overall survival and disease-free survival in the two groups. There was no difference in recurrence rates on the operating field, the axilla and the supraclavicular fossa. The 10-year update of the multicenter study that was published 2 years later confirmed no difference in survival and in relapse-free survival [4]. This first large trial attempted to explore the impact of more aggressive surgery failed the goal and inspired myself to look at opposite solutions. The passage from "maximally tolerated" to "minimally effective" treatment has not been easy, and the idea of conserving a large portion of an affected organ was challenged by many surgeons and medical oncologists. It was only the large randomized trials performed in breast cancer patients that made possible the acceptance of breast conservation and led to a complete modification of the principles of breast surgery.

U. Veronesi
European Institute of Oncology,
Via Ripamonti 435, Milan 20141, Italy
e-mail: umberto.veronesi@ieo.it

U. Veronesi et al. (eds.), *Breast Cancer*, DOI 10.1007/978-3-319-48848-6_23

23.3 Breast-Conserving Surgery

Over the years, Halsted mastectomy has been replaced by lumpectomy or quadrantectomy, with external high-energy radiotherapy as an integrated component of treatment (Figs. 23.1 and 23.2).

A milestone was the publication in 1981 of the results of a randomized trial that compared Halsted mastectomy with breast-conserving surgery plus complete axillary dissection plus full-dose radiotherapy to the breast [5]. The trial, which recruited 701 patients with tumor ≤2 cm, showed no difference in survival between the two groups. The findings of the Milan trial were confirmed by long-term follow-up published in 1981 [6] (Figs. 23.3 and 23.4).

In the USA, Fisher and colleagues, 5 years later, adopted a slightly more conservative approach. Their trial, published in 1985 [7], compared a more limited tumor resection (initially defined partial mastectomy and later lumpectomy) with a total mastectomy that included removal of the fascia overlying the muscles but not the muscles themselves. As in the Milan trials, patients with stage I–II breast cancer were eligible, but maximum tumor diameter was 4 cm. Patients were treated with lumpectomy only if resection margins were negative. Axillary dissection was generally more limited than in the Milan trial.

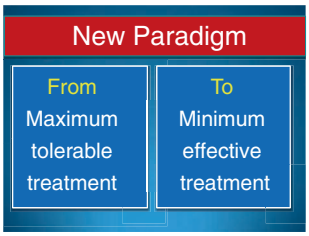


Fig. 23.1 Cancer surgery revolution from 1970

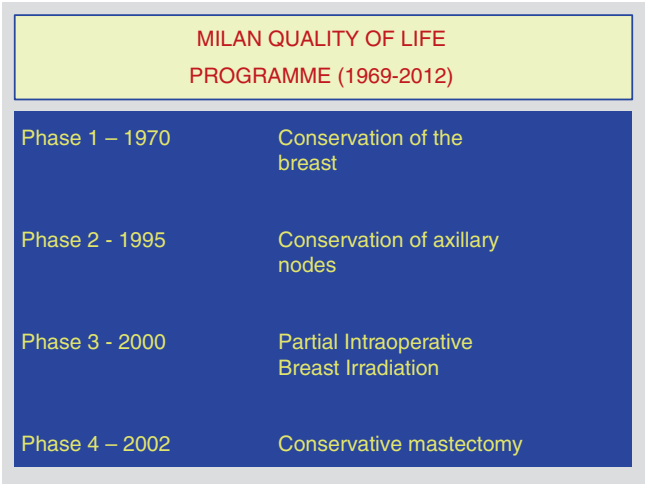


Fig. 23.2 Milan program for quality of life for breast cancer patients

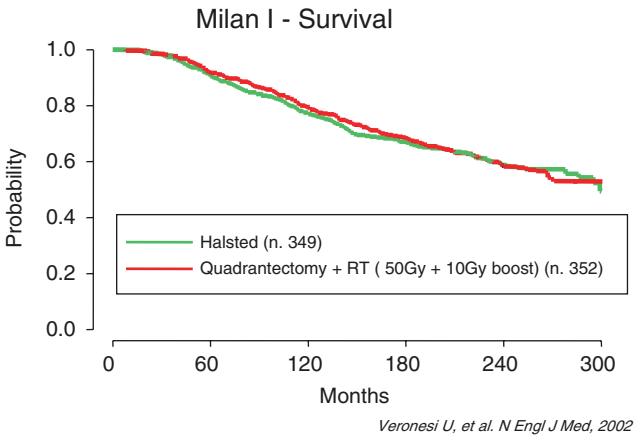


Fig. 23.3 Long-term survival of patients treated with Halsted mastectomy (349 patients) and quadrantectomy plus radiotherapy (352 patients)

Fisher found that distant disease-free survival and overall survival were no worse in the lumpectomy arm than mastectomy arm. The results were confirmed after a long-term follow-up [8].

In 1979, the National Cancer Institute conducted a prospective randomized study comparing modified radical mastectomy vs. lumpectomy—with resection margins, either positive or negative, with axillary dissection and adjuvant radiotherapy [9]. After 20 years of follow-up of 237 patients, OS and DFS were comparable; however according to the authors, "breast failures continued to occur throughout the follow up" [10].

A study with a similar design was launched in 1980 by EORTC. The trial randomized 868 patients with T1 and T2 tumors until 1986 to either modified mastectomy or lumpectomy—with positive or negative resection margins—with axillary dissection and adjuvant radiotherapy [11]. At 10 years, the results were similar to those of the NCI trial. Overall survival and distant metastasis-free survival were similar; however local recurrences were higher in the lumpectomy group.

Between 1983 and 1989, the Danish Breast Cancer Cooperative Group after randomizing 905 patients to either modified radical mastectomy or lumpectomy with axillary dissection and radiotherapy concluded that OS and DFS did not differ significantly [12].

