Management of Malignant Phyllodes Tumours of the Breast

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Abstract

Background: Malignant phyllodes tumours are rare cancers of the breast. Surgery is the primary mode of treatment and current adjuvant treatments appear ineffective. Survival is extremely poor when distant metastasis develops.

Aims: We retrospectively reviewed 30 women who underwent surgery for malignant phyllodes tumours at our unit over a 16-year period. Clinical outcome, particularly the development of distant metastasis, was examined and factors associated with distant metastasis were evaluated.

Results: Median age was 55 years. All but 2 women presented with a palpable breast mass, which was larger than 10 cm in 8. In total, 21 women underwent mastectomy and 9 a wide local excision. Margins remained involved in 4 women even after a mastectomy and 3 received post-operative radiation. Distant metastasis was found in 1 woman on staging scans done in the immediate post-operative period and in another 6 women a median of 5.3 months after surgery. None received chemotherapy and median survival after the development of distant metastasis was 2.2 months. Surgical margin involvement was the only factor associated with distant metastasis (P=0.031, OR 16.499, 95% CI 0.005 to 0.740), but was not significant after adjusting for tumour size (P=0.135, OR 8.348, 95% CI 0.518 to 134.650). Overall survival was 25.5 months and was strongly associated with distant metastasis (P<0.001, HR495.1, 95% CI 55.84 to 4390).

Conclusion: Distant metastasis was found in 23% of women with malignant phyllodes tumours and carried a poor prognosis.

Keywords: Malignant phyllodes tumours; Distant metastasis; Surgery

Introduction

Phyllodes tumours are uncommon tumours of the breast, the majority of which are benign [1]. Surgical excision is the primary mode of treatment and the tumour is often enucleated since a definitive pre-operative diagnosis of phyllodes tumour is seldom made. Apart from the large size that some tumours can grow to, most phyllodes tumours are indistinguishable from the more common fibroadenoma. There are no pathognomonic clinical or radiological features, and many are reported as fibroepithelial lesions on biopsy [2]. Consequently, the recommended surgical margin clearance of 1cm is not often achieved at the initial surgery [3]. A wait and watch approach is often adopted for benign and borderline tumours, even when margins are involved, as metastasis is rare and local recurrences are amendable to further surgery [4]. Malignant phyllodes tumours, however, necessitate more aggressive treatment because of the potential for distant metastasis, which carry an extremely poor prognosis [5]. Malignant phyllodes tumours are uncommon and definitive diagnosis is often only made after histological analysis of the surgical specimen. Treatment involves surgical excision, but with a greater emphasis on obtaining adequate surgical margins. The role of adjuvant treatments remains controversial. In this present study, we retrospectively reviewed a series of malignant phyllodes tumours treated at our unit over a 16-year period. Clinical outcome after definitive surgery was examined. We were particularly interested in the development of distant metastasis and also evaluated factors associated with distant metastasis.

Materials and Methods

We identified 30 patients who were diagnosed and who underwent surgery for malignant phyllodes tumour at our unit from 1st January 2001 to 31st December 2016. Histological analysis was performed by accredited pathologists at our hospital in accordance with the World Health Organization (WHO) recommendations [6]. A diagnosis of phyllodes tumour was made when the fibroepithelial lesion showed an exaggerated intra-canicular pattern with leaf-like fronds extending into cystic dilated spaces and stromal hypercellularity. Tumours were graded as malignant when
they exhibited marked stromalcellularity and atypia, a high mitotic
index of at least 10 per 10 hpf and infiltrative borders. Demographic,
clinical, treatment and outcome data were obtained from a
prospective database (TTSH/2016-00024). Women who default
definitive surgery were excluded from the analyses. The association of
distant metastasis with clinicopathological parameters was examined
with univariate analyses, using Chi squared test, Chi squared test
test for trend and Fishers’ exact test, where appropriate. Overall survival
was examined with Kaplan-Meier survival curves. A 2-tailed P value
test was used for all analyses and a value of P<0.05 was considered
statistically significant. These tests were performed with Graph Pad
Prism, version 6 (Graph Pad Software, San Diego, CA).

