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Primary Chemo-Radiotherapy in the Treatment of Locally Advanced and Inflammatory Breast Cancer

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Abstract

Background.

The best management of large, diffuse or inflammatory breast cancers is uncertain and the place of radiotherapy and/or surgery is not clearly defined.

Methods.

A cohort of 123 patients with non-metastatic locally advanced or inflammatory breast cancer 3 cm or more in diameter or T4, was treated between 1989 and 2006. All patients received primary chemotherapy followed by radiotherapy, 40 Gy in 15 fractions with 10 Gy boost. Patients with ER positive tumours received Tamoxifen. Assessment was carried out 8 weeks post-treatment and surgery was reserved for residual or recurrent disease.

Results.

For each stage there were T2/3: 63, T4b: 31 and T4d: 29 patients. 80 had complete clinical response (65%) but 18 patients were never free of inoperable local disease. 25 patients had residual operable disease at assessment and 12 patients who initially had a complete response developed operable local recurrence (LR). 37 patients (30%) had surgery at a mean of 15 months post diagnosis. At 5 years, overall survival (OS) of the two surgical groups was not significantly different from those 68 patients who had complete remission without surgery, p=0.218 HR 1.46 (0.80-2.55). Surgery as an independent variable to predict survival was not significant on a Cox proportional hazards model (p=0.97)

. LR in the surgical groups was 13.5% v. 17.5% in the non-surgical patients. The median OS was 64.5 months and disease free survival (DFS) was 52.5 months. 5-year OS was 54% and DFS survival 43%.

Conclusion.

In patients with a complete or partial response to chemo-radiotherapy for locally advanced or inflammatory breast cancer, reserving surgery for those with residual or recurrent local disease did not appear to compromise survival. This finding would support examination of this treatment strategy by a randomised controlled trial

Keywords

inflammatory breast neoplasms; radiation therapy; chemotherapy; tamoxifen; cohort studies.

Introduction

Neo-adjuvant chemotherapy has become an acceptable standard of care for the management of locally advanced and inflammatory breast cancer in the expectation that the downsized tumour may be more amenable to breast conserving surgery.[1] Post operative radiotherapy is then recommended to reduce the risk of local recurrence. There has also been a trend to treat primary breast cancers of 3 cm or more in diameter with primary chemotherapy especially where the lesion is Grade III, heavily node positive or in a young woman, although this may not improve the outcome.[2] Pre-operative chemotherapy increases the rate of breast conserving surgery[3] but complete pathological remission remains low and this may not improve overall survival [2,4,5] although one long-term study does show survival benefit.[6]

For inflammatory breast cancer there is general agreement that surgery is not appropriate primary treatment but mastectomy and post-operative radiotherapy have been recommended when there has been a complete response to chemotherapy.[7]

However, Bonadonna's group in 1981 reported a randomised trial of chemotherapy followed by surgery or radiotherapy in locally advanced breast cancer and found no

difference in the outcome [8] and there are several subsequent reports of primary chemo-radiotherapy in the management locally advanced and inflammatory tumours.[9,10,11]

The combination of chemotherapy and radiotherapy, given either concurrently or sequentially, is now the standard of care for locally advanced cancer of the naso & oropharynx[12], oesophagus[13], cervix[14] and anal canal[15] with subsequent salvage surgery where necessary. There are a number of studies in breast cancer patients where radiotherapy has been given in combination with chemotherapy but any subsequent surgery has been reserved for those cases with residual or recurrent local disease.[16] This latter management strategy, although unconventional in the management in breast cancer has been followed in this breast unit and the outcome of a cohort of patients with large, diffuse or inflammatory tumours, treated with primary sequential chemotherapy, radiotherapy and hormone therapy is presented.

Method

The period of study was from January 1st 1989 to June 31st 2006. Patients were identified from the prospective breast unit database with near complete follow up, and further data were sourced from the oncology, and pathology databases, as well as the case notes. Ethical approval was obtained for the retrospective study.

Patients with a biopsy proven invasive breast cancer were clinically staged according to the TNM classification. Those patients with a tumour 3 cm or more in diameter (T2/3) or had a diffuse (T4b) or an inflammatory carcinoma (T4d) and whose clinical node status was N0 or N1, were treated with primary chemo-radiotherapy. Axillary node status was determined by clinical examination, NX. Those who presented with metastatic disease or who developed metastases within 3 months of diagnosis were excluded from the study.

Patients received chemotherapy according to the local protocol at the time. In the early part of the study 4 patients received a CMF regime, cyclophosphamide 500mg/m^2, 5 FU 500mg/m^2 & methotrexate 35mg/m^2 intravenously on day 1 & 8 with a 28 day cycle. All subsequent patients received an anthracycline based chemotherapy, with either six cycles of AC, cyclophosphamide 600mg/m^2 & adriamycin 60 mg/m^2 with a 21 day cycle or FEC(75), 5FU 600mg/m^2, epirubicin 75 mg/m^2 & cyclophosphamide 600mg /m^2 with a 21 day cycle. Nine patients received only 4 cycles of AC. Following chemotherapy, radiotherapy was administered, tailored to the individual patient. The majority of patients received a total dose of 40 Gy in 15 fractions over 3 weeks with a mini-tangent boost to the tumour site of 10Gy in 10 fractions in 1 week. The axilla was included with the breast fields as per local protocol but the supraclavicular fossa was not irradiated routinely. From 1989 all patients were simulated for treatment planning and CT simulation was used from 2001. 3D planning and IMRT were not routinely used within the study period but the planning techniques were considered standard UK practice at the time. All patients with ER positive tumours were treated with adjuvant tamoxifen with the exception of two postmenopausal women who received an aromatase inhibitor. Three patients with ER negative tumours and 5 with unknown receptor status also received tamoxifen. Four pre-menopausal patients received goserelin in addition to tamoxifen. No patient received trastuzumab as primary therapy which was not available at the time of the study. At 6 to 8 weeks following completion of treatment, patients were assessed clinically and radiologically by mammography and ultrasound examination, and with typically 6 ultrasound or clinically guided biopsies of the tumour site. When there was no residual tumour on imaging, multiple freehand core biopsies were taken from the site in the breast of the original tumour. Patients then underwent three monthly follow-up with clinical examination and annual radiological surveillance. Delayed

