ORIGINAL ARTICLE

Should young age be a contra-indication to breast conservation treatment in Chinese women? Twelve-year experience from a public cancer centre in Hong Kong

CME

TK Yau 游子覺
CW Choi 蔡卓偉
Henry Sze 施俊健
Inda S Soong 宋 崧
Anne WM Lee 李詠梅

Objective It has been proposed that young women should not be treated by breast conservation treatment because of a higher risk of local recurrences and worse survival. We therefore examined whether breast conservation treatment in young Chinese women yielded inferior clinical outcomes compared to modified radical mastectomy.

Design Retrospective study.

Setting Clinical oncology department in a public hospital in Hong Kong.

Patients A total of 258 Chinese women with invasive breast cancer, aged below 40 years, and referred between January 1994 and July 2006.

Results A total of 124 (48%) and 134 (52%) patients were treated by breast conservation treatment and modified radical mastectomy, respectively. Mastectomy patients tended to have larger primary tumours (P<0.001) and more nodal involvement (P<0.001). At a median follow-up of 6.5 years, there was no significant difference in the local failure-free survival rate (92% vs 93%, P=0.324) and loco-regional failure-free survival rate (89% vs 88%, P=0.721) in patients having breast conservation treatment and mastectomy. Probably due to their earlier presentation with disease, the former actually had better 6-year distant failure-free survival (88% vs 71%, P=0.002) and overall survival (92% vs 81%, P=0.173) rates. Multivariate analyses showed that both the resection margin status (hazard ratio=2.77, P=0.050) and the presence of peritumoural vascular invasion (hazard ratio=3.01, P=0.038) were independent predictors of local recurrence; the nodal status (hazard ratio=3.91, P<0.001) was the only predictive factor for overall survival. The choice of breast conservation treatment (vs modified radical mastectomy) had no apparent adverse impact on all the clinical outcome parameters analysed.

Conclusion Breast conservation treatment is a reasonable option for many suitably selected young Chinese women.

Key words
Breast neoplasms; Disease-free survival; Mastectomy; Middle aged; Neoplasm recurrence, local

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Department of Clinical Oncology, Pamela Youde Nethersole Eastern Hospital, 3 Lok Man Road, Chai Wan, Hong Kong
TK Yau, MD, FHKAM (Radiology)
CW Choi, MSc
H Sze, MB, BS
IS Soong, FRCR, FHKAM (Radiology)
AWM Lee, MD, FHKAM (Radiology)

Correspondence to: Dr TK Yau
E-mail: tkokyau@gmail.com

Introduction

Similar to many other Asian countries, breast conservation treatment (BCT) was relatively uncommon in Hong Kong until the late 1990s.[1,2] Despite their smaller breast sizes and low percentage of mammographically detected lesions,[3] the clinical and cosmetic outcomes of BCT in Hong Kong are quite comparable to those in many western series.[4-6] Not surprisingly, Chinese women who underwent BCT were reported to have a significantly better perceptions of their body and sexual image than those who underwent modified radical mastectomy (MRM),[7] but there were no differences in other aspects of measured quality of life.[8] Probably related to the unpopularity of breast screening, low breast cancer awareness, misconception and other psychosocial factors,[9-11] the BCT rate for T1-2 breast cancers in Hong Kong remains only around 22 to 30% in recent years.[3,11] Nevertheless, a higher rate (39%) was observed in patients younger than 50 years.[3]

Although many randomised trials have confirmed overall equivalent survival after

BCT or MRM,[12,13] a higher local recurrence rate and worse survival in young women was often observed in BCT studies.[6,14-16] Hence there was controversy as to whether the survival of young patients might be improved following MRM instead of BCT. Some international practice guidelines have also proposed that age of 35 years or younger should be a relative contra-indication for BCT.[17] This proposed policy was particularly unwelcome in Asia, where there is a relatively high proportion of young breast cancer patients[18] who understandably have the greatest desire for breast conservation.

Accordingly we conducted a retrospective study to evaluate whether the clinical outcomes of young Chinese women treated by BCT have been compromised compared with those treated by MRM.

