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Management Of Primary Breast Cancer

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Summary

The current management of primary breast cancer is based on a selective combination approach using surgery of lesser extent, radiotherapy and systemic therapy. It aims at achieving excellent locoregional control and improved survival with minimal morbidity. This article describes a rational approach to the management of primary operable breast cancer < 5 cm in size. Its success is measured by the rates of locoregional recurrence and long-term survival, which would be separately addressed. A brief discussion would also be made on the management of ductal carcinoma in situ and the follow-up policy for women after treatment of the primary cancer. (HK Pract 1997; 19: 256-263)

Introduction

The management of primary breast cancer has evolved from radical surgery introduced by William Stewart Halsted more than a century ago to a selective combination approach using surgery of lesser extent, radiotherapy and systemic therapy. It aims at achieving excellent locoregional control and improved survival with minimal morbidity. This article describes a rational approach to the management of primary operable breast cancer < 5 cm in size.

Local control – management of the breast

Surgery

Halsted’s operation of radical mastectomy is no longer popular since modified radical mastectomy of Patey where the pectoralis major is preserved offers similar local control. The local recurrence rate of modified radical mastectomy is similar to that of breast conservation with wide local excision followed by intact breast irradiation. Recent large-scale randomised studies also confirm no difference in survival.

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the absence of multifocal disease on a mammogram are the two most important preoperative criteria to recommend breast conservation as an option of treatment. The location of the cancer and the size of the breast are certainly factors that could affect the cosmetic outcome. Proximity of the cancer to the nipple-areola complex does not preclude breast conservation. Only 10% of subareolar cancers require excision of the nipple-areola complex to obtain adequate margin. After wide local excision, the specimen is carefully examined. In case of involved or inadequate margin e.g. < 0.5 cm at one place, a re-excision should be considered though some would give an boost dose of irradiation to the area concerned. On the other hand, if the margin is involved or inadequate in multiple areas, or if there is lymphovascular permeation, especially in younger women, conversion to mastectomy (necessary in approximately 10% of cases) should be carried out owing to an unacceptably high chance of local recurrence after breast conservation when these histological factors are present. Using such strict selection criteria, a 2.2% local recurrence rate in 3 years could be achieved.

Women with cancer failing these criteria undergo mastectomy. Plastic reconstruction should be offered. Methods include simple implant insertion, pedicled latissimus dorsi flap with an implant, pedicled or free transverse rectus abdominis myocutaneous (TRAM) flap, depending on the condition of the skin, previous irradiation, presence of scars in the donor area and very importantly the woman's choice.

Subcutaneous mastectomy, preserving the nipple, with implant insertion is also a simple and safe option since no significant difference in local recurrence rates could be demonstrated, provided that the nipple ducts are carefully examined histologically to ensure absence of tumour. Immediate reconstruction is favoured since it is associated with better psychological outcome but no adverse effect on additional therapy.

Radiotherapy

The use of intact breast irradiation after conservative surgery has been addressed. On the other hand, in the mastectomy group, the rate of local recurrence, as defined by a histologically proven lesion in or deep to the mastectomy skin flaps, remained as high as 23% and multiple risk factors of flap recurrence have been identified viz. poor histological grade, positive nodal status and lymphovascular permeation. Selective addition of flap irradiation when these factors are present has dramatically reduced the local recurrence rate to around 5%.

Assessment of local control

The success of the management of the breast is reflected by the local recurrence rate which should be less than 10% in 5 years. In fact over 70% of flap recurrence develop within the first 2 years. Most of them are manageable by simple excision with or without radiotherapy and systemic therapy. Using strict selection criteria for breast conservation and judicious addition of flap irradiation after mastectomy have virtually eliminated uncontrollable local recurrence commonly seen in the old days.

Regional control – management of the axilla

The success of the management of the axilla is reflected by the rate of regional recurrence, defined by lymph node recurrence in the ipsilateral axilla, as well as by treatment related long-term morbidity. Similarly, an acceptable regional recurrence rate is less than 10% in 5 years. A watch policy previously advocated leads to a regional recurrence rate of 20% and has now been dropped by most centres. Axillary surgery is required to obtain adequate staging of the disease since nodal status is an important prognostic factor and 30% of cases with no clinically palpable lymph nodes have histologically positive nodes in the axilla. The regional recurrence rate would be high if involved lymph nodes are not treated, either by surgery or radiotherapy. However one has to find a balance between regional control and morbidity due to axillary surgery. The more extensive the surgery is, the more accurate the staging would be but the chance of nerve injury and lymphoedema is also higher.