primary surgery was reserved for residual disease at the time of treatment assessment or for patients who subsequently developed local recurrence which was amenable to operative intervention.

Statistical Methods

Overall and disease-free survival was calculated by the Kaplan-Meier method and compared by the log rank test, (MedCalc, Schoonjans 2005). Potential prognostic factors and survival were examined by a Cox model analysis.

Results

There were 123 female patients and the mean age at presentation was 50.6 years (range 27-73). The mean and age ranges for the tumour stages were T2: 51.4, (35-72), T3: 48.1, (27-71), T4b: 51.5, (33-65), T4d: 53.5, (28-73). There were only 12 patients over the age of 65 (10%). Over the same period 2652 patients with breast cancer were treated with a mean and median age of 62. The tumour characteristics are shown in Table 1. The mean length of follow up of the 55 survivors was 103 months and the mean follow-up of all cases was 71 months.

Eighty patients were apparently free of systemic and local disease at post-treatment assessment (65%) but of these, 24 subsequently developed local recurrence of whom 12 were operable and were treated by delayed surgery at a mean of 27.7 months (median 20). Sixty-eight patients had a complete clinical remission (55%) and were managed without surgery, apart from one patient who requested prophylactic mastectomy with complete pathological remission. Fig.1.

Core biopsy by protocol was not carried out in 29 patients (25%) and the absence of residual disease relied on clinical examination and imaging. Thirty-eight patients (33%) were found to have residual disease on post-treatment core biopsy and a further 5 had evidence of progressive disease. Of these 43 patients, 18 had progressive inoperable disease and 25 patients had operable residual disease and underwent subsequent primary surgery, 4 by wide local excision and the remainder by mastectomy at a mean of 9.2 months (median 9 months) post diagnosis. Local recurrence in the surgical groups was 13.5% v. 17.6% in non-surgical patients. Concurrent regional recurrence was respectively 2.7% v. 4.4%. Fig.1

Eight patients (6.5%) died with uncontrolled local disease, four of whom had an inflammatory cancer, T4d and two a diffuse tumour T4b. Seven of these patients had progressive disease from the outset but one initially had a complete clinical remission

Overall survival at 5 years was 54%, median 64.5 months and recurrence-free survival was 43%, median 52.5 months. Survival analysis following local treatment failure and salvage surgery (n=37) showed no significant difference in overall survival between those patients who had surgery for residual local disease at post-treatment assessment (n=25) and those with subsequent recurrent disease (n=12). p=0.646 HR 1.31 95% CI. (*0*.42-3.95). Fig 2. There was no significant overall survival advantage to those patients treated by surgery compared with those who had a complete clinical remission and no operation (n=68) p=0.218 HR 1.47 (0.81-2.55). Fig 3, or in disease free survival p=0.18 HR 1.49 (0.84-2.55). Those patients with inoperable progressive disease at post treatment assessment (n=18) had poor overall survival, 11% at 5 years. Fig 4. On comparison of those patients with (37) or without (86) salvage surgery, the tumour stage, grade, age, node and ER status were similar. A Cox proportional hazards model which excluded those patients with progressive disease, was used to

assess whether surgery could be viewed as an independent variable to predict survival but the result was not significant (p=0.97).

There was no significant difference in survival in patients who were clinically node positive (n=44) compared with those who were node negative (n=79) p = 0.28 95% C.I. (0.4-1.3). Pathological node status was not available. (pNx: n=123)

Survival in patients who were oestrogen receptor (ER) positive (49%) was significantly improved compared with those who were ER negative p=0.028 HR 1.79 CI (1.06-3.13). Patients with Grade III tumours (57%) had a marginally worse survival than those with Grade II tumours but this was not statistically significant. P=0.076, HR 0.61, 95% CI (0.36-1.05).

There was no significant difference in survival by T-stage, T2/T3 v T4 p=0.29 HR 0.775 CI (0.48-1.25). Fig 7. T2 v T3 p=0.114 HR 1.73 CI (0.86- 3.78). T4b v T4d p= 0.96 HR 1.01 CI (0.52-1.95). Fig 5b. Patients aged less than 40, (n=21) showed no difference in survival from older patients. p=0.47 HR 1.25 CI (0.66-2.45) or on age by decade.

Of 68 deaths, 58 were certified as due to breast cancer, 6 as not due to breast cancer and breast cancer was not present and 4 were uncertain or unknown.

Discussion

The aim of this study was to assess the outcome of patients treated with primary sequential chemo-radiotherapy, and to assess the role that any subsequent surgery played in maintaining local control of the disease. Primary chemoradiotherapy is now

standard practice for tumours of the nasopharynx, oesophagus, cervix and anus [12-15] with reservation of surgery for residual or recurrent disease and this policy may be adopted for some rectal cancers.[17] Many breast cancers are sensitive to chemotherapy and or radiotherapy and yet this treatment modality is not widely used.

