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Attaining pathological complete regression for breast conservation – A pilot experience in a developing country

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HIGHLIGHTS

- Extended chemotherapy sessions alongside re-excisions are successful in achieving much enhanced rates of pathologically complete remissions even for T3 tumours.
- Our findings shows a much higher PCR rates than previous studies on the subject.
- Neoadjuvant/adjuvant chemotherapy and serial re-excisions were utilized succesfully in attaining pathologically complete remission.
- The use of pathologically complete remissions as endpoints in breast conservation for breast cancer may be fraught with less controversy than negative margins.

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ABSTRACT

Context: Local recurrence is a formidable risk consideration in employing breast conservation for breast cancer. However pathological complete regression (PCR) from chemotherapy has been associated with improved rates of recurrence. Lower PCR rates have been reported from earlier studies and our approach seeks to obtain higher PCR rates utilizing a two pronged approach of surgery and chemotherapy.
Objective: To determine success rates in attaining pathologically complete regression for breast conservation in non-metastatic breast cancer cases in a developing country and their clinical outcome.
Patients and methods: Patients diagnosed with early stage breast cancers had sequential anthracycline/taxane based neoadjuvant/adjuvant chemotherapy administered at three weekly intervals. Following an initial excision, re-excisions were done following three courses of doxorubicin based chemotherapy. Subsequent re-excisions in cases with failed complete pathological regression were repeated following additional three doxorubicin based chemotherapy cycles or at sequel third taxane based cycle. Endpoint was pathologically complete regression as determined on permanent sections.
Results: Patients ages ranged between 27 and 67 years, mean age 43years, SD 10.34 years, N = 20 Initial breast tumour sizes ranged between 0.5 and 9 cm, mean 4.05 cm, SD 2.38. There were three T4, four T3 tumours, seven T2 and six T1 tumours. Clinical axillary lymphadenopathy with pathological involvement was present in 11 cases. Histological diagnosis showed 13 cases of invasive ductal carcinoma (65.0%), 2 cases of ductal carcinoma insitu (10.0%), 1 papillary carcinoma (5.0%), 3 cases of invasive lobular carcinoma (15.0%) and non-specific type 1 (5.0%). Immunohistochemistry assessment available in 15 cases was positive for estrogen and progesterone receptors in 10 cases. Two cases (10.0%) exhibited 20% positivity for human epidermal growth factor receptor. Pathological complete regression (PCR) defined as no invasive or insitu tumour residuals in the excised tumour bed, was achieved in the 18 cases assessed. (100%) This was consistent with clinical complete response obtained. It was not determined in 2 cases though clinical complete response was obtained. PCR was determined in ten cases (50.0%) at the first reexcision, second reexcision in 4 cases (20.0%) and third reexcision in 4 cases (20.0%). Mean no of re-excisions 1.67 cm, SD 0.84. Six sequential anthracycline/taxane cycles were administered in 17 cases while three cases received anthracycline based chemotherapy only. Median duration of followup from diagnosis was 48 months ranging between 8 months and 144 months. There were two demises at 48 months and 36 months follow up.

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Conclusion: Extended chemotherapy sessions alongside re-excisions were successful in achieving much enhanced rates of pathologically complete remissions at 100% in this yet early report, thus improving breast conservation rates even for T3 and T4 tumours. Our study reports higher PCR rates.