The most popular way of managing the axilla is axillary dissection which accurately stages the cancer and carries low morbidity in experienced hands. The other
option is axillary lymph node
sampling followed by treatment of
the axilla with either formal
dissection or radiotherapy. Axillary
sampling is completed by performing
excisional biopsy of lymph nodes
in the axilla below the
intercostobrachial nerve. At least 4
lymph nodes subsequently proven
by histology must be obtained to
give a representative sample for
staging. Unfortunately the regional
recurrence rate following this
approach seems higher. There are
centres advocating axillary lymph
node sampling for small invasive
cancer as well as ductal carcinoma
in situ (DCIS). Furthermore a
combination of axillary dissection
and radiotherapy is not advisable
owing to high morbidity.

Management of internal mammary
lymph nodes

Most centres do not recommend
routine biopsy or empirical treatment
of the internal mammary lymph
nodes since only 10% of cancer
which have positive internal
mammary lymph nodes do not have
axillary lymph node involvement.
And most of these cancers are
medially situated. In centres
practising axillary lymph node
sampling, there might be a place to
carry out internal mammary lymph
node biopsy for medial cancer to
improve staging.

Adjuvant systemic therapy

Fisher’s theory emphasizes the
importance of micrometastases in
breast cancer, which in most of the
time, is a systemic disease from the
very beginning. Adjuvant systemic
therapy improves the long-term
survival with a 5-15% absolute
reduction in 10-year mortality. It is
indicated whenever the chance of
micrometastases is high. Nodal
status was previously used as the
single most important indicator of
micrometastases. However, survival
analysis showed that women with
small, node positive cancer could
have long life expectancy while a
significant proportion of women with
node negative cancer died shortly
from carcinomatosis. To date the
most important independent
prognostic indicators are nodal status
(cancers with 4 nodes involved
behave worse than those with
less), histological grade and size of
the cancer. The Nottingham
Prognostic Index (NPI) is a
combination of these factors: NPI =
Size (cm) x 0.2 + histological grade
(1 - 3 = I - III) + nodal status (1
= no nodes, 2 = 1 - 3 nodes, 3 =
≥4 nodes). The good (NPI <3.4),
moderate and poor (NPI >5.4)
prognostic groups have respectively
29%, 54% and 17% of all women
with primary operable invasive
cancer and 80%, 42% and 13% 15-
year survival (Table 1 and Figure
1). Since a survival of 80% in
the first group is comparable to that
of age-matched women (83%),
adjuvant systemic therapy is not
indicated. All others require
systemic therapy to attain survival
benefit.

Conventionally, premenopausal
women receive chemotherapy with
cyclophosphamide, methotrexate and
5-fluorouracil (CMF) while
postmenopausal women have
tamoxifen if the cancer is oestrogen
receptor (ER) positive or CMF if it
is ER negative. However there is
evidence that the efficacy of CMF,
surgical oophorectomy, radiation
menopause or LHRH agonist such as
goserelin in reducing the circulating
oestradial level is the same. Their
differences lie in the morbidity,
compliance, ease of application and
cost of the therapy. Therefore,
some centres employ methods other
than CMF as adjuvant systemic
therapy in premenopausal women
with ER positive cancers. Addition

| Table 1: Distribution of invasive primary breast cancer according to the Nottingham Prognostic Index (NPI) in screened (prevalent round) and unscreened population |
|------------------------|-----------------|-----------------|------------------|-----------------|
| NPI                   | Screened n | % | Unscreened n | % |
|<3.4                   | 102 | 76% | 470 | 29% |
|3.4 - 5.4              | 27 | 20% | 879 | 54% |
|>5.4                   | 5 | 4% | 280 | 17% |


Figure 1: Patient survival according to the Nottingham Prognostic Index (NPI)

![Graph showing patient survival according to NPI with three lines representing different NPI categories: NPI < 3.4, NPI 3.4 - 5.4, NPI > 5.4.](image)

of an anthracycline to the CMF regimen may be considered for women with more aggressive cancers, such as those with more than 10 lymph nodes involved, only after serious discussion with the woman concerned since its long-term benefit in this already poor prognostic group may be minimal and the morbidity is certainly higher.

There are controversies on the duration of adjuvant therapy. No additional benefit has been shown if chemotherapy is given for more than 6 months. The most popular regimen therefore includes six 3-weekly cycles of CMF. On the other hand, in spite of the long-term risk of endometrial hyperplasia and carcinoma for women taking tamoxifen, tamoxifen is still recommended since its beneficial effect on breast cancer significantly outweighs its minimal risk on the uterus. Furthermore, using high doses of tamoxifen does not offer extra advantage. Until an answer comes out from ongoing randomised trials, the usual tamoxifen regimen is 20 mg daily for 5 years.

The management algorithm described is summarised in Figure 2.

Management of ductal carcinoma in situ

Mastectomy has been the gold standard in the treatment of DCIS with minimal local recurrence rates. With efficacy of breast conservation clearly demonstrated in invasive breast cancer, recently there are increasing numbers of women undergoing wide local excision followed by intact breast irradiation for DCIS. The selection criteria of small tumour without demonstrable multifocality, as well as adequate histological margins should be followed. In general, axillary surgery is avoided due to the low incidence of nodal involvement. When the diagnosis of DCIS is uncertain preoperatively, it is probably justified to perform axillary surgery at the time of mastectomy. On the contrary, if the cancer is suitable for breast conservation, it would be more reasonable to wait for the histology results prior to contemplating axillary surgery via a different incision. Adjuvant systemic therapy is not indicated since DCIS has an excellent prognosis after adequate initial treatment.