The number of patients is relatively small but over the period of study confidence in this unconventional treatment strategy gradually increased. In the early years breast referrals to the unit were lower and latterly the incidence of locally advanced breast cancer appears to have fallen with the advent of the screening programme in the UK which started in 1988.

The complete clinical remission rate of 65% in patients with locally advanced or inflammatory breast cancer after chemo-radiotherapy is higher than would be expected after neo-adjuvant chemotherapy alone. However if all patients had had immediate surgical treatment post therapy, as would be the case with neo-adjuvant chemotherapy, the remission rate would probably have been lower since some of the post treatment core biopsies may have been false negative. Subsequent local recurrences would have been apparent at earlier stage as residual disease. Nevertheless, if all 24 subsequent local recurrences are taken as residual disease the complete remission rate would have been 45% in this poor-risk group of patients.

. The locoregional recurrence rate of 13.5% in the surgical patients and 17.5% in the non-surgical group is high but no more than would be expected from a recent large study.[18] 86 patients (70%) avoided any surgery although of these 12 had a local recurrence which was not amenable to subsequent salvage surgery. It is therefore possible that as many as twelve patients (10%) may have been disadvantaged by the lack of primary surgery. Against this must be considered the poor prognosis of this group of patients with locally advanced disease, half of whom had diffuse or

inflammatory tumours [7, 19,20,21,22,23] and as expected, the greatest risk to overall survival was the progression to metastatic disease rather than local recurrence. There was no evidence of survival benefit from surgery on multivariate analysis and there is therefore no support from this study for surgery having an independent effect on survival.

Walshe[21] has suggested that inflammatory breast cancer is a distinct disease entity although Montagna et al[23] found no difference in recurrence free or overall survival between inflammatory and non-inflammatory breast cancer, Another large study from the MD Anderson[22] reported that that the outcome from inflammatory cancers was significantly worse and this finding has been supported by a subsequent analysis of SEER data.[24] There was no significant difference in outcome in the present study when such tumours were compared with those which were designated as advanced on the basis of size and although there was a trend for the diffuse and inflammatory cancers to fare worst the difference was not significant 24 patients had T2 tumours 3 to 5cm in diameter which were nevertheless judged to be locally advanced on clinical grounds. This small group had a non-significantly worse outcome than those with T3 tumours (Fig 5b)

The lack of a significant difference in survival on the basis of node status might be unexpected but only 27 patients were operated on and the pathological node status of the cohort was therefore not available. Clinical evaluation of the axilla is well recognized to be a poor determinant of node status and ultrasound examination with needle biopsy of any suspicious node was not practiced at the time of this study. Given that the tumours were advanced, many of the patients who were rated Clinically N0 (NX) would in fact have been Pathological N1 with an expected worse survival.

The EORTC trial[10] showed that the best outcome from neoadjuvant therapy was in the group given chemotherapy, radiotherapy and hormone treatment, as in the present study but aromatase inhibitors and trastuzumab were not available at this time. Data from the more recent NOAH study has shown that trastuzumab increased event free survival in this group of patients.[25] There was a survival advantage for ER positive tumours but the difference in outcome between histological Grade 2 and less well differentiated Grade 3 tumours was not significant. Smoot et al[20] found that premenopausal status and palpable axillary nodes predicted poor survival in inflammatory breast cancer but Gajdos et al[2] found these trends non significant. In the present study the only positive prognostic factor was the oestrogen receptor status but the numbers in all these observational studies are relatively small and the risk of a type II error for negative findings is high.

In an observational study of neoadjuvant chemotherapy followed by either surgery or radiotherapy from the Royal Marsden [11] there was no difference in survival although there was a non-significant increase in local recurrence in the radiotherapy group. In the present study there has been no local recurrence in those patients having surgery for residual disease after chemoradiotherapy but this has not impacted on survival. A meta-analysis[16] of nine randomised trials of neoadjuvant versus adjuvant chemotherapy also shows an increased rate of local recurrence (LR) in patients treated by neoadjuvant therapy. It is apparent that this effect was due to non-randomised radiotherapy without surgery in those patients with complete clinical remission in the neoadjuvant groups and this trend was most marked in three trials.[3, 9, 26] It was concluded that neoadjuvant chemoradiotherapy should not be used without subsequent surgery. However, we have found that provided the breast is carefully monitored and surgery is confined to those with residual or recurrent disease, that overall survival is

not compromised and the incidence of uncontrolled LR is relatively low. There was a high mastectomy rate for residual disease in the present study 21/25 (84%) but at least two trials have found that conservative surgery in this situation leads to a high local recurrence rate with a secondary mastectomy rate of circa 20%.[3,9] The hypofractionation of the radiotherapy was unconventional at the time of this study but the safety of this treatment regime has subsequently been confirmed.[27]

The overall survival of the patients who had subsequent surgery for local treatment failure was not significantly better than the majority with a complete remission (Fig. 4) and there was no disadvantage to those with a delayed operation for recurrent disease (Fig.2). In a non-randomised observational study this non-significant finding should be viewed with caution but it does give some reassurance that delay in offering surgery does not appear to disadvantage patients with residual or recurrent disease, a policy which is supported by the long-term results from the Institut Curie(28)

With an overall 5-year survival rate of 54% comparable to the published literature, [29, 30] the use of primary combined chemotherapy, radiotherapy and endocrine treatment has been shown to provide effective treatment for locally advanced breast cancer. However, the optimal treatment of this disease remains uncertain and the need for further clinical studies is clear[18,31] The present findings from a careful surveillance policy, where the use of surgery was reserved for the treatment of residual disease or local recurrence would support examination of this treatment strategy by a randomised clinical trial.