These large randomized trials conducted in the 70s and early 80s showed the way to "less surgery" and practically changed the principles of breast cancer surgery. Furthermore, they confirmed the hypothesis that the prognosis of breast cancer patients is linked to the presence or absence of distant metastasis and changes in local treatment do not affect the overall survival. Breast conservation became a standard treatment, and the updates published at the beginning of the twenty-first century confirmed that mutilating interventions such as Halsted radical mastec-

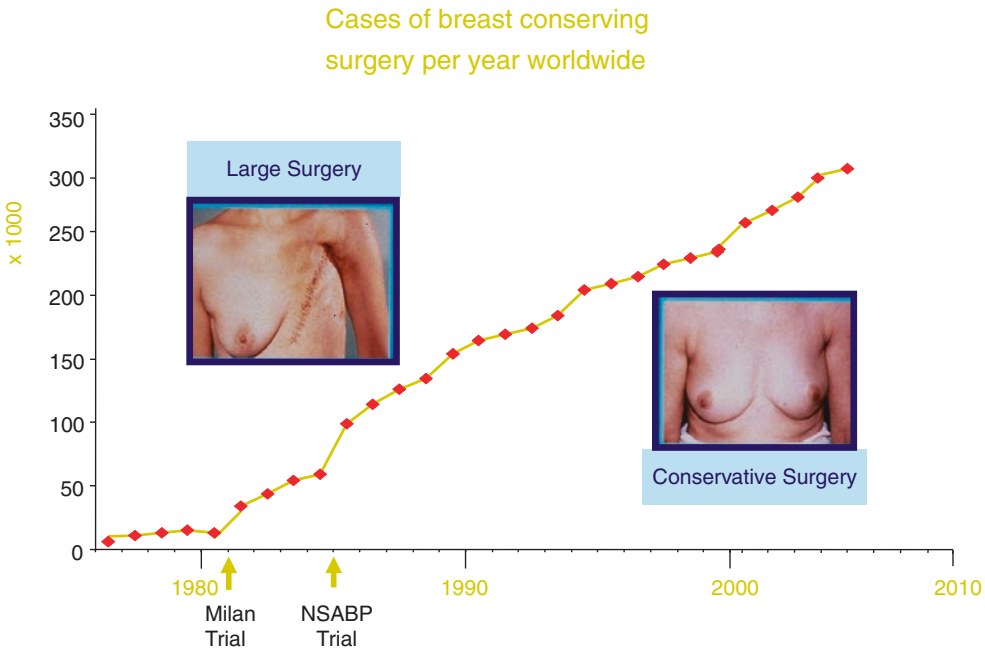


Fig. 23.4 Rough estimate of the increase of conservation of the breast worldwide

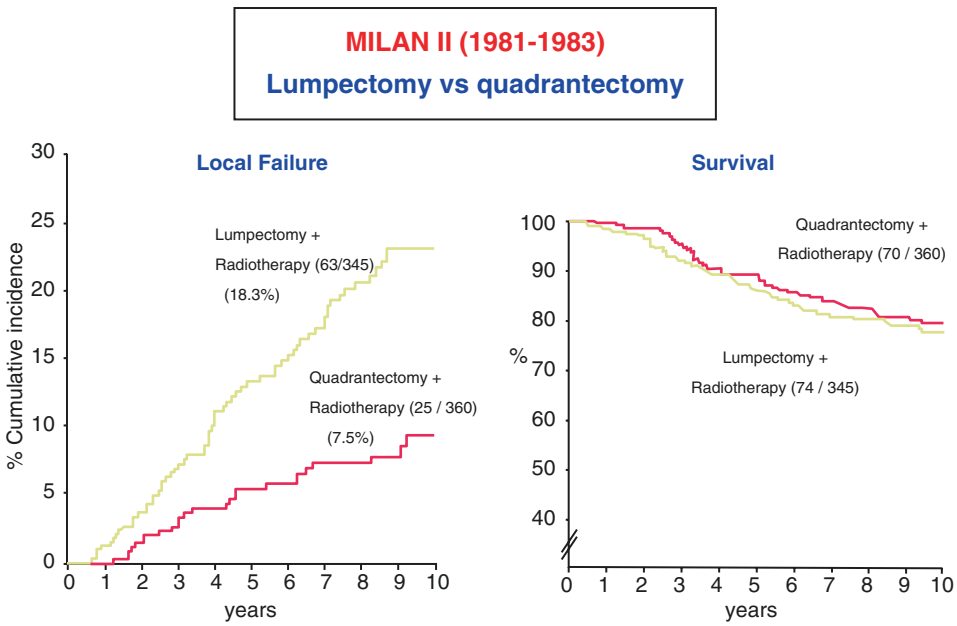


Fig. 23.5 Ten-year results of the randomized trial (705 cases) comparing lumpectomy vs. quadrantectomy (*left* Local Failure, *right* Survival)

tomy belong to the past. However, some uncertainty remained about the extent of the breast conservation. This issue was further investigated with a randomized study (Milan II) that was conducted between 1985 and 1987, and its results were published in 1990 [13]. Seven hundred and five patients with tumors up to 2.5 cm were randomized to receive either quadrantectomy or lumpectomy. All patients underwent axillary dissection and radiotherapy. In quadrantectomy, 2–3 cm of normal tissue surrounding the tumor was excised, as well as the tumor overlying the skin and the underlying fascia. In lumpectomy, only a rim of 1 cm around the tumor was excised. After a follow-up of 10 years, OS and distant metastasis rate were not different, while in breast tumor recurrence was significantly higher in the lumpectomy group [14] (Fig. 23.5).

23.4 Postsurgical Radiotherapy

Following the establishment of breast conservation as treatment of choice for early breast cancer, the role of radiotherapy on locoregional control remained to be clarified. The effects of adjuvant radiotherapy were evaluated by two randomized trials. The first was conducted at the Milan Cancer

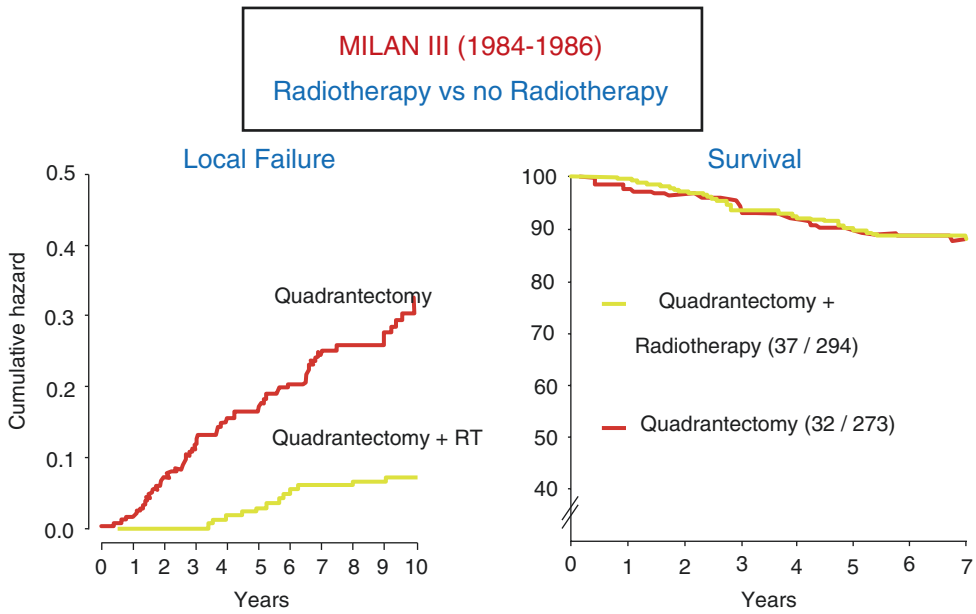


Fig. 23.6 Ten-year results of the randomized trail (567 patients) comparing postoperative radiotherapy vs. no radiotherapy (*left* Local Failure, *right* Survival)