1. Introduction

Conservative breast management (CBM) has become attractive for breast surgeons following the several large international trials showing equivalent survivals between mastectomy and conservative breast management for suitable cases [1–6]. This has taken several decades for acceptability, the first observation haven being made after Geoffrey Keanes reported equal outcomes following local tumour excision with radium irradiation to Halstead mastectomy in the early 20th century [7]. Being the standard of care for early breast cancer, the advantage of preserving the breast is balanced against the risk of local recurrence comparable to that from mastectomy. This is demonstrated with various series reporting similar recurrence rates for CBM and mastectomy at 10–20% of ipsilateral breast tumour recurrence (IBTR) or chest wall failure over 10 years [1,5]. While such local recurrences have been reported to be clinically isolated events in 75% of cases, they may herald the onset of distant metastases in up to 15% of cases [8]. Among the factors reported to promote local recurrence following breast conservation has been presence of residual tumour or incomplete pathological regression of tumour (positive margins of excision). Camp et al. [9] have shown that local recurrence depends on the status of the lumpectomy margin [10]. With local recurrence rates at 7% and 27% reported for negative and extensively positive margins respectively [11], achieving negative margins is extremely desirable if adequate local control rates must be attained in breast conservation.

Tumour negative margin describes an absence of tumour cells > 2 mm from the excised tumour margin. This has been bedeviled by controversy with various schools of thought concerning what constitutes the optimum margin. However, pathologically complete remission defined as absence of tumor residuals in breast and nodes, has been reported to be associated with favourable outcomes [12]. We believe that the use of pathologically complete remissions as endpoints in breast conservation for breast cancer may be fraught with less controversy than negative margins. It has been further enunciated that breast cancer patients who achieve pathological complete remission have an improved prognosis than their stage of disease. We think it to be a desirable endpoint in conservative breast management.

The bulk of literature on the subject has sought to employ the use of neoadjuvant chemotherapy only to achieve pathologically complete remission with varying degrees of success reported based on the hormonal and the HER 2neu receptor status [13]. One study reported a PCR rate at 11% [14]. Green et al. reported 28.2% and 15.7% PCR rates in their series for weekly and three weekly interval chemotherapy respectively [15]. We seek to employ neoadjuvant-adjuvant chemotherapy and surgery (excision) in achieving higher success rates as we perceive that the resultant lesser local tumour burden following surgery may enable earlier onset of PCR hence achieve complete remission even for tumours that may be perceived as having the least chance of PCR by older studies.

Determining pathological complete remission justifies the employment of breast conservation. However mastectomy is yet the treatment of choice and strong bias for breast surgeons in Nigeria, even in early cases [16]. Conserving breast surgery even though internationally acceptable still faces considerable hurdles to its implementation as the philosophy of 'more is better' still has an enormous following in Nigeria. Hoover et al. have stated in the United States that despite decades of work resulting in the declaration of conserving breast surgery at a National Institute of health Consensus development more than two decades ago as the treatment of choice for early breast cancer, there was an enormous disconnect on its utilization [17]. We are not aware of studies done in the West African subregion as breast conservation is regrettably at an infancy stage in the country and indeed the subregion. For breast conservation to gain popularity in the country, quality control measures must be set up, geared towards achieving local control rates comparable with mastectomy. It is our view that determining pathological complete remission employing a two pronged approach of excision and chemotherapy constitutes the avenue to achieve this. It is our conviction that higher success rates utilizing this approach may be achievable even for larger tumours.

2. Objective

To determine success rates at achieving pathological complete remission emanating from the employ of surgery (excisions) and chemotherapy in breast conservation for breast cancer.