Results

A total of 30 women with malignant phyllodes tumour were
included in this study. Median age was 55 years (ranging from 26
to 75 years); 25 (83.3%) women were Chinese, 3 (10%) were Malay,
and 2 (6.7%) were of other ethnicity. The majority of women had
presented with a breast lump, ranging in size from 1cm to 30 cm. Eight
women presented with a mass larger than 10cm and ulceration of the
overlying skin was present in one woman with a 25 cm mass. None
of the women had clinically palpable axillary nodes, although one
was found with radiologically prominent nodes; all nodes removed
at axillary dissection were eventually proven negative for metastasis.
Only 2 women had presented with a non-palpable screen-detected
nodule. Only 1 woman had a pre-operative confirmation of malignant
phyllodes on biopsy. The initial surgery was an excision biopsy in
7 women (where fibroadenoma was thought the most probable
diagnosis) and surgical margins were inadequate (either involved or
close, less than 1mm) in all. All 7 women underwent a second surgery
(4 a re-excision, 3 a mastectomy). Wide local excision was performed
in 9 women (suspected of having phyllodes tumour pre-operatively)
and 5 required repeat surgery for inadequate margins (1 a re-excision,
4 a mastectomy). At the second surgery, residual tumour was found
in 3 women, all of whom had involved margins at the initial surgery.
Residual tumour was not found in any of the 7 women who had close
margins. Another 14 women underwent a mastectomy, with 2 opting
for immediate autologous transrectus abdominis myocutaneous
flap reconstruction at the same setting and 2 requiring coverage of
the post-mastectomy defect (1 with a vertical rectus abdominis
myocutaneous flap and 1 with split skin grafting). Three women who
had presented with tumours larger than 20 cm received chest wall
radiation (50 Gy in 25 fractions) after margins were still involved
after mastectomy; distant recurrence later developed in all 3 women
and chest wall recurrence was also present in 2. Radiation was not
offered to women with close or clear margins. Local recurrence
developed in 6 women, a median of 3.8 months (ranging from 1.8 to
36 months) after surgery. Two women had involved margins, 1 close
margin and 3 clear margins. Only one woman (with clear margins
after a mastectomy) did not also develop distant metastasis. Distant
metastasis was found in 7 of 30 women (23.3%). One woman was
diagnosed on staging scans done in the immediate post-operative
period and another 6 women relapses a median of 5.3 months (ranging
from 2.1 to 11 months) after surgery. Systemic disease involved the
lungs in all 7 women, and also the muscle and subcutaneous tissue
in 1, and also the pericardium, peritoneum and bones in the other.
Local recurrence was also present in 5 of the 6 women with distant
recurrence and preceded the diagnosis of distant recurrence in 2
patients. Involved surgical margins were the only factor associated
with distant metastasis (P=0.031, OR 16.499, 95% CI 0.005 to 0.740)
(Table 1), but were no longer significant after adjusting for tumour
size (P=0.135, OR 8.348, 95% CI 0.518 to 134.650). Women with
distant metastasis tended to have larger tumours, but this did not
reach statistical significance (P=0.068). No association was found
between tumour size and stromal hypercellularity (P=0.142), atypia
(P=0.978) or mitotic index (P=0.457). Six of the 7 women with
distant metastasis had died by the end of the study period; the only
surviving woman had been diagnosed only one month prior. None
of the women with distant metastasis received chemotherapy and
median survival after the diagnosis of metastasis was 2.2 months
(ranging from 0.1 to 9.3 months). Overall survival in this group of 30
women was 25.5 months (ranging from 1 to 199 months); 9 women
had survived longer than 5 years and 3 longer than 10 years. Survival
was strongly associated with the development of distant metastasis
(P<0.001, HR495.1, 95% CI 55.84 to 4390) (Figure 1).

Discussion

The potential for distant metastasis is the single most worrisome
factor for malignant phyllodes and occurs in 10% to 28% [7-9].
Like others, we found the lungs to be most frequently involved, in
keeping with the haematogenous route of spread [10]. Prognosis is
extremely poor after the diagnosis of distant metastasis [10-12]. The
only patient who had not died by the end of our study follow-up
period had only been diagnosed a month prior; the rest had survived
not more than 9 months after the diagnosis of distant metastasis.
Conventional chemotherapy has not been found effective [3,13].
None of the women in our study received chemotherapy. Many had
been hesitant given the uncertain benefit and in fact, the disease
was often rapidly progressive and death occurred soon after. In our
study, we found involved surgical margins to be the single most
important factor associated with distant metastasis. The significance
of surgical margins is well reported [14,15], though some have also
found no association between margin clearance and survival [16,17].
However, it is not known how wide a margin is necessary to minimize
recurrence rates [12,18,19]. A 1 cm margin clearance has been
recommended [7,9], but this can be difficult to achieve even with a
mastectomy as phyllodes tumours can present as very large masses.
In fact, 26% of the women in our study presented with tumours
greater than 10 cm. Tumour size was found to positively correlate
size (P=0.135, OR 8.348, 95% CI 0.518 to 134.650). Women with
distant metastasis (n = 30). Includes 1 patient with isolated local recurrence (overall survival 110.07 months).
public awareness activities, it is still not uncommon to see women presenting with large advanced tumours in Singapore [21]. Several authors have found radiation to reduce local recurrence rates, but unlike with the usual invasive breast cancers, radiation did not improve survival in malignant phyllodes [22-24]. Local recurrence still developed in 2 of the 3 patients who received radiation in our study, but both these women had large tumours and involved surgical margins, which rendered them at high risk of recurrence regardless. We did not find tumour size to have a significant association with distant metastasis, unlike previous studies [20,25]. Also, in contrast to others, we found no association with stromal overgrowth, atypia or mitotic index [20,25]. Tan and colleagues developed a nomogram to predict recurrence-free survival, based on stromal atypia, mitoses, stromal overgrowth and surgical margins [26]. Even though the nomogram was not developed specifically for distant metastasis, it is likely still relevant since recurrences are more often systemic, rather than isolated local recurrences, in malignant phyllodes. However, details of stromal overgrowth and atypia are not always included in the histology report. More recent studies have implicated aberrant expression of markers such as CD10, Axl, st6galnacii and Epidermal Growth Factor Receptor (EGFR) in malignant progression and the development of distant metastases [27-29]. Further studies will be needed to validate these findings, and the main difficulty in obtaining more conclusive results lie in the rarity of malignant phyllodes tumours.

**Conclusion**

Malignant phyllodes are rare cancers of the breast. Surgery is the only effective treatment modality at present, and complete resection with clear surgical margins appears to be the best predictor of a good outcome. Involved margins are associated with distant metastasis and conventional chemotherapy and radiation treatments do not appear effective. Consequently, prognosis is very poor after the occurrence of distant metastasis.

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