Institute (Milan III) between 1987 and 1989 and recruited 567 patients with tumors up to 2.5 cm [15, 16]. They were randomized to quadrantectomy with axillary dissection with or without adjuvant radiotherapy. The radiotherapy group had a significantly lower local recurrence rate; however the 5-year overall survival was comparable. Similarly, the Uppsala-Orbero Breast Cancer Study Group reported the same conclusions in a study of 381 patients with pT1 tumors [17]. Radiotherapy is considered an important component of breast conservation, at least in women who are younger than 60 years old. For patients over 60 years old, a multicenter randomized trial was conducted, in order to assess the necessity of radiotherapy. Between 2001 and 2005, 749 patients with early breast cancer were assigned to either surgery only or to surgery and breast radiotherapy, and after 5 years of follow-up, a difference in breast recurrence (2.5% vs. 0.7%) was found, but no difference in overall survival and in distant disease-free survival [18] (Fig. 23.6).

23.5 Intraoperative Radiotherapy

Up to 85% local recurrences after conservative treatment develop in the scar area. This finding suggests that in many patients, only the tumor bed needs to be irradiated [18]. Furthermore, if this partial-breast irradiation could be given in single session and was noninferior to conventionally fractionated whole-breast irradiation, it would substantially ease the difficulties of women who have to contend with long waiting lists for radiotherapy or who live distant from a radiotherapy center. Such treatment would also be simpler and less expensive than conventional whole-breast irradiation. For these reasons, the European Institute of Oncology developed an intraoperative radiotherapy ELIOT (electron intraoperative therapy) technique that can deliver full-dose irradiation (21 Gy) over a few minutes during the surgery. The method employs a mobile linear accelerator that delivers an electron beam via an arm to which is attached a sterile cylindrical applicator. After cancer removal, the surgeon detaches the residual breast from the underlying fascia and inserts an aluminum-lead disk between the fascia and the gland to protect deep structures. The breast is temporarily reconstructed and the skin retracted out of the way. The energy of the electron beam (variable from 3 to 12 MeV) is selected based on gland thickness as measured by a needle [19–21].

In the year 2000, a randomized study was started at the European Institute of Oncology (Milan, Italy). Women aged 48–75 years with early breast cancer, a maximum tumor diameter of up to 2.5 cm, were assigned in a 1:1 ratio to receive either whole-breast external radiotherapy or intraoperative radiotherapy with electrons (ELIOT). Study coordinators, clinicians, and patients were aware of the assignment. Patients in the intraoperative radiotherapy group received one dose of 21 Gy to the tumor bed during surgery. Those in the external radiotherapy group received 50 Gy in 25 fractions of 2 Gy, followed by a boost of 10 Gy in five fractions. This was an equivalence trial; the prespecified equivalence margin was local recurrence of 7.5% in the intraoperative radiotherapy group.

One thousand three hundred five patients were randomized (654 to external radiotherapy and 651 to intraoperative radiotherapy) between November 20, 2000, and December 27, 2007. After a medium follow-up of 5–8 years (IQ 4.1–7.7), 35 patients in the intraoperative radiotherapy group and four patients in the external radiotherapy group had an IBTR ($p < 0.0001$). The 5-year event rate for IBRT was 4.4% (95% CI 2.7–6.1) in the intraoperative radiotherapy group and

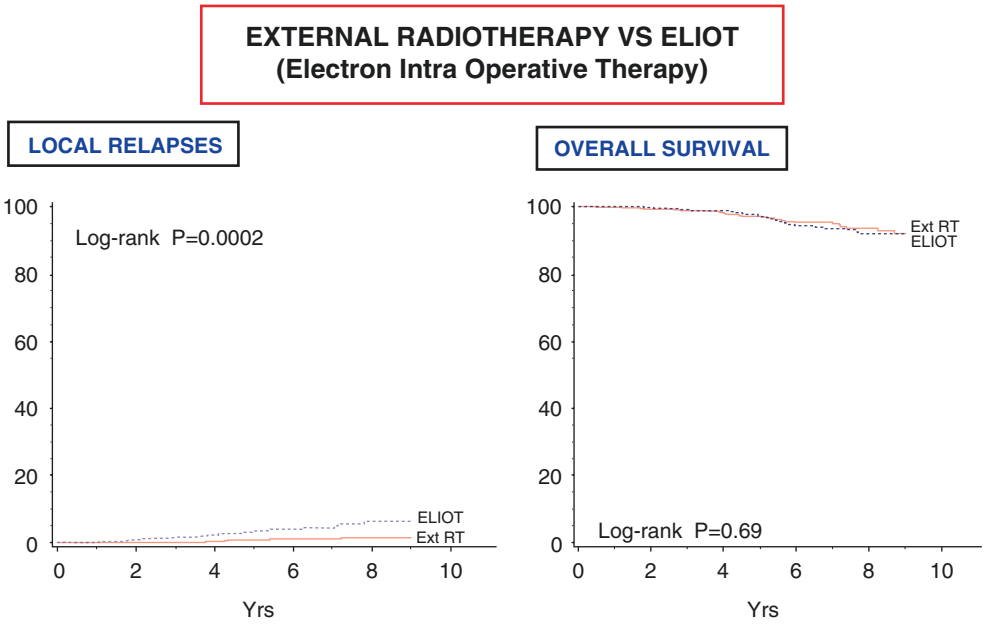


Fig. 23.7 Ten-year results of the randomized trial comparing external radiotherapy vs. intraoperative radiotherapy with electrons (1305 cases)

0.4% (0.0–1.0) in the external radiotherapy group (hazard ratio 9.3 [95% CI 3.3–26.3]). During the same period, 34 women allocated to intraoperative radiotherapy and 31 to external radiotherapy died ($p = 0.59$). Five-year overall survival was 96.8 (95% CI 95.3–98.3) in the intraoperative radiotherapy group and 96.9% (95.5–98.3) in the external radiotherapy group. In patients with data available ($n = 464$ for intraoperative radiotherapy; $n = 412$ for external radiotherapy), we noted significantly fewer skin side effects in women in the intraoperative radiotherapy group than those in the external radiotherapy group ($p = 0.0002$) [22].

In conclusion, although the rate of IBTR in the intraoperative radiotherapy group was within the prespecified equivalence margin, the rate was significantly greater that with external radiotherapy, and overall survival did not differ between groups. Improved selection of patients could reduce the rate of IBTR with intraoperative radiotherapy with electrons (Fig. 23.7).