3. Patients and methods

Patients presenting to the Author with a breast lump or mass from 2004 up to 2015 at the Central hospital Warri, Delta Nigeria and Curatio medicare Oncology clinics, Warri, Delta Nigeria were evaluated with history taking, general and systemic examination with emphasis on a clinical breast exam. Diagnosis of breast cancer was made following biopsy and histopathological confirmation by trained pathologist. Immunohistochemistry assessment was done with some of the samples. Staging was done with the benefit of mammogram, chest xray and abdominal ultrasound. Unavailability of technetium bone scan in the centre precluded its request. Those with early breast cancer were counselled on the surgical options of breast conservation and a total mastectomy. For breast conservation, gross excision of the tumour was done and specimens sent for histology. With adequacy of bone marrow function determined by a full blood count before chemotherapy cycles, doxorubicin and cyclophosphamide at three weekly intervals for 6 cycles was administered. Paclitaxel or docetaxel administered at three weekly intervals or weekly intervals was then administered sequentially. (AC/P) Further re-excisions of the tumour bed were timed between chemotherapy cycles to assess for pathologically complete remissions based on the clinical perception of response. Bone marrow function was assessed before each cycle and patients with white cell counts below 1,500 mm3 had granulocyte colony stimulating factor administered to booster counts. Pathologically complete remissions were defined histopathologically as no residual invasive or insitu tumour cells at tumour bed. Serial clinical breast exams were done during chemotherapy sessions to assess for clinical complete response. Clinical complete response was defined by no palpable breast lump or axillary lymph node, restoration of normal soft tissue consistency of the breast from earlier post surgical

Table 1
Clinicopathological details of cases.

Age	Histology	Immunohisto-chemistry	Size of lump	Clinical axillary lymphnode	No of re-excisions to ascertain PCR	Chemotherapy regimen
32	Intra ductal	Not available	0.5cm	Negative	Not done	CAF
27	Invasive ductal	Not available	2cm	Negative	1	AM
49	Invasive ductal	Not available	4cm	Positive	Not done	CAF
32	Invasive lobular	Er–, Pr–, Her–	4cm	Positive	3	AM/P
32	Invasive lobular in pregnancy	Er–, Pr–, Her–	3cm	Negative	2	CAF/P
42	Invasive ductal	Er+, Pr+, Her–	5cm	Positive	1	CAF
39	Invasive lobular	Er+, Pr+, Her–	7cm	Positive	1	AC/P
62	Invasive ductal	Er+, Pr+, Her–	2cm	Negative	3	AC/P
67	Intraductal	Er-, Pr-, Her–	1cm	Negative	3	AC/P
45	Invasive ductal	Er+, Pr+, Her–	7cm	Positive	2	AC/P
38	Invasive ductal	Er+, Pr+, Her–	4.5cm	Positive	1	AC
45	Invasive ductal	Er+, Pr+, Her–	6cm	Positive	1	AC/P
39	Invasive ductal	Er–, Pr–, Her–	4cm	Positive	1	AC/P
37	Papillary carcinoma	Er+,Pr+,Her–	6.5cm	Positive but negativ histology	1	AC/P
33	Invasive ductal	Er+,Pr+her–	2cm	Negative	1	AC/D
47	Invasive ductal	Er+Pr+Her–	1.5cm	Negative	3	AC/D
46	Non-specific type	Er+Pr+her–	4cm	Positive	2	AC/D
47	Invasive ductal	Er+PrHer–	2cm	Negative	2	AC/D
57	Invasive ductal		7cm	Positive	1	AC
44	Invasive lobular	Er– Pr+Her–	9cm	Positive	1	AC/D

A-adriamycin, C-cyclophosphamide, M-methotrexate, P-paclitaxel, D -Docetaxel.