年輕是否患乳癌女性接受保乳治療的禁忌？香港一所公營癌症治療中心的12年經驗

目的 由於較高復發率及較低生存率，過往一直認為患有乳癌的年輕女性不應接受保乳治療。本研究探討患有乳癌的年輕女性中，接受保乳治療的與接受改良根治性乳房切除術的比較，前者是否有較差的臨床結果。

設計 回顧研究。

安排 香港一所公營醫院的臨床腫瘤部門。

患者 1994年1月至2006年7月期間，獲轉介的258名患有侵犯性乳癌、40歲以下的華籍女性。

結果 124名（48%）病人接受保乳治療，另134名（52%）接受改良根治性乳房切除術。接受乳房切除術的病人通常有較大的原發性腫瘤（P<0.001）及較多淋巴結轉移（P<0.001）。中位數為6.5年的隨訪期間，保乳治療及乳房切除術兩組病人在無局部復發生存率（92%比93%；P=0.324）及無局部區域復發生存率方面（89%比88%；P=0.721）皆沒有顯著差別。可能由於接受保乳治療的病人大多於早期確診，她們的6年無遠處轉移生存率（88% vs 71%；P=0.002）及總生存率（92% vs 81%；P=0.173）較佳。多因素分析顯示環周切緣情況（風險比=2.77；P=0.050）和腫瘤周血管侵犯（風險比=3.01；P=0.038）是局部復發的獨立預測因素。淋巴結轉移（風險比=3.91；P<0.001）是總生存率的唯一預測因素。與改良根治性乳房切除術比較，保乳治療於本研究的臨床結果並無負面影響。

結論 對於很多經篩選患有乳癌的年輕女性來說，保乳治療是一個適切的選擇。

Methods

We retrospectively reviewed the medical records of all operated breast cancer patients referred to the Department of Clinical Oncology, Pamela Youde Nethersole Eastern Hospital, Hong Kong between January 1994 and July 2006. Breast surgeries were performed in our own hospital, other public hospitals, or private/overseas hospitals. All patients included in this study were Chinese women with T1-2 (≤5 cm) breast cancers, aged below 40 years, and with no history of prior breast cancer or evidence of systemic failure within 3 months of surgery. Patients with unclear T classification, pure ductal carcinoma in situ (DCIS), DCIS with micro-invasion, pathological or clinical T3-4 breast cancers, and supraclavicular node secondaries at diagnosis were excluded from this study. Patients who were not primarily managed in this centre at initial diagnosis (ie referred at the time of relapse) were also excluded. Outcome data were updated in July 2008 before the final statistical analysis.

Treatment

All patients had definitive breast surgery performed, with or without induction chemotherapy to downsize the tumour. Wide local excision, quadrantectomy, and partial mastectomy were all considered as breast-conserving surgery. All patients with breast-conserving surgery underwent postoperative whole breast irradiation as standard treatment. Wedged opposing tangential fields with 6 MV photons (linear accelerators) were used to deliver 50 Gy in 2-Gy daily fractions over 5 weeks. No bolus was used. Electron boost (9-12 MeV) to the tumour bed was given for patients with microscopic margins of less than 1 cm. The routine boost dose, prescribed at 90% isodose level, was 10 Gy in five daily fractions but a higher dose of 16 Gy in eight daily fractions was used if the microscopic margin was smaller than 1 mm. Post-mastectomy patients also received chest wall radiotherapy if their axillary nodes were involved, resection margins were close, or if the size of the invasive element was 4 cm or more. The technique was similar to that used in BCT, except that a bolus of 0.5 cm was added to the chest wall and no further boost dose was given after 50 Gy. Regional radiotherapy covering the ipsilateral axilla and supraclavicular fossa was also offered to BCT or MRM patients with more than three positive axillary nodes or gross extranodal extension; a separate anterior field was used to deliver 50 Gy in 2-Gy daily fractions.

Radiotherapy was started immediately after recovery from surgery, unless it had to be deferred until the completion of chemotherapy. Systemic adjuvant hormonal therapy and/or chemotherapy were added at the discretion of the attending clinicians.