23.6 Conservation of Axillary Nodes

The concept of "less surgery" was extended to the treatment of the axilla. The role of radiotherapy on the axilla was evaluated in a study conducted in Milan between 1995 and 1998 [23]. Four hundred and thirty five patients with small tumors, ≤1.2 cm, were randomized to either axillary radiotherapy or nothing. After 63 months of follow-up, the axillary metastases presented were lower than expected in both groups, suggesting that axillary dissection can be avoided in this subgroup of patients and that radiotherapy has a protective effect.

The introduction of the sentinel lymph node biopsy puts under investigation the role of axillary dissection. It was already anticipated that the positivity of the axilla was an element of prognosis and not a reason to perform more extensive surgery. Sentinel lymph node biopsy is a method of "predicting" the axillary status sparing the patient from axillary dissection and its often devastating complications, like arm lymphedema. As soon as the technique of sentinel lymph node biopsy was standardized, a series of randomized control studies started worldwide. The first was the Milan Trial that in 1998 and 1999 randomized 506 patients with tumors up to 2 cm to two arms, one receiving immediate axillary dissection and the other receiving the dissection only if the sentinel node was involved [24]. After 79 months of follow-up, OS and DFS were equal. Only one case of axillary recurrence was observed among the patients in the group who did not receive axillary dissection. The long-term analysis showed that patients had less mortality rates after sentinel lymph node biopsy policy than after immediate dissection (18 vs. 25 deaths).

An identical study was conducted between 1999 and 2004 that randomized 5,611 women with invasive breast cancer up to 4 cm from 80 centers in the USA and in Canada to either axillary dissection or to sentinel lymph node biopsy alone with axillary dissection only if the SLN was positive [25, 26]. After 95.6 months of follow-up, OS and DFS were similar in the two groups. A sub-study reported that up to 12 months postoperatively, patients with axillary dissection had significantly higher arm morbidity and significantly more restricted social activity and impaired QoL.

A multicenter UK trial, ALMANAC trial, studied the QoL in patients with SLN vs. axillary dissection between 1999 and 2003 [27]. One thousand and thirty one patients participated, and at 12 months, it was evident that lymphedema was higher in the axillary dissection group; operative time, drainage use, and hospitalization were much longer in

axillary dissection group, while in SLN group, patients had better arm functioning score. The results of the Danish Breast Cancer Cooperative Group confirmed the ones of ALMANAC. Arm lymphedema and dysfunction were significantly higher in the axillary dissection group at 12 months for ALMANAC and at 18 months for DBCCG [28].

It appeared clear that in case of absence of metastatic nodes, axillary dissection is not only unnecessary but also harmful. But what if the axillary lymph nodes are positive? Is axillary dissection still necessary or can it be avoided? The answer to this question is nowadays under investigation. The NSABP Z0011 trial has randomized 891 patients with T1 and T2 tumors and positive SLN from 115 centers from 1999 to 2004 to receive axillary dissection or no further treatment [29]. At 6.3 years of follow-up, the 5-year OS and the DFS were not different in the two groups, suggesting that prophylactic axillary dissection may not be necessary. The EORTC AMAROS trial has randomized patients with positive SLN to either axillary dissection or axillary radiotherapy from 2001 to 2010 [30]. At the European Institute of Oncology, a multicenter randomized, non-inferiority, phase 3 trial was conducted on 465 patients who had clinically nonpalpable axillary lymph node(s) and a primary tumor of 5 cm or less and who, after sentinel-node biopsy, had one or more micrometastatic (≤2 mm) sentinel lymph nodes with no extracapsular extension. Patients were randomly assigned (in a 1:1 ratio) to either undergo axillary dissection or not to undergo axillary dissection. Between April 1, 2001, and February 28, 2010, 465 patients were randomly assigned to axillary dissection and 469 to no axillary dissection. After a median follow-up of 5–0 (IQR 3.6–7.3) years, we recorded 69 disease-free survival events in the axillary dissection group and 55 events in the no axillary dissection group. Breast cancer-related events were recorded in 48 patients in the axillary dissection group and 47 in the no axillary dissection group [31] (Fig. 23.8). Another multicentric randomized trial