Follow-up

The main aim of follow-up of women after treatment of primary breast cancer is to detect and offer treatment to locoregional recurrence, as well as contralateral breast cancer, since the risk of having a new primary increases at a rate of 1% per year. The follow-up schedule, therefore, involves regular physical examination, generally at 6-monthly interval for 5 years since most locoregional recurrence would have developed within this period, together with screening mammogram for the opposite breast or both breasts in case of breast conservation, at an interval of 1–2 years (Table 2).
Routine metastatic screening is not cost-effective since it could only detect less than 12% of metastases at the asymptomatic stage, depending on the nature of tests performed. Furthermore, at the time of metastases, the median survival is 2 years and the objective of treatment is to palliate symptoms and to maintain the highest possible quality of life. The value of offering therapy in the absence of symptoms is therefore doubtful.

**Table 2: Follow-up algorithm for primary breast cancer**

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<tr>
<td>Physical examination</td>
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<tr>
<td>Mammogram</td>
<td>Yearly for intact breast after irradiation</td>
</tr>
<tr>
<td></td>
<td>1 – 2 years for contralateral breast</td>
</tr>
<tr>
<td>Metastatic screening</td>
<td>Not indicated if asymptomatic</td>
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**Figure 2: Management algorithm for invasive primary breast cancer**

All $\rightarrow$ Clinical/Radiological size $> 3$ cm or multifocal disease on mammogram

$\downarrow$

Choice of treatment $\rightarrow$ Mastectomy* $\rightarrow$

$\downarrow$

Wide local excision* $\rightarrow$ Failed histological criteria (inadequate margins, lymphovascular permeation)

$\downarrow$

Intact breast irradiation

NPI $< 3.4$ $\rightarrow$ No adjuvant systemic therapy

NPI $> 3.4$

- Premenopausal: CMF
- Postmenopausal:
  - ER positive – tamoxifen
  - ER negative – CMF

* All have axillary dissection.

NPI = Nottingham prognostic index

ER = Oestrogen receptor

CMF = Cyclophosphamide, methotrexate and 5-fluorouracil
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Key messages

1. Primary breast cancer can be effectively treated with either mastectomy or breast conservation followed by radiotherapy, the choice of which does not affect the survival.

2. Excellent locoregional control is obtained by using strict selection criteria for breast conservation and judicious addition of flap irradiation after mastectomy, as well as by carrying out axillary dissection.

3. Women undergoing mastectomy should be offered the choice of breast reconstruction.

4. Adjuvant systemic therapy is indicated when the chance of micrometastases is high, as reflected by the nodal status, histological grade and size of the primary tumour. Conventional therapy includes chemotherapy or tamoxifen depending on the menopausal and oestrogen receptor status.

5. After the initial treatment of the primary cancer, women should be followed up by regular physical examination and mammogram.

6. Screening of breast cancer by mammogram is proven to produce a significant survival benefit in women above the age of 50.

Conclusion and future direction

With more precise patient selection and choice of treatment, locoregional recurrence rate has markedly decreased and uncontrollable gross locoregional recurrence has essentially been abolished. On the other hand, the outcome of breast cancer treatment in terms of survival still depends on the stage of the disease at the time of diagnosis. This is beautifully reflected by applying the NPI – only one-fourth of women with symptomatic primary breast cancer belong to the good prognostic group and have survival comparable to normal women. With the advent of breast cancer screening, the proportion of good prognostic cancers has dramatically increased: good, moderate and poor prognostic groups having a distribution of respectively 76%, 20% and 4% (Table 1), not to mention the increased proportion of women with DCIS. Mammographic screening for women above the age of 50 has been proven to produce a survival benefit approaching 40%, a gain which is far better than that achieved by any regimen of adjuvant systemic therapy for cancers that are diagnosed at a late stage. The feasibility of extending the benefit of screening to younger and other high-risk women should be explored.

Other ongoing trials include studies to optimize treatment for small invasive cancer or DCIS. Can radiotherapy and/or axillary surgery be safely avoided? No local recurrence was seen in 42 months after treatment of DCIS by wide local excision alone. Early results of primary systemic therapy are encouraging in increasing the rates of breast conservation but whether such therapy will have long-term survival benefit needs to be elucidated. High-dose chemotherapy...
with stem cell support using autologous bone marrow transplant has been proposed as adjuvant therapy for women with very aggressive cancers. However this is an expensive treatment with definite morbidity but unproven long-term benefit. The results of randomised control trials must be awaited before recommending it as a conventional modality.

References