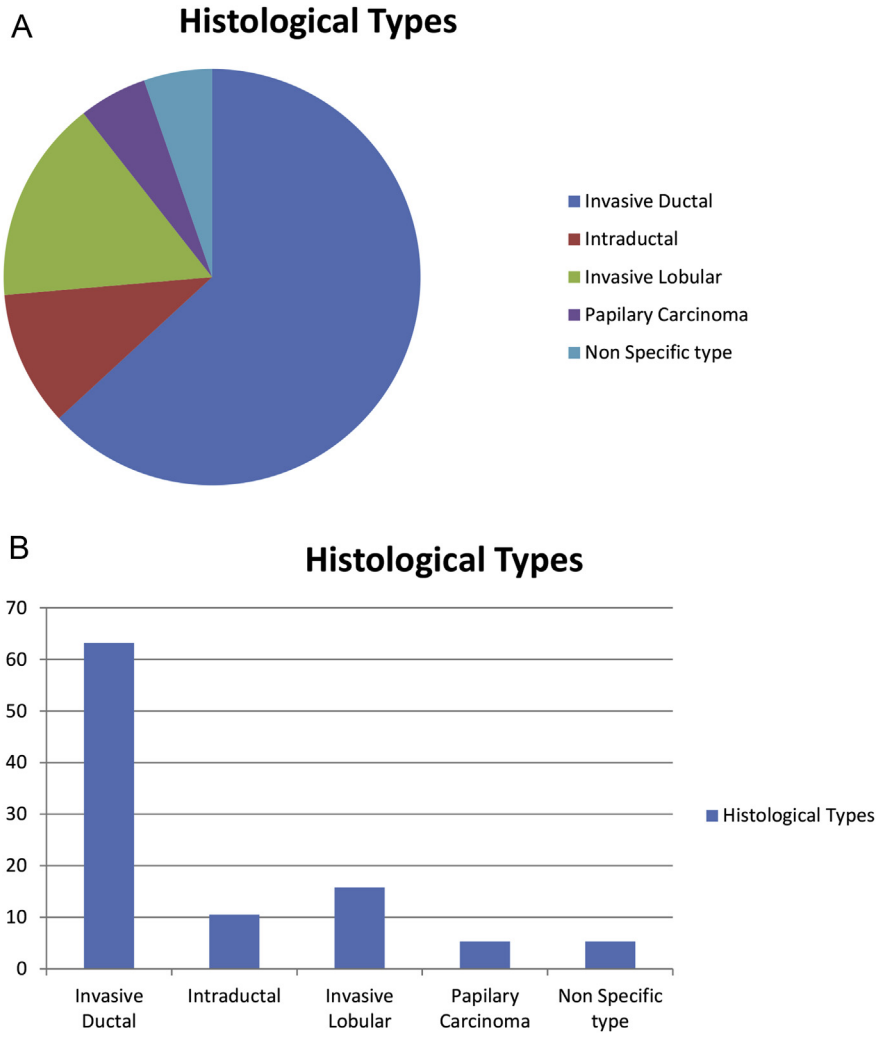

Fig. 1. A-Histological types of breast cancer. B-Histological types of breast cancer.

induration and absence of any breast skin changes. On attainment of PCR, the required numbers of chemotherapy cycles were continued. Ethical approval was obtained for this study.

4. Results

There were 66 breast cancer cases over the study period, twenty of whom were considered suitable candidates for PCR attainment for breast conservation(see Table 1). Their ages ranged between 28 and 67 years. Mean age 43 years SD, 10.34. Tumour sizes ranged between 1.5 cm and 9 cm, Mean size, 4.05 cm SD 2.38. There were 6 T1, 7 T2, 4 T3 and 2 T4 tumours. The T3 and T4 constituted locally advanced cases at 30%. Histological variant was invasive ductal carcinoma, 13 (63.2%), intraductal carcinoma 2 (10.5%), invasive lobular carcinoma 3 (15.8%), papillary carcinoma 1 (5.3%) and non specific type 1 (5.3%) Fig. 1 a and b. Axillary lymphadenopathy with pathological involvement was present in 10 cases. Pathological complete regression (PCR) was ascertained and confirmed in eighteen cases following re-excisions and systemic therapy while two did not get histological assessment but achieved clinical complete response. PCR was determined in 9 cases at the first reexcision (47.1%), second reexcision in 4 cases (23.5%) and third reexcision in 4 cases (23.5%). Mean number of re-excisions was 1.67, SD 0.84(see Fig. 2a and b). Sixteen cases had 6 sequential cycles of anthracycline/taxane based chemotherapy while 3 cases had anthracycline only. Eleven cases (55%), achieved PCR within 4,5th cycles of doxorubicin based chemotherapy, while seven cases (35%) attained this status with a sequential taxane chemotherapy following doxorubicin and prior excisions and re-excisions. The mean tumour size of the eleven cases was 3.8 cm, mean age 38.9 years. The seven cases had a mean size of 3.86 cm and mean age 49.14 years. Hormone positivity existed in five of the seven cases. Patients were followed up over varying degrees of time ranging from 8 months to 144 months post diagnosis. Two cases demised at 3 and 4 years post diagnosis. One of the demised case, a T3N1M0 developed ovarian cancer which was unrelated to the treated breast cancer. The other case, a T2N2M0 demised from unknown cause having been lost to follow up prior to her reported demise. There has been no disease recurrence in the other cases.