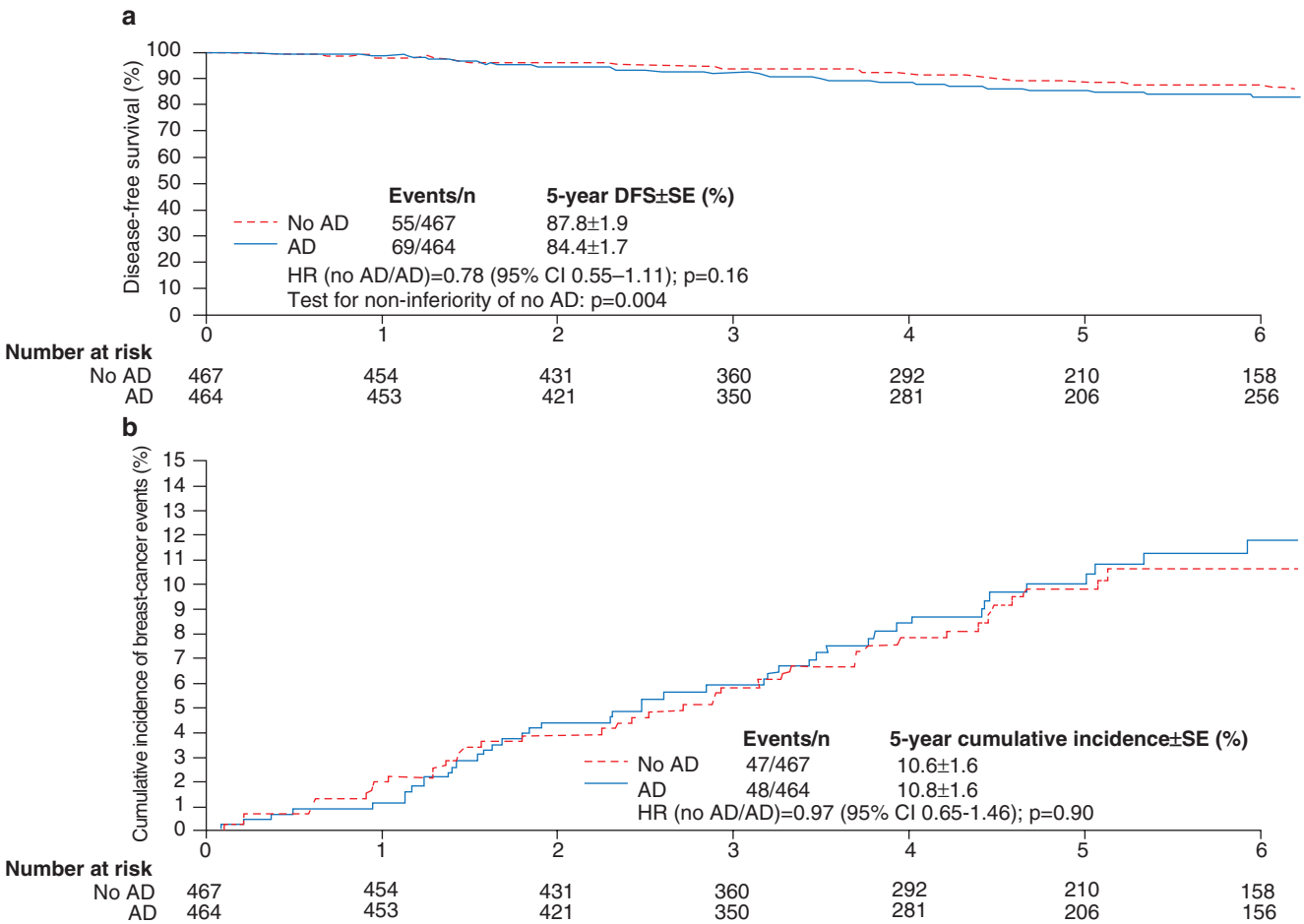
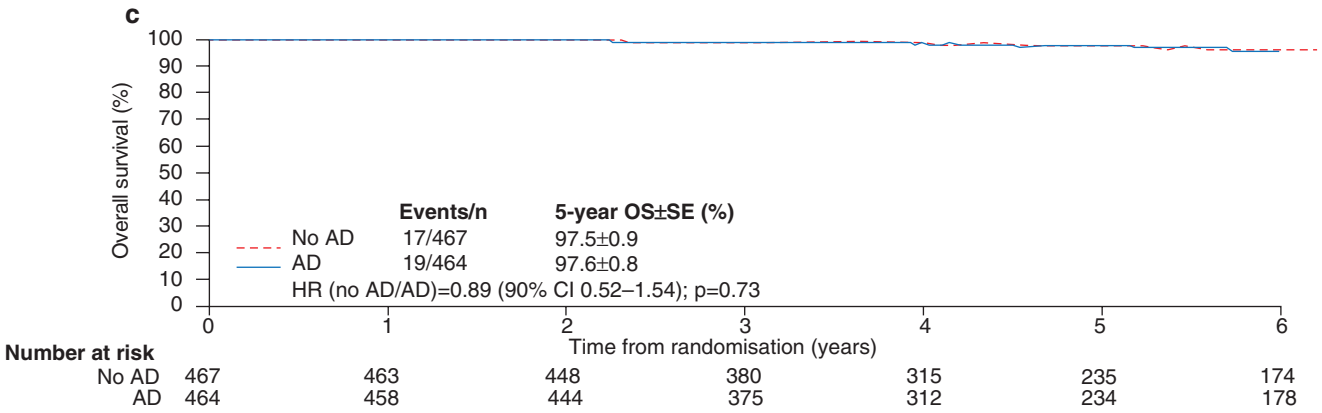


Fig. 23.8 Analysis of disease-free survival, cumulative incidence, and overall survival by intention to treat (n = 931 patients) *AD* axillary dissection. *DFS* disease-free survival. *OS* overall survival. (**a**) Disease-free survival. (**b**) Cumulative incidence of breast cancer events. (**c**) Overall survival in the intention-to-treat population of 931 patients



From Galimberti V, et al. Lancet Oncology 2013 Apr;14(4):297-305

Fig. 23.8 (continued)

studying the role of axillary treatment is the SOUND trial starting at the IEO, in Milan. Patients with pT1 tumors and negative axillary US scan are randomized to either SLN biopsy and axillary dissection if positive or to no sentinel biopsy at all. The results of this trial might completely change the approach to the axillary treatment, abandoning the sentinel node biopsy in patients with an uninvolved axilla at clinical and ultrasonographical examination.

23.7 Radioguided Occult Lesion Localization

Widespread use of mammography and ultrasound resulted in an increase in the number of nonpalpable breast lesions [32–34]. Various techniques are used to localize nonpalpable lesions and guide their removal, including wire-guided localization, carbon localization.

Radioguided occult lesion localization was developed in 1996 at the European Institute of Oncology [35]. Radioactive tracer is injected into the center of the lesion under ultrasound or mammographic control. During surgery, a gamma ray probe is used to locate the lesion and guide its removal. For malignant lesions, ROLL is used together with SNB, a technique called SNOLL [36]. In SNOLL, the patient receives two radiotracer injections: one directly into the lesion and another peritumorally. The first contains ^{99}Tc bound to colloid macroaggregates and serves to locate the lesion. In the second, the ^{99}Tc is bound to colloid microaggregates that move in the lymph ducts to reach the SN.

In recent decades, a steady improvement in imaging diagnostics has been observed together with a rising adherence to regular clinical breast examinations. As a result, the detection of small clinically occult (not palpable) lesions had progressively increased. At present in our institution, some 20% of the cases are treated when nonpalpable.

An analysis focused on 1,258 women who presented at the European Institute of Oncology [37] with a primary clinically occult carcinoma between 2000 and 2006, who underwent radioguided occult lesion localization (ROLL), axillary dissection when appropriate, whole-breast radiotherapy, or partial-breast intraoperative irradiation and received tailored adjuvant systemic treatment.

Median age was 56 years. Imaging revealed a breast nodule accompanied by microcalcifications in 9%. Microcalcifications alone were present in 17.1% of the cases, whereas distortion or thickening represented the remaining 24.6%. Most tumors were characterized by low proliferative rates (68.9%), positive estrogen receptors (92.3%), and non-overexpressed Her 2/neu (91.3%). After a median follow-up of 60 months, we observed 19 local events (1.5%), 12 regional events (1%), and 20 distant metastases (1.6%). Five-year overall survival was 98.6%.

The very high level of curability of patients whose breast carcinoma is not palpable and is discovered only with mammography, ultrasound, and MRI underlines the fundamental role of the imaging progress for the control of this disease.

23.8 Conservative Mastectomy

Conservative mastectomy might initially seem a contradiction in terms; however, if we regard conservation as the maintenance of body image, the expression is appropriate. Conservative mastectomy entails removal of breast parenchyma and saving the outer covering of the mammary gland

(subcutaneous fat, skin, and nipple), leaving the patient with a normal breast appearance. Substitution of the mammary gland for an implant is the only change made. The use of the term "conservative mastectomy" is, in our opinion, more appropriate than the alternative ones, such as "nipple and areola sparing mastectomy," which miss the notion that body image is the final objective.