Follow-up and reassessment

Patients had clinical examination by doctors every 2 to 3 months in the first 2 years, every 4 to 6 months

TABLE 1. Clinical, pathological, and treatment characteristics of the 258 young Chinese patients with invasive breast cancers*

	BCT (n=124)	MRM (n=134)	Total (n=258)	P value
Age (years)				
Mean	36	36	36	0.813
Range	24-40	28-40	24-40	
<35	43 (35%)	51 (38%)	94 (36%)	
35-40	81 (65%)	83 (62%)	164 (64%)	
Pathological size of invasive tumour (cm)				
Mean	1.9	2.4	2.2	<0.001
Range	0.2-4.6	0.3-5.0	0.2-5.0	
Pathological T classification†				
T1	79 (64%)	51 (38%)	130 (50%)	
T2	45 (36%)	83 (62%)	128 (50%)	<0.001
Pathological N classification†				
Nx	3 (2%)	3 (2%)	6 (2%)	
N0	81 (65%)	57 (43%)	138 (53%)	<0.001
N1-3	40 (32%)	74 (55%)	114 (44%)	
Histological grade (for infiltrating ductal carcinoma only)				
Grade 1	15 (12%)	12 (9%)	27 (10%)	
Grade 2	42 (34%)	50 (37%)	92 (36%)	0.600
Grade 3	49 (40%)	60 (45%)	109 (42%)	
Unknown/not applicable	18 (15%)	12 (9%)	30 (12%)	
Resection margins				
Clear (>2 mm)	92 (74%)	102 (76%)	194 (75%)	0.866
Close (≤2 mm)	28 (23%)	29 (22%)	57 (22%)	
Positive	4 (3%)	3 (2%)	7 (3%)	
Hormonal receptor status				
Positive	90 (73%)	87 (65%)	177 (69%)	0.291
Negative	29 (23%)	38 (28%)	67 (26%)	
Unknown	5 (4%)	9 (7%)	14 (5%)	
HER2 overexpression				
Positive	26 (21%)	33 (25%)	59 (23%)	0.093
Negative	81 (65%)	61 (46%)	142 (55%)	
Unknown	17 (14%)	40 (30%)	57 (22%)	
Adjuvant radiotherapy				
Yes	124‡ (100%)	83 (62%)	207 (80%)	<0.001
No	0 (0%)	51 (38%)	51 (20%)	
Adjuvant or neoadjuvant chemotherapy‡				
Yes	76 (61%)	113 (84%)	189 (73%)	<0.001
No	48 (39%)	21 (16%)	69 (27%)	
Adjuvant tamoxifen				
Yes	80 (65%)	69 (51%)	149 (58%)	0.034
No	44 (35%)	65 (49%)	109 (42%)	

* BCT denotes breast conservation treatment, and MRM modified radical mastectomy; because of rounding, not all percentages total 100

† UICC classification, 2002 edition; UICC, International Union Against Cancer

‡ Three patients had induction chemotherapy before breast-conserving surgery

in the third to fifth years, and annually thereafter. Annual bilateral mammograms with or without supplementary ultrasound examinations were also performed in patients with BCT.

Statistical methods

Chi squared and two-sided *t* tests were used to estimate the potential imbalance of clinical and pathological factors among patients treated by different surgical approaches. Survival analyses were performed with Kaplan-Meier estimates and Cox's regression; forward stepwise selection was used in the multivariate Cox's regression analyses. All statistical tests were performed at the 0.05 level of significance. The Statistical Package for the Social Sciences (Windows version 12.0; SPSS Inc, Chicago [IL], US) was used for all analyses.

Results

Between January 1994 and July 2006, 258 of all referred patients fulfilled the above selection criteria. Their mean age was 36 (range, 24-40) years. In all, 243 (94%) presented with breast lumps and only five (2%) had non-palpable lesions first detected by mammography or ultrasonography. Their breast surgeries were performed in our own hospital (67 patients, 26%), other public hospitals (68 patients, 26%), or local private/overseas hospitals (123 patients, 48%). Overall, 124 (48%) and 134 (52%) patients received BCT and MRM, respectively; 30 mastectomy patients also underwent immediate reconstructive surgery. Concerning the axillary surgical treatment, six patients refused axillary dissection; 14 had sentinel node biopsy only, and the remaining 238 underwent axillary dissection with or without preceding sentinel node sampling.