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Tables and Figures.

Table 1.

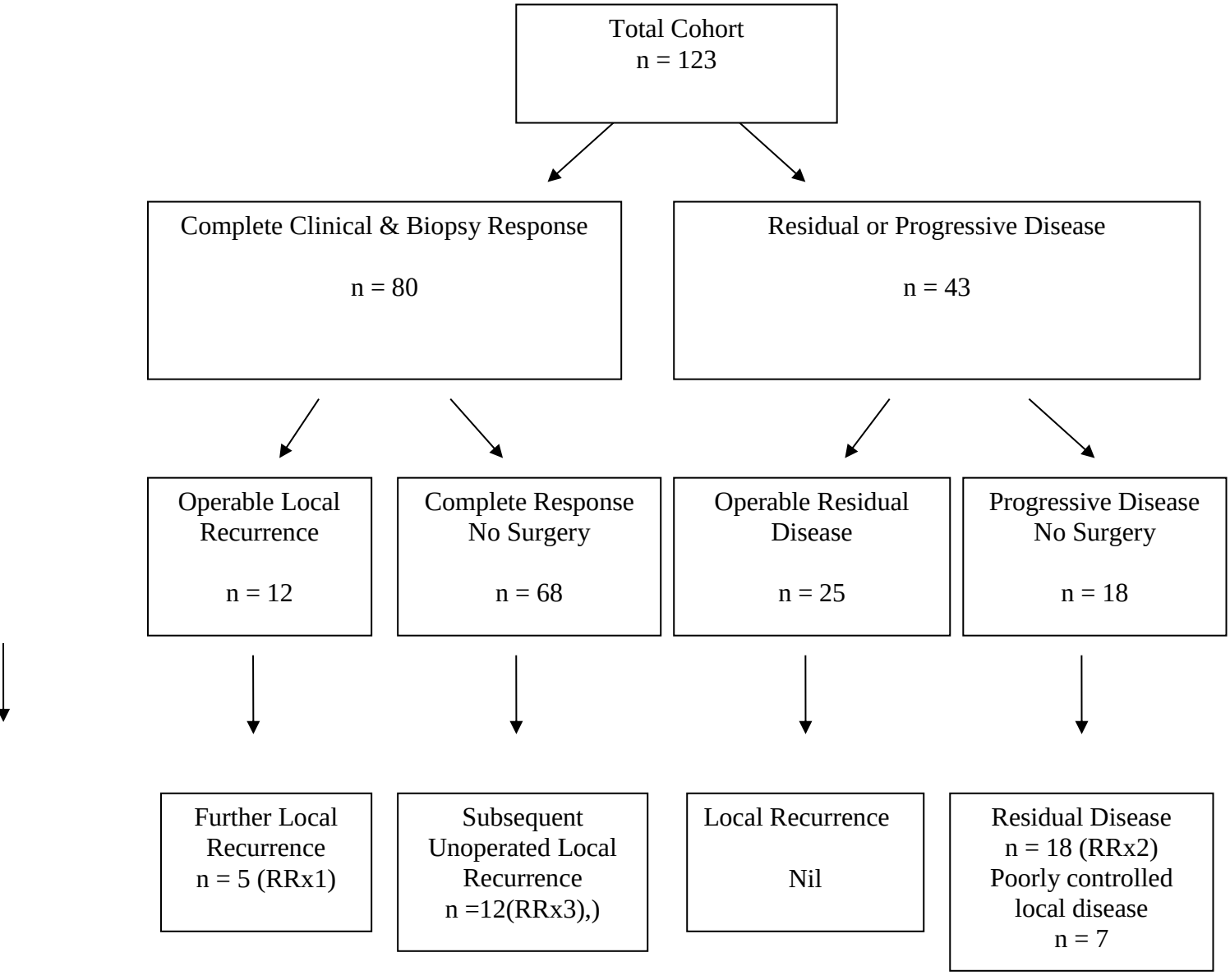
Tumour Characteristics (n=123)

Tumour	Number of Cases
T2 > 3 cm	24
T3 > 5 cm	39
T4b diffuse (peau d'orange)	31
T4d inflammatory (erythema)	29
Clinical Node Status	
No	79
N1	44
pNx (AJCC)	123
Distant metastasis	
M0	123
Grade I	2*
II	41
III	59
NR	21
ER Status +ve	50
-ve	56
NR	17
Tumour Type	
Invasive ductal ca.	101
Invasive lobular ca.	14
Mixed IDC /ILC.	3
Carcinosarcoma	3
Medullary ca.	1
NR	1

