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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)

摘要

現今原發性乳癌之處理，乃透過選擇性地合併運用外科手術，放射治療及系統治療而達成，其目標在於有效地減低局部復發率及改善生存率，並同時將由治療引起之罹病率降至最低。

本文描述處理直徑5厘米以下原發性乳癌之處理方法，並就原位性乳腺管癌處理及乳癌治療完成後之隨訪方法作出簡略討論。

Introduction

The management of primary breast cancer has evolved from radical surgery introduced by William Stewart Halsted more than a century ago¹ 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.² The local recurrence rate of modified radical mastectomy is similar to that of breast conservation with wide local excision followed by intact breast irradiation.^{3,4} Recent large-scale randomised studies also confirm no difference in survival.⁵

From the oncological point of view, a cancer of small size e.g. < 3 cm (larger cancer may be suitable if the breast is of large size), and

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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.⁶ 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.⁷

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.⁸ 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.⁹ 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.¹⁰ In fact over 70% of flap recurrence develop within the first 2 years.¹¹ 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.¹⁰ 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

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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.¹⁰ 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.¹² 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: $NPI = \text{Size (cm)} \times 0.2 + \text{histological grade (I - 3 = I - III)} + \text{nodal status (1 = no nodes, 2 = 1 - 3 nodes, 3 = } \geq 4 \text{ nodes)}$. 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).¹³ 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.

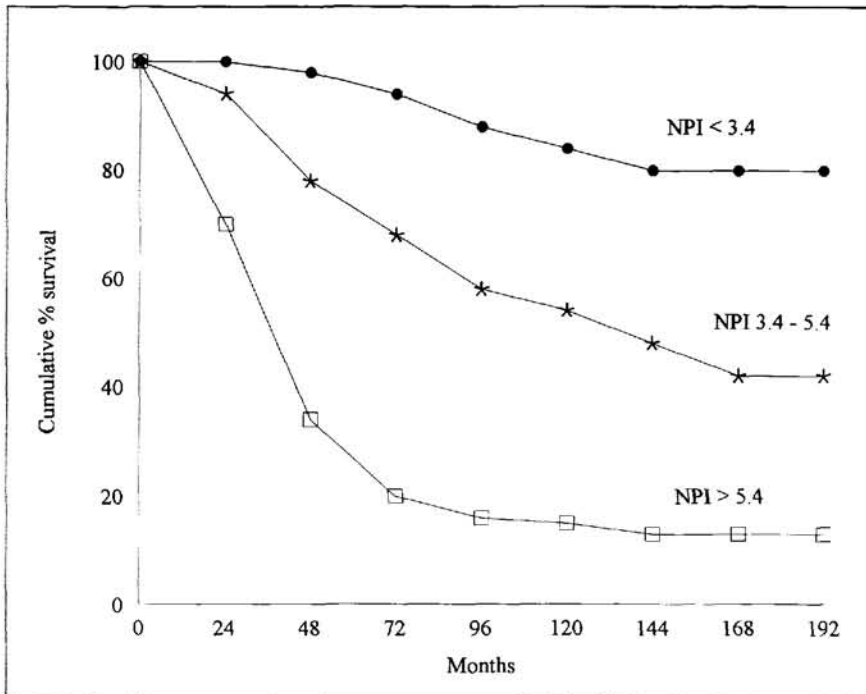
Conventionally, premenopausal women receive chemotherapy with cyclophosphamide, methotrexate and 5-fluorouracil (CMF) while postmenopausal women have tamoxifen if the cancer is oestrogen receptor (ER) positive or CMF if it is ER negative.¹⁴ However there is evidence that the efficacy of CMF, surgical oophorectomy, radiation menopause or LHRH agonist such as goserelin in reducing the circulating oestradiol level is the same.¹⁵ 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		Unscreened	
	n	%	n	%
< 3.4	102	76%	470	29%
3.4 - 5.4	27	20%	879	54%
> 5.4	5	4%	280	17%

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



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**).