Other demographic and clinical characteristics are shown in Table 1. Around a quarter of the patients had close or even positive resection margins, which was similar for those having BCT and MRM. The mastectomy patients tended to have larger primary tumours (P<0.001), more nodal involvement (P<0.001), more frequent use of neoadjuvant or adjuvant chemotherapy (P<0.001), and less frequent use of adjuvant radiotherapy (P<0.001). The proportions of very young women (aged <35 years) were similar in both treatment groups (35% vs 38%, respectively).

The median follow-up time was 6.5 years (range, 0.2-14.5 years). Twelve (10%) of the patients in the BCT group and eight (6%) having mastectomy developed in-breast recurrences or chest wall relapses, respectively. The 6-year local failure-free survival and loco-regional failure-free survival rates for the BCT versus MRM groups were 92% versus 93% (P=0.324; Fig a) and 89% versus 88% (P=0.721), respectively. Of the 12 patients with in-breast recurrences after BCT, three had simultaneous distant failures at the time of relapse; the remaining nine patients underwent salvage mastectomy but five developed subsequent distant failures. Only four (33%) patients with in-breast recurrences remained disease-free at last assessment. Of the eight patients with post-mastectomy chest wall recurrences, six had simultaneous distant failures; the remaining two (25%) underwent local excision and both remained disease-free at last assessment.

The distant failure-free survival and overall

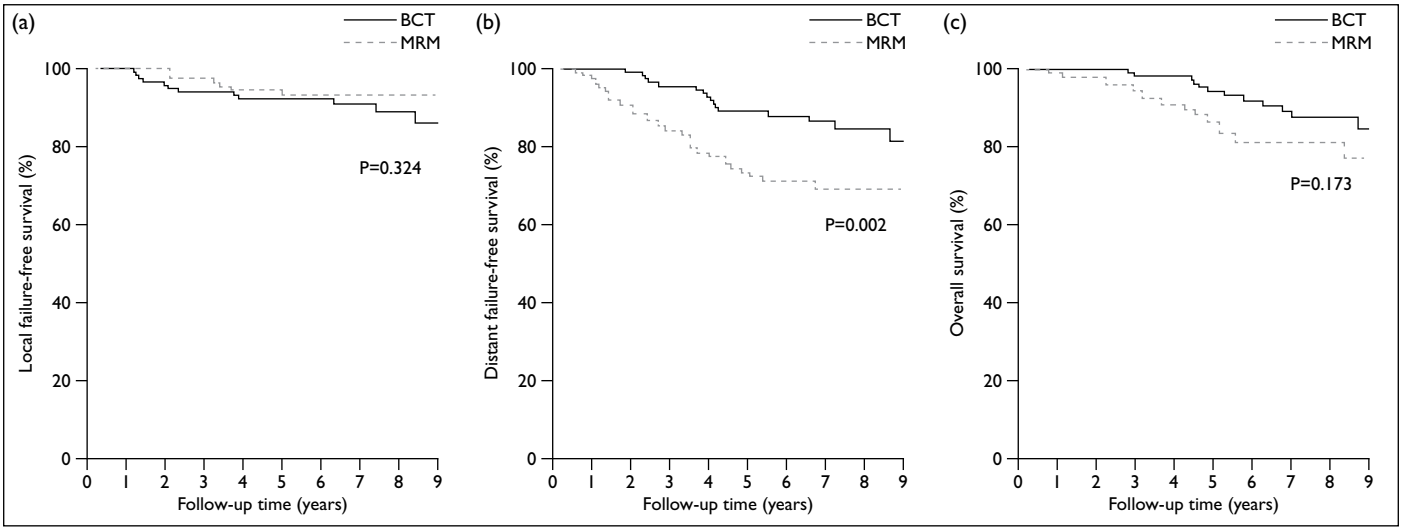

FIG. (a) Local failure-free survival, (b) distant failure-free survival, and (c) overall survival rates of 258 young Chinese women treated by breast conservation treatment (BCT) or modified radical mastectomy (MRM)

survival rates are shown in Figures b and c, respectively. Paradoxically, patients treated by BCT had better 6-year distant failure-free survival (88% vs 71%, P=0.002) and overall survival (92% vs 81%, P=0.173) rates than those treated by MRM, though the difference in overall survival did not reach statistical significance.