*Both T4 tumours confirmed on review of grade. NR: Not recorded

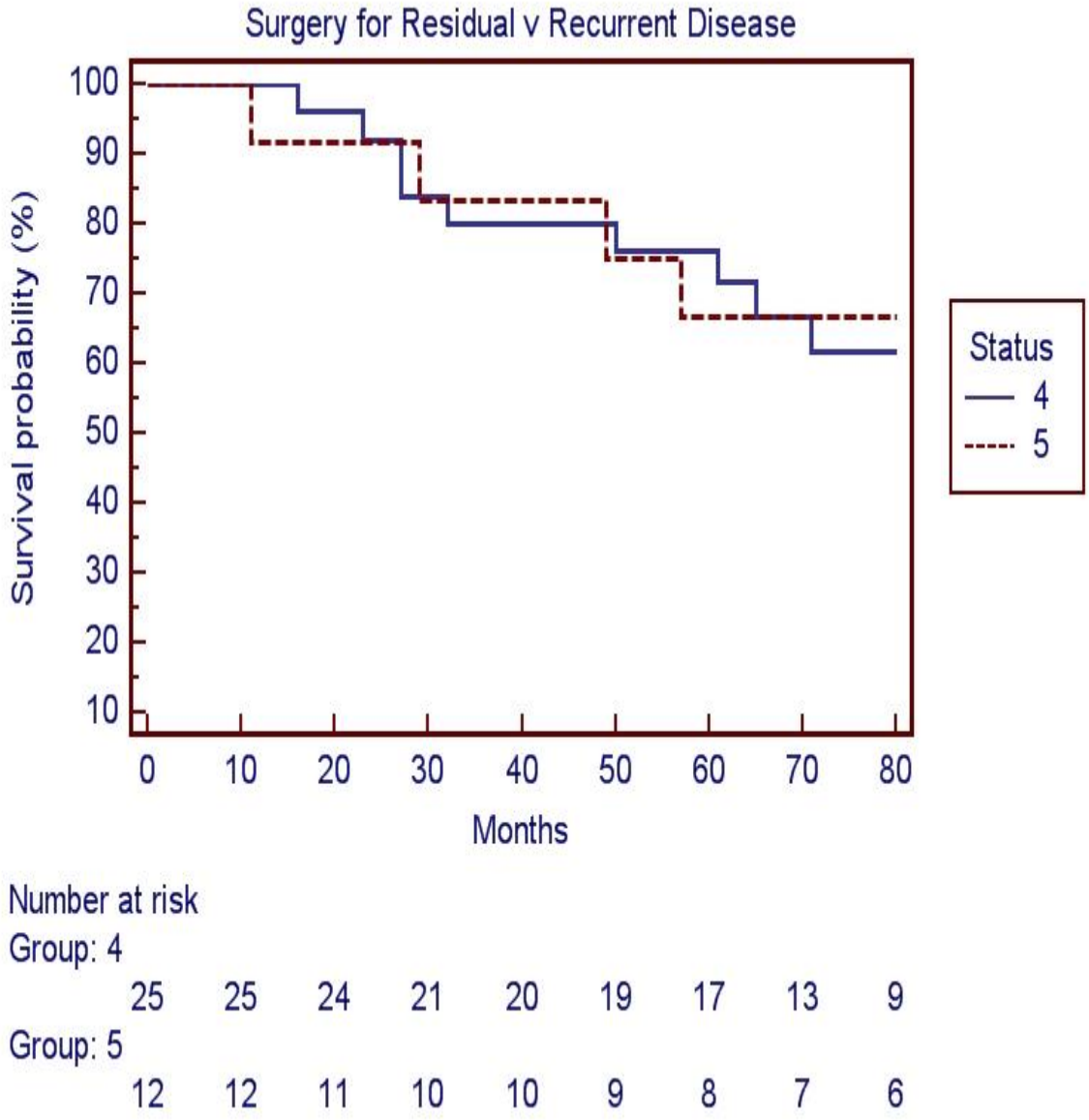
Fig. 1

Treatment Outcome of Cohort of Patients with Locally