5. Discussion

Eligibility for breast conservation has been determined by availability of radiotherapy, breast cosmesis and ability to obtain negative margins [18]. With non-availability of frozen section analysis for tumourectomy cavity assessment, initial lumpectomy was done guided by gross examination of the macroscopic margins. Thus pathological complete remissions could only be determined

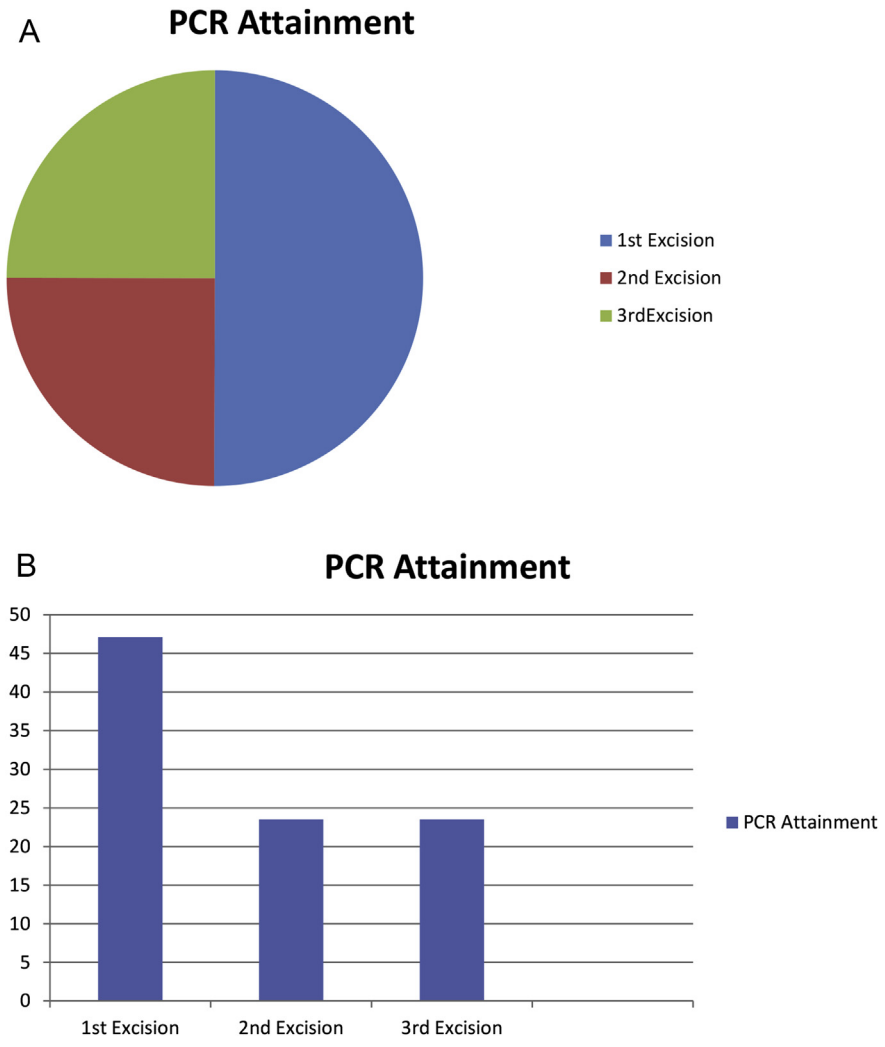

Fig. 2. A-Pathological complete regression attainment B-Pathological complete regression attainment by excisions.