The independent impact on local recurrence and overall survival by the choice of surgical options and other potential risk factors studied further by univariate and multivariate analyses are shown in Tables 2 and 3. For the risk of local recurrence, only the resection margin status (hazard ratio [HR]=2.77, P=0.050) and the presence of peritumoural invasion (HR=3.01, P=0.038) were significant independent risk factors. For overall survival, nodal status (HR=3.91, P<0.001) was the only independent risk factor in multivariate analysis. The choice of surgical options (BCT vs MRM) had no apparent adverse impact on all the clinical outcome parameters analysed. There was also no apparent difference between the very young (aged <35 years) and young women (35-40 years) in terms of clinical outcomes.

TABLE 2. Univariate and multivariate analyses of potential risk factors for local recurrence*

Factor	Univariate		Multivariate	
	Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
Age <35 (vs 35-40) years	0.41 (0.14-1.23)	0.110	-	-
BCT (vs MRM)	1.56 (0.64-3.83)	0.328	-	-
T classification T2 (vs T1)	0.74 (0.30-1.82)	0.507	-	-
N classification ≥N1 (vs N0)	1.27 (0.51-3.13)	0.610	-	-
Histological grade Grade 3 (vs grade 1-2)	1.98 (0.78-5.05)	0.151	-	-
HER2 overexpression	2.60 (1.02-6.58)	0.045	-	0.650
Peritumoural vascular invasion	2.46 (0.91-6.63)	0.075	3.01 (1.06-8.54)	0.038
Negative hormonal receptors	0.74 (0.24-2.23)	0.587	-	-
Close (≤2 mm)/positive final resection margins	2.72 (1.12-6.60)	0.028	2.77 (1.00-7.68)	0.050

* BCT denotes breast conservation treatment, MRM modified radical mastectomy, and CI confidence interval

Discussion

In Hong Kong, the proportion of young breast cancer patients is substantially higher than that in western countries. For example, between 2001 and 2005, women aged below 45 years accounted for 27% of all breast cancers in Hong Kong, whereas in the United States, only 12.5% occurred in patients aged 45 years or less.[18,19] Young age is a well-recognised adverse factor for distant failure, and this feature has been incorporated into many practice guidelines dealing with decisions about systemic adjuvant therapies.[17,20,21] In addition, a higher risk of in-breast recurrences was also commonly observed in younger patients after BCT, although different reports used a range of cut-off ages (from 35 to 45 years).[14-16] Compared with the often quoted in-breast recurrence rate of 1% per year, in this study the observed 8% local failure rate at 6 years after BCT was consistent with other reports of higher local recurrence rates in young women.[14-16] Although in-breast recurrences after BCT are more readily salvageable and thought to have less adverse implications than post-mastectomy chest wall recurrence, its association with subsequent distant failure and poor survival is now increasingly

TABLE 3. Univariate and multivariate analyses of potential risk factors for overall survival*

Factor	Univariate		Multivariate	
	Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
Age <35 (vs 35-40) years	0.90 (0.48-1.69)	0.741	-	-
BCT (vs MRM)	0.65 (0.35-1.21)	0.176	-	-
T classification T2 (vs T1)	2.07 (1.10-3.90)	0.025	-	0.399
N classification ≥N1 (vs N0)	3.91 (2.00-7.65)	<0.001	3.91 (2.00-7.65)	<0.001
Histological grade Grade 3 (vs grade 1-2)	1.17 (0.63-2.17)	0.627	-	-
HER2 overexpression	1.78 (0.88-3.61)	0.110	-	-
Peritumoural vascular invasion	2.49 (1.29-4.78)	0.006	-	0.128
Negative hormonal receptors	0.79 (0.38-1.62)	0.516	-	-
Close (≤2 mm)/positive final resection margins	1.34 (0.66-2.71)	0.418	-	-

* BCT denotes breast conservation treatment, MRM modified radical mastectomy, and CI confidence interval

recognised.[16,22-25] Our previous report has also shown that in-breast recurrence is a highly significant independent risk factor for distant failure-free survival.[6] However, whether in-breast recurrence is an indicator of more aggressive disease from the outset or a cause of subsequent distant failure remains controversial. In this study, although most young patients with in-breast recurrences had no evidence of distant failure at the time of relapse and successfully underwent salvage mastectomy, only four (33%) remained disease-free at last assessment, which is not much better than mastectomy patients with chest wall recurrences.