Advanced or Inflammatory Breast Cancer



RR=Regional recurrence

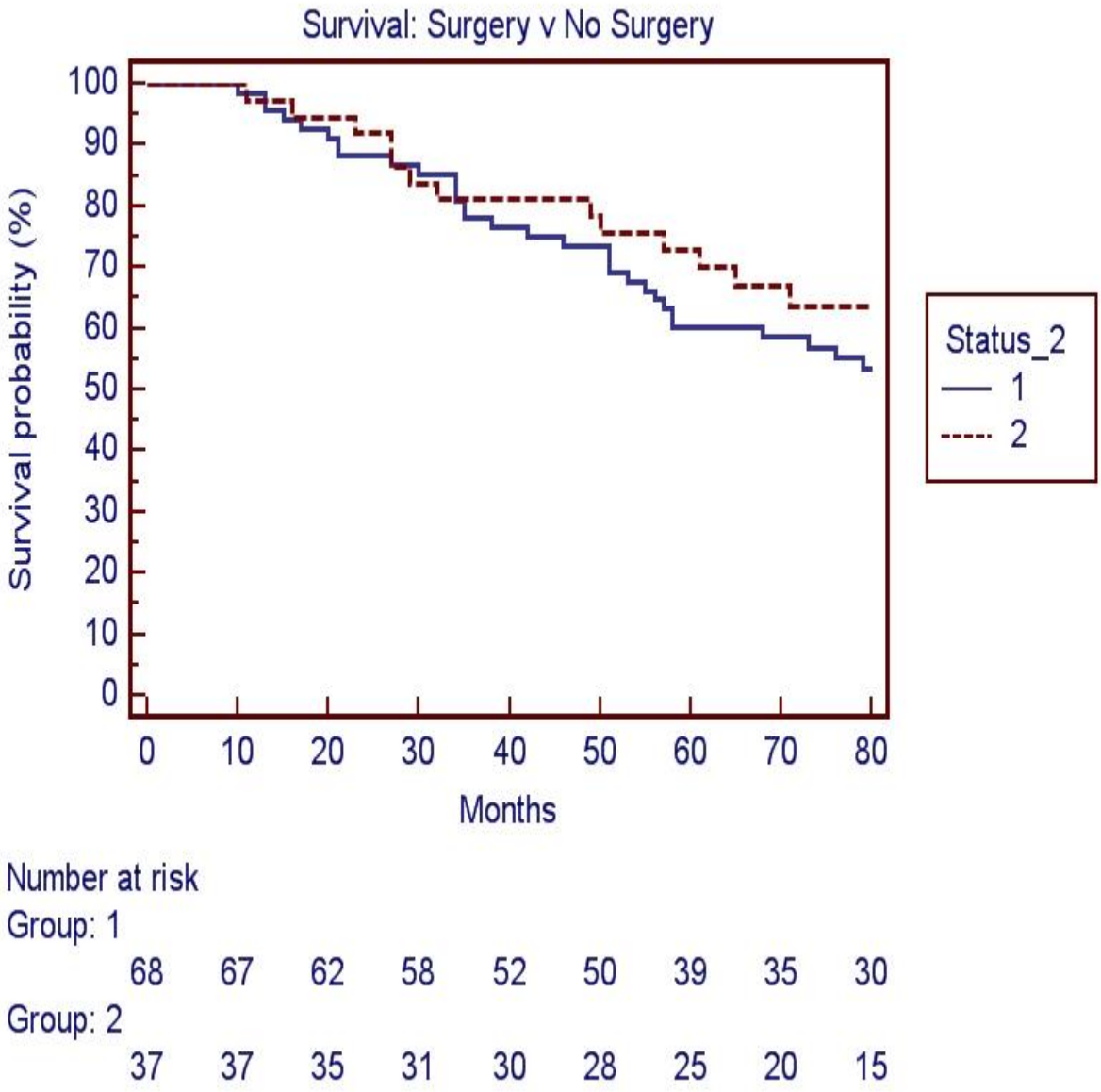
Fig.2 **Surgery for Residual v Recurrent Disease**