on permanent sections. This is comparable with occurrences in Western worlds where Jorns et al. reported that most institutions do not utilize intraoperative analysis of lumpectomy specimen and even fewer offer frozen section due to technical limitations when using standard frozen section techniques [19]. Another report from the Western world showed just 48% of Surgeons examined the margins grossly with a pathologist and fewer used frozen section or imprint cytology [20]. However our mini-series did not rely on gross determination of tumour negative margins as we are cautioned by the report of Balchi et al. that in at least one quarter of cases, gross appearance did not correlate with margin status [21].

Our pilot series required re-excisions in achieving pathologically complete remissions. Poor cosmetic outcome, anaesthetic risks and psychological concerns have been ascribed to re-excisions [22]. However, our re-excisions were done largely under local anaesthesia with minimal risk. The patients apprehension for repeat breast surgery was balanced out by their resentment for total mastectomy and hence a dedication towards breast conservation. Morrow et al. have asserted that multiple re-excisions during lumpectomy to achieve negative margin does not compromise cosmesis, so long as the Surgeon does not reapproximate the lumpectomy cavity [23]. Our series achieved a 100% pathologic complete remission rate utilizing extended cycles of chemotherapy, timed excisions and re-excisions. For example although a majority (67.7%) of the series attained this status within 4,5th cycles of doxorubicin based chemotherapy and surgery, 33.3% attained this status with a sequential taxane chemotherapy following doxorubicin and surgery. This meant that a third of the cases would have been perceived to have failed pcr attainment if chemotherapy was aborted at the anthracyclines.

The issue of local recurrence continues to be a consideration in breast conservation. However Veronesi et al. reported local recurrence following lumpectomy/radiotherapy, quandrantectomy/radiotherapy at a yearly rate of 2.45 and 0.46 respectively. This was compared against Halstead mastectomy at 0.20 [24]. Local recurrence was reported to be higher in patients less than 45 years though survival curves were similar for breast conservation and Halstead mastectomy [24]. A local recurrence rate of 7% has been reported for focally positive margins similar to rate obtained for negative margins when systemic therapy was incorporated [11]. Hence systemic therapy and margin status have been reported as the strongest predictors of local recurrence [11]. Neoadjuvant chemotherapy has been reported as being an in vivo assessment of the sensitivity of the tumour for the chemotherapeutic drug [25]. It played a key role in attaining pathologically complete remissions in our pilot series. It has been reported to achieve significant tumour downgrading in larger breast tumours hence better chances at being candidates for breast conservation with great expectation of long term survival [25]. Additionally, better breast cosmesis has been reported, a gain for breast conservation achieved by less extensive resections [26]. This was seen in six of our cases with locally advanced tumours T3 and T4 at 30% of the cases, which were downstaged and subsequent PCR attainment permitting breast conservation where a mastectomy would have been required. Earlier treatment of micrometastases upon systemic treatment with reduced chances of development of resistant subclones and disease progression with tumour resections have all being adduced as innumerable benefits from systemic treatment. [27,28], Cortzan et al. have determined that pathological complete response as occurred in our cases, indicated improved event free survival and overall survival than those with residual invasive cancer [26]. This is consistent with the impressive results so far obtained in our series.

The available immunohistochemistry in 12 of our cases showed hormone positivity in 8 cases, negativity in 4 cases and a 20% positivity for Her positive in a case; all attaining pathologically complete remission. The rate of pathologically complete regression attainment has been reported to be increased with her 2neu positive tumours treated with herceptin as well as triple negative tumours. Additionally, a higher rate of response was observed with high grade hormone positive tumours than low grade hormone positive tumours [26]. Hormone receptor positive cancers had the least chance of PCR especially with the low grade [13]. This was demonstrated in 4 (22.2%) of our patients who were hormone positive, Her negative who had a delayed attainment of PCR. It was also determined that triple negative cancers and her 2neu positive but hormone negative tumours, exhibited the most long term association with pathologically complete response [13].