In view of the higher local recurrence rates in young women after BCT and the adverse implications of in-breast recurrences, whether young women should be offered BCT remains controversial. Study from the Fox Chase Cancer Center[26] suggested that patients aged below 35 years were not at higher risk of local recurrence when treated by BCT. This was true if an extensive intraductal component was absent and if margin proximity (<2 mm) was taken into account. In another recent study in young women[27] examining whether MRM improves outcomes compared with BCT, outcomes were not statistically different by type of local treatment though overall outcomes were worse for the younger age-group. There was also no statistically significant difference in loco-regional relapse-free survival, distant relapse-free survival, and breast cancer–specific survival rates at 10 years among women aged 20 to 39 years who were considered 'ideal' BCT candidates (tumour size ≤2 cm, pathologically negative axillary nodes, negative margins, and no reported DCIS). The authors concluded that young age alone should not be a contra-indication to BCT.[27] In general, our study results support the above findings, both in terms of survival estimates by the Kaplan-Meier method and multivariate analyses by Cox's regression.

Although we have a relatively high proportion of young women with breast cancers in Hong Kong, studies focusing on outcomes are scarce. Being a retrospective study, our findings must be interpreted with caution, because of the imbalance of prognostic factors and bias in treatment selection, not to mention the relatively small total number of patients studied and the limited follow-up duration. For example, the paradoxically inferior outcome of mastectomy patients is likely related to the inclusion of more patients with positive nodes and/or larger breast primaries, which are well-known important prognostic factors. In addition, the presence or absence of an extensive intraductal component was often not clearly reported and so was not analysed in this study. The resection margin status after MRM and BCT may also have different implications and analysing this in a multivariate analysis may also complicate the interpretation. Our study result should not be interpreted as dismissing the adverse effect of young age for BCT; instead, what we have shown is that with the careful selection by surgeons, up to half of these young Hong Kong women can be offered BCT without jeopardising survival outcomes, and the in-breast recurrence risk rate is only slightly higher than that usually quoted. The paramount importance of good resection margins cannot be over-emphasised, which is particularly critical for younger women who have a higher tendency to local recurrences. If sufficient margins cannot be obtained without compromising cosmetic outcomes, mastectomy with or without reconstruction should be considered as an alternative.

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References

1. Chow LW, Au GK, Poon RT. Breast conservation therapy for invasive breast cancer in Hong Kong: factors affecting recurrence and survival in Chinese women. Aust N Z J Surg 1997;67:94-7.