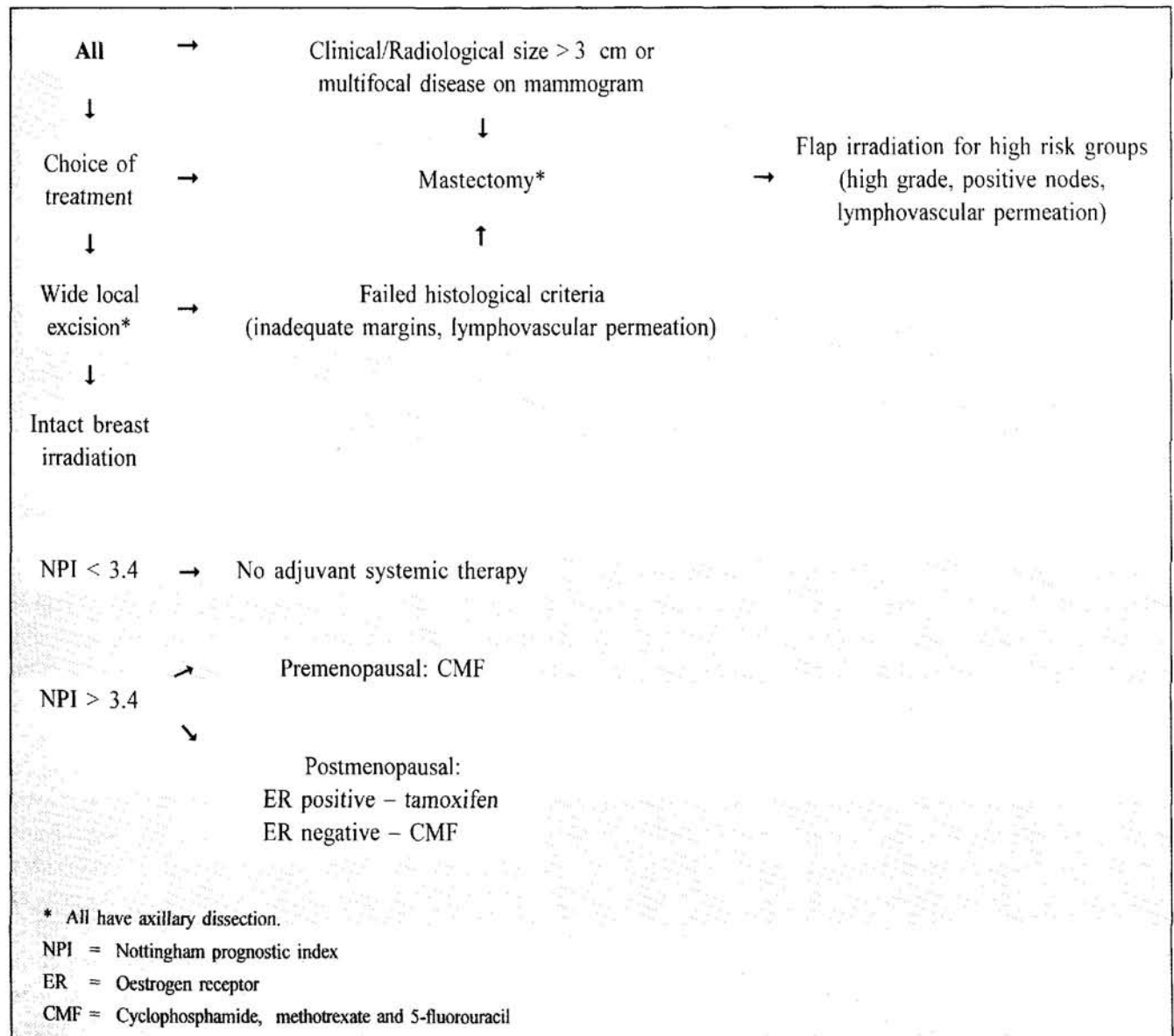
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Table 2: Follow-up algorithm for primary breast cancer

Method	Interval
Physical examination	6-monthly for 5 years, then yearly
Mammogram	Yearly for intact breast after irradiation 1-2 years for contralateral breast
Metastatic screening	Not indicated if asymptomatic

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.¹⁶ 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.¹⁰ The value of offering therapy in the absence of symptoms is therefore doubtful.

Figure 2: Management algorithm for invasive primary breast cancer



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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),¹⁷ 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%,^{18,19} 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.²⁰ Early results of primary systemic therapy are encouraging in increasing the rates of breast conservation²¹ but whether such therapy will have long-term survival benefit needs to be elucidated. High-dose chemotherapy

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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.²² ■

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