Our findings are limited by the yet appreciating sample size. Additionally our definition of a pathological complete regression has examined the tumour bed largely in contradistinction to studies that examined the mastectomised specimen. However we have corroborated the tumour bed findings following breast conservation with a clinical complete response in both breast and axilla. This correlates with the yet disease free state of our cases.

Ethical approval

Ethical approval was given by the Central Hospital Warri ethical committee.

Sources of funding

There are no sources of funding for this research.

Author contribution

Dr E.A Sule conceived the study, managed the patients, collected the data and wrote up the report. Dr Nzegwu read the pathology slides, read and made contributions to the report and agreed with the final version.

Conflicts of interest

We declare no conflict of interest.

Guarantor

Dr E. A Sule.

Research Registration Unique Identifying Number (UIN)

Study has been registered. Researchregistry145.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.amsu.2016.05.019.

References

[1] R. Arriagada, M.G. Le, F. Rochard, G. Contesso, Conservative treatment versus mastectomy in early breast cancer: patterns of failure with 15 years of follow-up data, J. Clin. Oncol. 14 (1996) 1558–1564.
[2] M. Blichert-Toft, C. Rose, J.A. Andersen, et al., Danish randomized trial comparing breast conservation therapy with mastectomy: six years of life-table analysis, J. Natl. Cancer Inst. Monogr. (11) (1992) 19–25.
[3] B. Fisher, S. Anderson, J. Bryant, et al., Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer, N. Engl. J. Med. 347 (2002) 1233–1241.
[4] M.M. Poggi, D.N. Danforth, L.C. Sciuto, et al., Eighteen-year results in the