2. Kwan WH, Teo PM, Yeo W, et al. Conservative surgery and radiotherapy for early-staged breast cancer. Hong Kong Med J 1996;2:47-55.
3. Yau TK, Soong IS, Sze H, et al. Trends and patterns of breast conservation treatment in Hong Kong: 1994-2007. Int J Radiat Oncol Biol Phys. In press. Epub 2008 Dec 18.
4. Yeo W, Kwan WH, Teo PM, Leung WT, King W, Johnson PJ. Cosmetic outcome of breast-conserving therapy in Chinese patients with early breast cancer. Aust N Z J Surg 1997;67:771-4.
5. Yau TK, Lau Y, Kong J, et al. Breast conservation treatment in Hong Kong—early results of 203 patients: retrospective study. Hong Kong Med J 2002;8:322-8.
6. Yau TK, Soong IS, Chan K, et al. Clinical outcome of breast conservation therapy for breast cancer in Hong Kong: prognostic impact of ipsilateral breast tumor recurrence and 2005 St. Gallen risk categories. Int J Radiat Oncol Biol Phys 2007;68:667-72.
7. Yeo W, Kwan WH, Teo PM, et al. Psychosocial impact of breast cancer surgeries in Chinese patients and their spouses. Psychooncology 2004;13:132-9.
8. Fung KW, Lau Y, Fielding R, Or A, Yip AQ. The impact of mastectomy, breast-conserving treatment and immediate breast reconstruction on the quality of life of Chinese women. ANZ J Surg 2001;71:202-6.
9. Chua MS, Mok TS, Kwan WH, Yeo W, Zee B. Knowledge, perceptions, and attitudes of Hong Kong Chinese women on screening mammography and early breast cancer management. Breast J 2005;11:52-6.
10. Lam WW, Fielding R, Ho EY, Chan M, Or A. Surgeon's recommendation, perceived operative efficacy and age dictate treatment choice by Chinese women facing breast cancer surgery. Psychooncology 2005;14:585-93.
11. Suen D, Chow L, Kwong A. Breast-conserving surgery in Hong Kong Chinese women. World J Surg 2008;32:2549-53.
12. Fisher B, Anderson S, Redmond CK, Wolmark N, Wickerham DL, Cronin WM. Reanalysis and results after 12 years of follow-up in a randomized clinical trial comparing total mastectomy with lumpectomy with or without irradiation in the treatment of breast cancer. N Engl J Med 1995;333:1456-61.
13. van Dongen JA, Voogd AC, Fentiman IS, 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 2000;92:1143-50.
14. Bernstein V, Truong PT, Speers C, et al. How young is too young? The impact of age on premenopausal breast cancer prognosis. Breast Cancer Res Treat 2002;76(Suppl):47S.
15. Voogd AC, Nielsen M, Peterse JL, et al. Differences in risk factors for local and distant recurrence after breast-conserving therapy or mastectomy for stage I and II breast cancer: pooled results of two large European randomized trials. J Clin Oncol 2001;19:1688-97. Erratum in: J Clin Oncol 2001;19:2583.
16. Elkhuizen PH, van de Vijver MJ, Hermans J, Zonderland HM, van de Velde CJ, Leer JW. Local recurrence after breast-conserving therapy for invasive breast cancer: high incidence in young patients and association with poor survival. Int J Radiat Oncol Biol Phys 1998;40:859-67.
17. NCCN Clinical Practice Guidelines in Oncology. Breast cancer V.2.2008. National Comprehensive Cancer Network website: http://www.nccn.org/professionals/physician_gls/PDF/breast.pdf. Accessed 1 Oct 2008.
18. Hong Kong Cancer Registry. Hospital Authority website: http://www3.ha.org.hk/cancereg/eng/default.asp. Accessed 28 Oct 2008.
19. Search Cancer Statistics Review, 1975-2005. National Cancer Institute, Surveillance Epidemiology and End Results website: http://seer.cancer.gov/cgi-bin/csr/1975_2005/search.pl#results. Accessed 30 Oct 2008.
20. Goldhirsch A, Wood WC, Gelber RD, et al. Progress and promise: highlights of the international expert consensus on the primary therapy of early breast cancer 2007. Ann Oncol 2007;18:1133-44.
21. Olivotto IA, Bajdik CD, Ravdin PM, et al. Population-based validation of the prognostic model ADJUVANT! for early breast cancer. J Clin Oncol 2005;23:2716-25.
22. Veronesi U, Marubini E, Del Vecchio M, et al. Local recurrences and distant metastases after conservative breast cancer treatments: partly independent events. J Natl Cancer Inst 1995;87:19-27.
23. Kemperman H, Borger J, Hart A, Peterse H, Bartelink H, van Dongen J. Prognostic factors for survival after breast conserving therapy for stage I and II breast cancer. The role of local recurrence. Eur J Cancer 1995;31A:690-8.
24. Haffty BG, Reiss M, Beinfield M, Fischer D, Ward B, McKhann C. Ipsilateral breast tumor recurrence as a predictor of distant disease: implications for systemic therapy at the time of local relapse. J Clin Oncol 1996;14:52-7.
25. Fortin A, Larochelle M, Laverdière J, Lavertus S, Tremblay D. Local failure is responsible for the decrease in survival for patients with breast cancer treated with conservative surgery and postoperative radiotherapy. J Clin Oncol 1999;17:101-9.
26. Freedman GM, Hanlon AL, Fowble BL, Anderson PR, Nicolaou N. Recursive partitioning identifies patients at high and low risk for ipsilateral tumor recurrence after breast-conserving surgery and radiation. J Clin Oncol 2002;20:4015-21.
27. Coulombe G, Tyldesley S, Speers C, et al. Is mastectomy superior to breast-conserving treatment for young women? Int J Radiat Oncol Biol Phys 2007;67:1282-90.