4= Residual Disease, 5=Recurrent

P=0.65 HR 1.31 (0.42-3.95)

Fig. 3 Overall Survival: Surgery v No Surgery

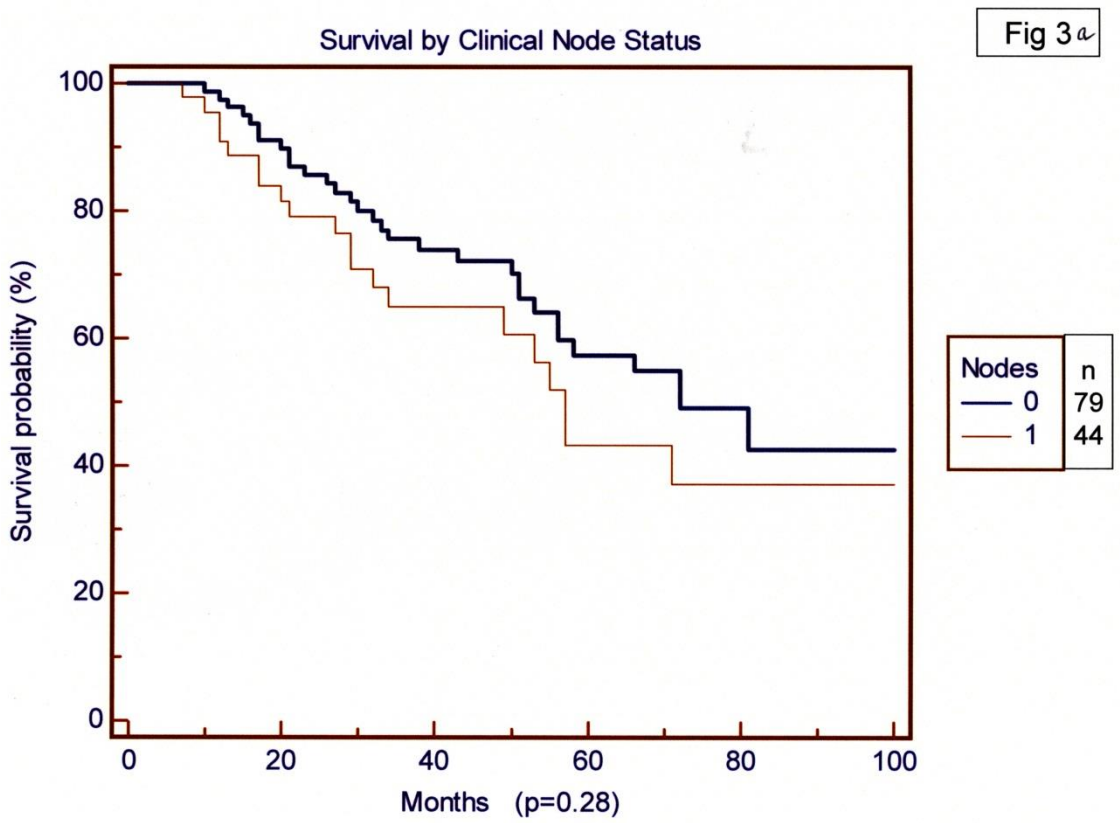


1= Complete Remission- No Surgery,

2= Surgery for Residual or Recurrent Disease

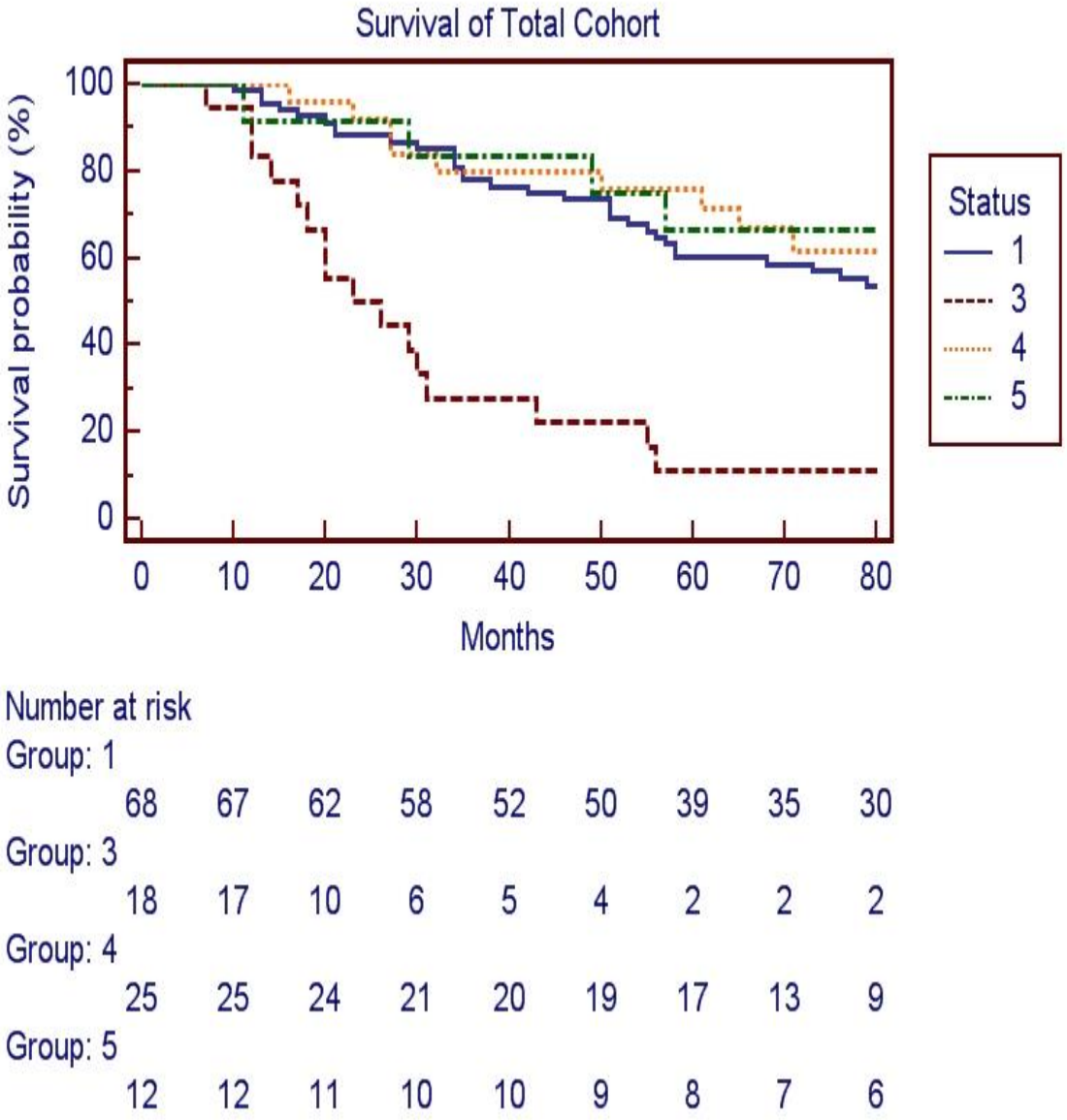
p = 0.218 HR 1.47 95% CI (0.81-2.55)

Fig. 3a **Survival by Clinical Node Status**



P=0.28 95% CI (0.4 - 1.3)