Mastectomy with preservation of the skin and nipple-areola complex was first described by Rice and Strickler in 1951 for benign disease [38]. In 1962, Freeman [39] used the term subcutaneous mastectomy, and in the past 15 years, the procedure was called either nipple-sparing or total skin-sparing mastectomy. The techniques are similar to those of skin-sparing mastectomy with regard to the dissection of the skin flaps; however, additional preservation of the nipple needs a technically demanding retro-areolar dissection aiming at balancing complete removal of ducts with protection of nipple vascularization.

Location of the incision can be periareolar, with or without lateral extension, on the submammary fold, radial, or an omega pexy incision [40–42]. Periareolar incisions have the highest risk of nipple necrosis, whereas lateral radial incisions facilitate glandular dissection and access to the axilla for sentinel lymph-node biopsy. Some surgeons advocate video-assisted or endoscopic techniques with a midaxillary line incision [43, 44]. Sentinel lymph-node biopsy should always be undertaken during conservative mastectomy, with the breast incision used as access to the axilla (Fig. 23.9).

Skin flaps are created during conservative mastectomy that follow the cleavage plane within the subcutaneous fat, ensuring excision of all glandular tissue while a thin subcutaneous layer is preserved to support the vascular network [45]. The technique of flap dissection is important to provide adequate vascularization yet guarantee complete excision of ducts. During dissection from the pectoralis muscle, the fascia should be preserved. For large-breasted women, this dissection is risky and demanding, and sometimes skin reduction might be mandatory to achieve a normal-looking breast shape with acceptable ptosis [46–48]. In this case, nipple-areola complex preservation can be difficult, because final positioning of the nipple and areola after reconstruction might not be symmetrical to the contralateral.

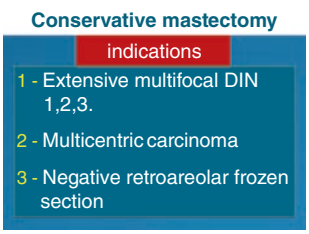


Fig. 23.9 Indications for conservative (or nipple sparing) mastectomy

The most challenging part of conservatory mastectomy is the subareolar excision because of the risk of nipple ischemia. Jensen [49] and Palmieri [50] both attempted to precondition the nipple-areola complex by dissecting it under local anesthesia from the underlying breast tissue several days before the mastectomy procedure, to stimulate blood flow from the peripheral skin. This approach has the advantage of retroareolar biopsy before mastectomy. Routinely, at the time of conservative mastectomy, the duct bundle and all retroareolar tissue are removed, and the specimen is analyzed by frozen section. This method is reliable, but some clinicians advocate the use of imprint cytology instead [51].

Intraoperative radiotherapy of the nipple-areola complex has been implemented in some centers when the frozen section of retroareolar tissue is negative, as a risk-reducing technique for local recurrence [21, 52]. However, radiotherapy is not used in all studies, yet favorable results are reported [53, 54].

The areola and a margin of 1 cm around it are included in the 90% isodose, and the dose administered must be equivalent to a fractionated dose ranging from 40 to 45 Gy [52]. In rare cases of impaired nipple vascularization diagnosed intraoperatively, external radiotherapy to the nipple-areola complex can be delivered in one session on the first postoperative day. Is radiotherapy really needed, and would a specific subgroup of patients benefit from it? A randomized trial is planned at our institute.

Heterologous implants are used extensively in breast reconstruction, and the option of fixed-volume silicone or expander implants is available. Expander implants are preferred in cases of compromised blood supply because they offer the advantage of minimal retroareolar pressure in the immediate postoperative days, when the areola is still at risk. The implant is positioned under a muscular pocket created by the pectoralis major and the serratus muscle [55]. Expanders are also preferred over fixed-volume implants, to avoid excess skin tension and flap ischemia [56, 57]. Autologous myocutaneous flap reconstruction is preferred for large-breasted women with a large skin envelope after glandular excision (Fig. 23.10).

Between March 2002 and December 2011, 2,487 patients underwent conservative mastectomy at the European Institute of Oncology. Exclusion criteria were nipple retraction, bloody discharge from the nipple, inflammatory changes of the breast, Paget's disease, and previous radiation therapy. Furthermore, tumor size needed to be less than 4 cm in diameter, and distance from the nipple-areola complex to the tumor had to be at least 2 cm. Clinical lymphadenopathy was not criterion for exclusion. A series of 934 women underwent surgery between March 2002 and December 2007 with a median follow-up of 50 months. Five-year overall survival was 96.4%, and women with invasive cancer had 5-year survival of 95.5%, and a 5-year cumulative incidence

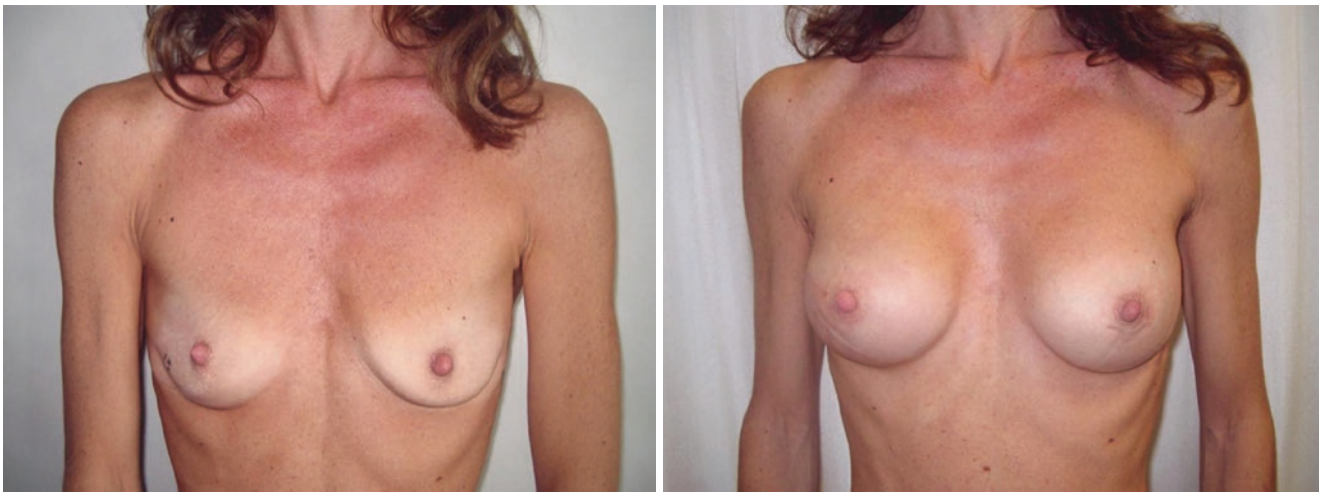


Fig. 23.10 Forty-one year-old patient before and after nipple sparing mastectomy (right breast)

of breast-related events was 14.7%. Patients with ductal intraepithelial neoplasia has 5-year overall survival of 100%. The high survival rates of our series suggest that conservative mastectomy combines safety with good cosmesis [58].