treatment of early breast carcinoma with mastectomy versus breast conservation therapy: the national cancer institute randomized trial, Cancer 98 (2003) 697–702.
[5] J.A. van Dongen, A.C. Voogd, I.S. Fentiman, et al., 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 (2000) 1143–1150.
[6] U. Veronesi, N. Cascinelli, L. Mariani, et al., Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer, N. Engl. J. Med. 347 (2002) 1227–1232.
[7] G. Keynes, Breast cancer: a case for conservation, Br. Med. J. 282 (6273) (1981) 1392.
[8] E. Touboul, L. Buffat, Y. Belkacémi, et al., Local recurrences and distant metastases after breast-conserving surgery and radiation therapy for early breast cancer, Int. J. Radiat. Oncol. Biol. Phys. 43 (1999) 25–38.
[9] E.R. Camp, P.F. McAuliffe, J.S. Gilroy, et al., Minimizing local recurrence after breast conserving therapy using intraoperative shaved margins to determine pathologic tumour clearance, J. Am. Coll. Surg. 201 (2005) 855–861.
[10] M. Morrow, R. Jagsi, A.K. Alderman, et al., Surgeon recommendations and receipt of mastectomy for treatment of breast cancer, JAMA 302 (2009) 1551–1556.
[11] C.C. Park, M. Mitsumori, A. Nixon, A. Recht, J. Connolly, R. Gelman, et al., Outcome at 8 years after breast conserving surgery and radiation therapy for invasive breast cancer; influence of margin status and systemic therapy on local recurrence, J. Clin. Oncol. 18 (2000) 1668–1675.
[12] G. Von Minckwitz, M. Untch, J.U. Blohmer, S.D. Coster, H. Eidtmann, P.A. Fasching, et al., Definition and impact of pathologically complete response on prognosis after neoadjuvant chemotherapy in various intrinsic breast cancer subtypes, J. Clin. Oncol. 30 (2012) 1796–1804.
[13] P. Cortazar, L. Zhang, M.N. Untch, K. Mehta, J.P. Constantino, N. Wolmark, et al., Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis, Lancet 384 (2014) 164–172.
[14] S. Luangdilok, N. Samarnthai, K. Korphaisarn, Association between pathological complete response and outcome following neoadjuvant chemotherapy in locally advanced breast cancer patients, J. Breast Cancer 17 (4) (2014) 376–385.
[15] M.C. Green, A.U. Buzdar, T. Smith, N.K. Ibrahim, V. Valero, M.F. Rosales, et al., Weekly paclitaxel improves pathologic complete remission in operable breast cancer when compared with paclitaxel every 3 weeks, J. Clin. Oncol. 23 (2005) 5983–5992.
[16] E.A. Sule, Mastectomy; the scourge of late presentations. Conservative breast management to the rescue, Ann. rural Suburb. Med. (2008).
[17] S. Hoover, E. Bloom, S. Patel, Review of breast conservation therapy: then and now, ISRN Oncol. 2011 (2011), http://dx.doi.org/10.5402/2011/617593. Article ID 617593, 13 pages.
[18] L.A. Newman, H.M. Kuerer, Advances in breast conservation therapy, J. Clin. Oncol. 23 (2005) 1685–1697.
[19] J.M. Jorns, D. Visscher, M. Sabel, M. Breslin, P. Healy, S. Daignaut, et al., Intraoperative frozen section analysis of margins in breast conserving surgery significantly decreases reoperative rates, Am. J. Clin. Pathology 138 (2012) 657–669.
[20] S.L. Blair, K. Thompson, J. Rococco, V. Malcarne, P.D. Beitsch, D.W. Ollila, Attaining negative margins in breast-conservation operations: is there a consensus among breast surgeons? J. Am. Coll. 209 (2009) 608–613.
[21] G.C. Balch, S.K. Mithani, J.F. Simpson, M.C. Kelley, Accuracy of intraoperative gross examination of surgical margin status in women undergoing partial mastectomy for breast malignancy, Am. Surg. 71 (2005) 22–27.
[22] C. Dener, A. Inan, M. Sen, S. Demirici, Intraoperative frozen section for margin assessment in breast conserving surgery, Scand. J. Surg. 98 (2009) 34–40.
[23] M. Morrow, E.A. Strom, L.W. Bassett, et al., Standard for breast conservation in the management of invasive breast carcinoma, CA Cancer J. Clin. 52 (2002) 277–300.
[24] U. Veronesi, B. Salvadori, A. Luini, M. Greco, R. Saccozzi, M. Del Vecchio, et al., Breast conservation is a safe method in patients with small cancer of the breast. Long-term results of three randomised trials on 1,973 patients, Eur. J. cancer 31 (1995) 1574–1579.
[25] G.F. Schwartz, C.A. Birchansky, L.T. Kormanicky, C.M. Mansfield, R.I. Cantor, W.A. Biermann, et al., Induction chemotherapy followed by breast conservation for locally advanced carcinoma of the breast, Cancer 73 (1994) 362–369.
[26] A. Makris, T.J. Powles, S.E. Ashley, J. Chang, T. Hickish, V.A. Tidy, A.G. Nash, H.T. Ford, A reduction in the requirements for mastectomy in a randomized trial of neoadjuvant chemoendocrine therapy in primary breast cancer, Ann. Oncol. 9 (1998) 1179–1184.
[27] J.H. Goldie, A.J. Coldman, A mathematic model for relating the drug sensitivity of tumors to their spontaneous mutation rate, Cancer Treat. Rep. 63 (1979) 1727–1733.
[28] B. Fisher, N. Gunduz, E.A. Saffer, Influence of the interval between primary tumor removal and chemotherapy on kinetics and growth of metastases, Cancer Res. 43 (1983) 1488–1492.