Fig. 4 **Survival Total Cohort**



1. Complete Remission (CR) at Assessment – No Surgery

3. Progressive Disease – No Surgery

4. Residual Disease at Assessment – Surgery

5. Recurrent Local Disease post CR - Surgery

Replace by Fig 5b

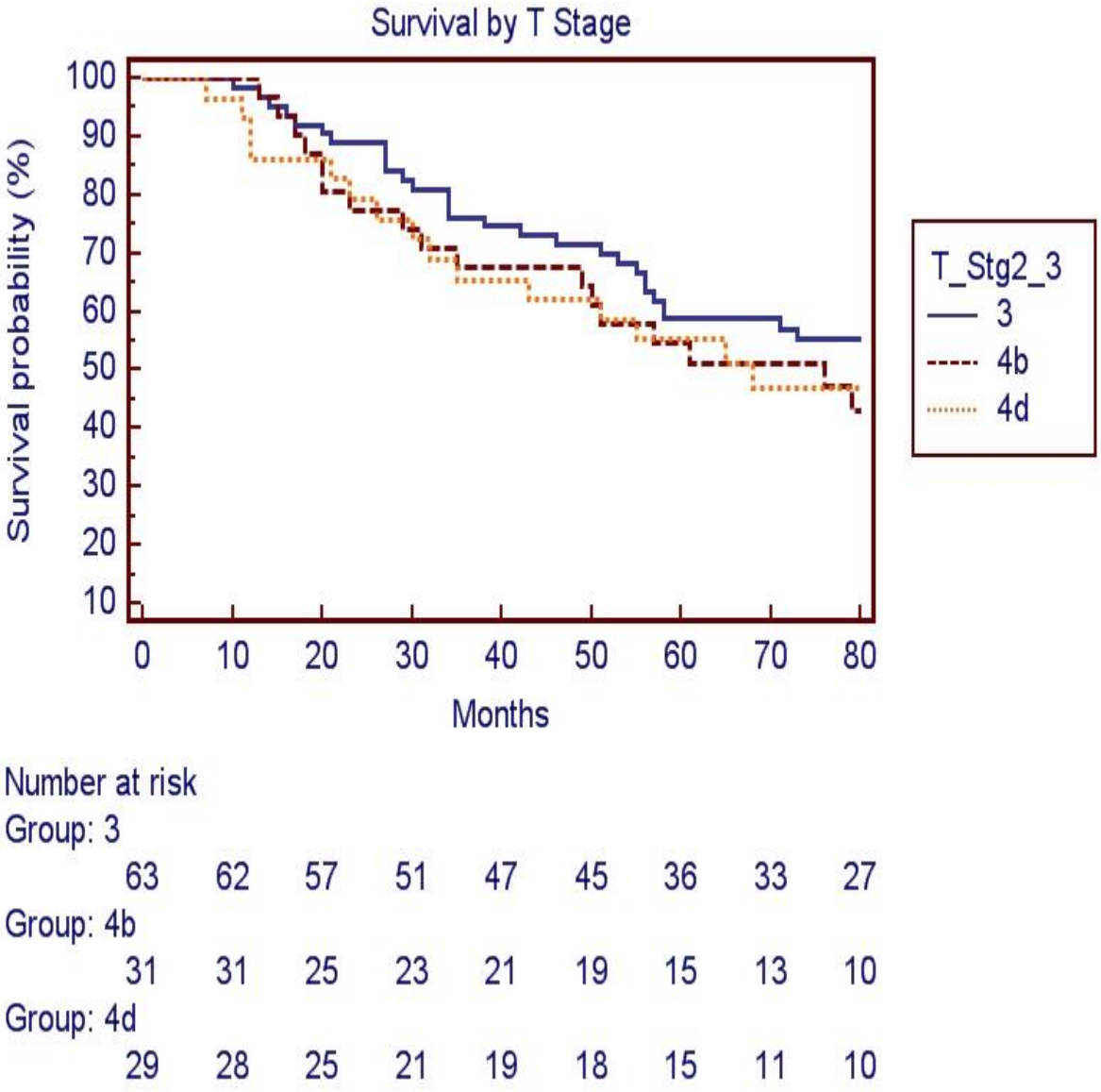
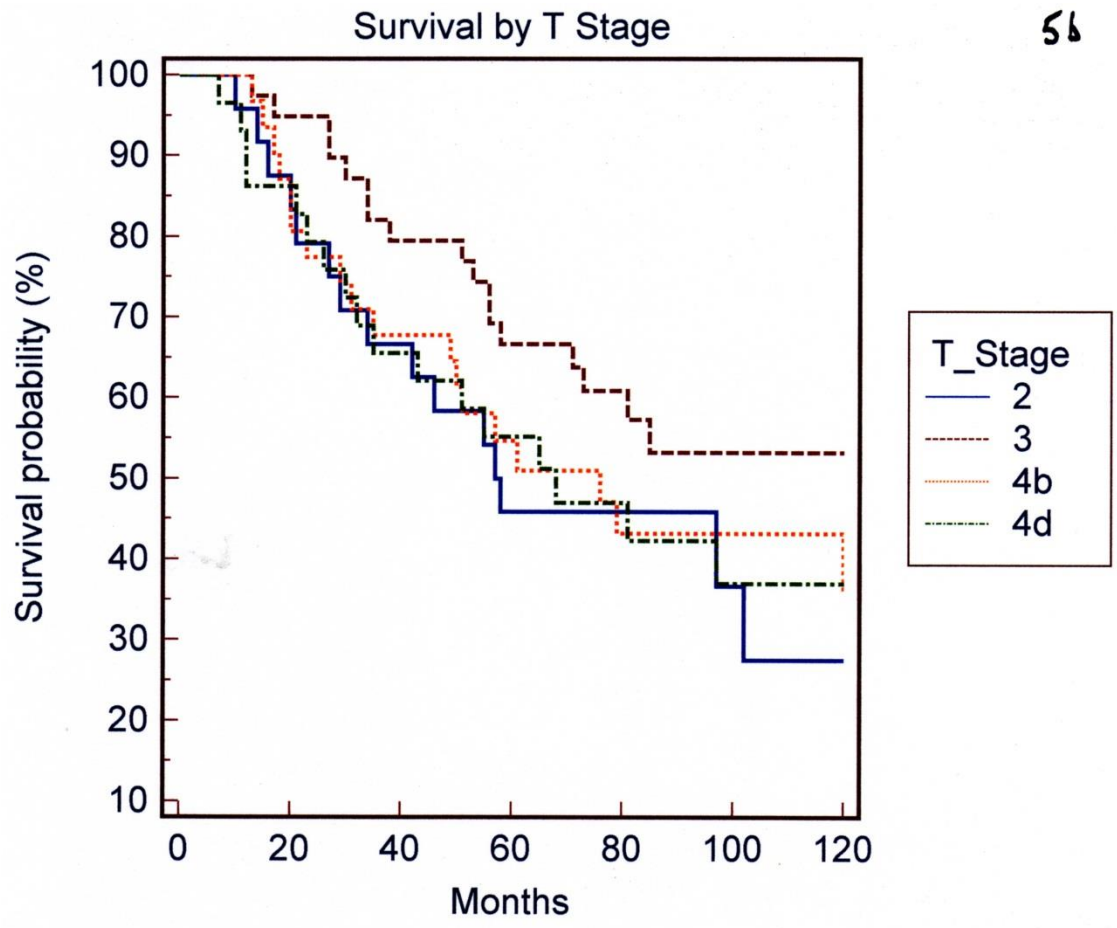


Fig 5b **Survival by TNM Stage**



Number at risk

Group: 2	24	20	16	10	10	4	1
Group: 3	39	37	31	26	17	8	6
Group: 4b	31	25	21	15	10	8	5
Group: 4d	29	25	19	15	10	7	6