References

1. Bonadonna G, Veronesi U, Brambilla C et al (1990) Primary chemotherapy to avoid mastectomy in tumors with diameters of three centimeters of more. J Natl Cancer Inst 19:1539–1545
2. Lacour J, Bucalossi P, Cacers E et al (1976) Radical mastectomy versus radical mastectomy plus internal mammary dissection. Five-year results of an international cooperative study. Cancer 37(1):206–214
3. Veronesi U, Valagussa P (1981) Inefficacy of internal mammary nodes dissection in breast cancer surgery. Cancer 47(1):170–175
4. Lacour J, Le M, Caceres E, Koszarowski T, Veronesi U, Hill C (1983) Radical mastectomy versus radical mastectomy plus internal mammary dissection. Ten year results of an international cooperative trial in breast cancer. Cancer 51(10):1941–1943
5. Veronesi U, Saccozzi R, Del Vecchio M et al (1981) Comparing radical mastectomy with quadrantectomy, axillary dissection, and radiotherapy in patients with small cancers of the breast. N Engl J Med 305(1):6–11
6. Veronesi U, Cascinelli N, Mariani L et al (2002) Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. N Engl J Med 347(16):1227–1232
7. Fisher B, Bauer M, Margolese R et al (1985) Five-year results of a randomized clinical trial comparing total mastectomy and segmental mastectomy with or without radiation in the treatment of breast cancer. N Engl J Med 312(11):674–681
8. Veronesi U, Paganelli G, Galimberti V et al (1997) Sentinel-node biopsy to avoid axillary dissection in breast cancer with clinically negative lymph-nodes. Lancet 349:1864–1867
9. Lichter AS, Lippman ME, Danforth DN Jr et al (1992) Mastectomy versus breast-conserving therapy in the treatment of stage I and II carcinoma of the breast: a randomized trial at the National Cancer Institute. J Clin Oncol 10(6):976–983
10. Poggi MM, Danforth DN, Sciuto LC et al (2003) Eighteen-year results in the treatment of early breast carcinoma with mastectomy versus breast conservation therapy: the National Cancer Institute Randomized Trial. Cancer 98(4):697–702
11. van Dongen JA, Voogd AC, Fentiman IS et al (2000) Long-term results of a randomized trial comparing breast-conserving therapy with mastectomy: European Organization for Research and Treatment of Cancer 10801 trial. J Natl Cancer Inst 92(14):1143–1150
12. Blichert-Toft M, Rose C, Andersen JA et al (1992) Danish randomized trial comparing breast conservation therapy with mastectomy: six years of life-table analysis. Danish Breast Cancer Cooperative Group. J Natl Cancer Inst Monogr 11:19–25
13. Veronesi U, Volterrani F, Luini A et al (1990) Quadrantectomy versus lumpectomy for small size breast cancer. Eur J Cancer 26(6):671–673
14. Mariani L, Salvadori B, Marubini E, Conti AR, Rovini D, Cusumano F, Rosolin T, Andreola S, Zucali R, Rilke F, Veronesi U (1998) Ten year results of a randomised trial comparing two conservative treatment strategies for small size breast cancer. Eur J Cancer 34(8):1156–1162
15. Veronesi U, Luini A, Del Vecchio M et al (1993) Radiotherapy after breast-preserving surgery in women with localized cancer of the breast. N Engl J Med 328(22):1587–1591
16. Veronesi U, Marubini E, Mariani L et al (2001) Radiotherapy after breast conserving surgery in small breast carcinoma. Ann Oncol 12:997–1003
17. Uppsala-Orebro Breast Cancer Study Group (1990) Sector resection with or without postoperative radiotherapy for stage I breast cancer: a randomized trial. J Natl Cancer Inst 82(4):277–282
18. Tinterri C, Gatzemeier W, Zanini V et al (2009) Conservative surgery with and without radiotherapy in elderly patients with early-stage breast cancer: a prospective randomised multicentre trial. Breast 18(6):373–377. Epub 2009 Nov 11
19. Orecchia R, Luini A, Veronesi P et al (2006) Electron intraoperative treatment in patients with early-stage breast cancer: data update. Expert Rev Anticancer Ther 6:606–611
20. Veronesi U, Orecchia R, Luini A et al (2010) Intraoperative radiotherapy during breast conserving surgery: a study on 1822 cases treated with electrons. Breast Cancer Res Treat 124:141–151
21. Orecchia R, Ciocca M, Tosi G et al (2005) Intraoperative electron beam radiotherapy (ELIOT) to the breast: a need for a quality assurance programme. Breast 14(6):541–546. Epub 2005 Oct 19
22. Veronesi U, Orecchia R, Maisonneuve P et al (2013) Intraoperative radiotherapy versus external radiotherapy for early breast cancer (ELIOT): a randomized controlled equivalence trial. Lancet Oncol 14:1269–1277

23. Veronesi U, Orecchia R, Zurrida S et al (2005) Avoiding axillary dissection in breast cancer surgery: a randomized trial to assess the role of axillary radiotherapy. Ann Oncol 16(3):383–388. Epub 2005 Jan 24
24. Veronesi U, Paganelli G, Viale G et al (2006) Sentinel-lymph-node biopsy as a staging procedure in breast cancer: update of a randomised controlled study. Lancet Oncol 7(12):983–990
25. Krag DN, Anderson SJ, Julian TB et al (2010) Sentinel-lymph-node resection compared with conventional axillary-lymph-node dissection in clinically node-negative patients with breast cancer: overall survival findings from the NSABP B-32 randomised phase 3 trial. Lancet Oncol 11(10):927–933
26. Land SR, Kopec JA, Julian TB et al (2010) Patient-reported outcomes in sentinel node-negative adjuvant breast cancer patients receiving sentinel-node biopsy or axillary dissection: National Surgical Adjuvant Breast and Bowel Project phase III protocol B-32. J Clin Oncol 28(25):3929–3936. Epub 2010 Aug 2
27. Mansel RE, Fallowfield L, Kissin M et al (2006) Randomized multicenter trial of sentinel node biopsy versus standard axillary treatment in operable breast cancer: the ALMANAC Trial. J Natl Cancer Inst 98(9):599–609
28. Husted Madsen A, Haugaard K, Soerensen J et al (2008) Arm morbidity following sentinel lymph node biopsy or axillary lymph node dissection: a study from the Danish Breast Cancer Cooperative Group. Breast 17(2):138–147. Epub 2007 Oct 24
29. Giuliano AE, Hunt KK, Ballman KV et al (2011) Axillary dissection vs. no axillary dissection in women with invasive breast cancer and sentinel node metastasis: a randomized clinical trial. JAMA 305(6):569–575
30. Rutgers EJ, Meijnen P, Bonnefoi H (2004) Clinical trials update of the European Organization for Research and Treatment of Cancer Breast Cancer Group. Breast Cancer Res 6:165–169
31. Galimberti V, Cole BF, Zurrida S et al (2013) Axillary dissection versus no axillary dissection in patients with sentinel-node micrometastases (IBCSG 23-01): a phase 3 randomised controlled trial. Lancet Oncol 14:297–305
32. Kelly KM, Dean J, Lee SJ, Comulada WS (2010) Breast cancer detection: radiologists' performance using mammography with and without automated whole-breast ultrasound. Eur Radiol 20:2557–2564
33. Nadeem R, Chagla LS, Harris O et al (2005) Occult breast lesions: a comparison between radioguided occult lesion localization (ROLL) vs. wire-guided lumpectomy (WGL). Breast 14:283–289
34. Luini A, Zurrida S, Paganelli G et al (1999) Comparison of radioguided excision with wire localization of occult breast lesions. Br J Surg 86:522–525
35. Monti S, Galimberti V, Trifirò G et al (2007) Occult breast lesion localization plus sentinel node biopsy (SNOLL): experience with 959 patients at the European Institute of Oncology. Ann Surg Oncol 14:2928–2931
36. Giacalone PL, Bourdon A, Trinh PD et al (2012) Radioguided occult lesion localization plus sentinel node biopsy (SNOLL) versus wire-guided localization plus sentinel node detection: a case control study of 129 unifocal pure invasive non-palpable breast cancer. Eur J Surg Oncol 38:222–229
37. Veronesi U, Luini A, Botteri E et al (2010) Nonpalpable breast carcinomas: long-term evaluation of 1,258 cases. Oncologist 15:1248–1252
38. Rice CO, Strickler JH (1951) Adeno-mammectomy for benign breast lesions. Surg Gynecol Obstet 93:759–762
39. Freeman BS (1962) Subcutaneous mastectomy for benign breast lesions with immediate or delayed prosthetic replacement. Plast Reconstr Surg 30:676–682
40. Maxwell GP, Storm-Dickerson T, Whitworth P, Rubano C, Gabriel A (2011) Advances in nipple-sparing mastectomy: oncological safety and incision selection. Aesthet Surg J 31(3):310–319
41. Regolo L, Ballardini B, Gallarotti E, Scoccia E, Zanini V (2008) Nipple sparing mastectomy: an innovative skin incision for an alternative approach. Breast 17(1):8–11. Epub 2007 Sep 17
42. Crowe JP Jr, Kim JA, Yetman R, Banbury J, Patrick RJ, Baynes D (2004) Nipple- sparing mastectomy: technique and results of 54 procedures. Arch Surg 139(2):148–150
43. Petit JY, Veronesi U, Orecchia R et al (2006) Nipple-sparing mastectomy in association with intra operative radiotherapy (ELIOT): a new type of mastectomy for breast cancer treatment. Breast Cancer Res Treat 96:47–51
44. Garwood ER, Moore D, Ewing C et al (2009) Total skin-sparing mastectomy: complications and local recurrence rates in 2 cohorts of patients. Ann Surg 249(1):26–32
45. Nakajima H, Fujiwara I, Mizuta N et al (2010) Clinical outcomes of video-assisted skin-sparing partial mastectomy for breast cancer and immediate reconstruction with latissimus dorsi muscle flap as breast-conserving therapy. World J Surg 34(9):2197–2203
46. Leff DR, Vashisht R, Yongue G, Keshtgar M, Yang GZ, Darzi A (2011) Endoscopic breast surgery: where are we now and what might the future hold for video-assisted breast surgery? Breast Cancer Res Treat 125(3):607–625
47. Larson DL, Basir Z, Bruce T (2011) Is oncologic safety compatible with a predictably viable mastectomy skin flap? Plast Reconstr Surg 127(1):27–33
48. Nava MB, Ottolenghi J, Pennati A et al (2012) Skin/nipple sparing mastectomies and implant-based breast reconstruction in patients with large and ptotic breast: oncological and reconstructive results. Breast 21(3):267–271. doi:10.1016/j.breast.2011.01.004. Published online March 25
49. Jensen JA, Orringer JS, Giuliano AE (2011) Nipple-sparing mastectomy in 99 patients with a mean follow-up of 5 years. Ann Surg Oncol 18(6):1665–1670. 2010 Dec 21
50. Palmieri B, Baitchev G, Grappolini S, Costa A, Benuzzi G (2005) Delayed nipple-sparing modified subcutaneous mastectomy: rationale and technique. Breast J 11(3):173–178
51. Boneti C, Yuen J, Santiago C et al (2011) Oncologic safety of nipple skin-sparing or total skin-sparing mastectomies with immediate reconstruction. J Am Coll Surg 212(4):686–693
52. Petit JY, Veronesi U, Orecchia R et al (2009) Nipple sparing mastectomy with nipple sparing areola intraoperative radiotherapy: one thousand and one cases of five years experience at the European Institute of Oncology of Milan (EIO). Breast Cancer Res Treat 117:333–338
53. Margulies AG, Hochberg J, Kepple J, Henry-Tillman RS, Westbrook K, Klimberg VS (2005) Total skin-sparing mastectomy without preservation of the nipple-areola complex. Am J Surg 190(6):907–912
54. Wang J, Xiao X, Wang J et al (2012) Predictors of nipple-areolar complex involvement by breast carcinoma: histopathologic analysis of 787 consecutive therapeutic mastectomy specimens. Ann Surg Oncol 19:1174–1980
55. Salzberg CA, Ashikari AY, Koch RM, Chabner-Thompson E (2011) An 8-year experience of direct-to-implant immediate breast reconstruction using human acellular dermal matrix (AlloDerm). Plast Reconstr Surg 127(2):514–524
56. Colwell AS, Damjanovic B, Zahedi B, Medford-Davis L, Hertl C, Austen WG Jr (2011) Retrospective review of 331 consecutive immediate single-stage implant reconstructions with acellular dermal matrix: indications, complications, trends, and costs. Plast Reconstr Surg 128(6):1170–1178
57. Petit JY, Veronesi U, Orecchia R et al (2012) Risk factors associated with recurrence after nipple-sparing mastectomy for invasive and intraepithelial neoplasia. Ann Oncol 23(8):2053–2058. Accessed 9 Jan 2012
58. Veronesi U, Stafyla V, Petit JY, Veronesi P (2012) Conservative mastectomy: extending the idea of breast conservation. Lancet Oncol 13(7):311–317