

# Comparison of clinical characteristics between ACOSOG Z0011–eligible cohort and sentinel lymph node–positive breast cancer patients in Hong Kong

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## ABSTRACT

**Introduction:** The American College of Surgeons Oncology Group (ACOSOG) Z0011 trial resulted in de-escalation of axillary surgery among early-stage breast cancer patients with low-volume sentinel lymph node (SLN) disease undergoing breast-conserving surgery and radiation therapy. Nevertheless, the mastectomy rate in the Chinese population remains high. This study compared the clinical characteristics of the ACOSOG Z0011–eligible cohort with SLN-positive breast cancer patients in Hong Kong.

**Methods:** This retrospective analysis of a prospectively maintained database at a university-affiliated breast cancer centre in Hong Kong was performed from June 2014 to May 2019. The database included all patients with clinical tumour (T) stage T1 or T2 invasive breast carcinoma, no palpable adenopathy, one or two positive SLNs on histological examination, and no prior neoadjuvant systemic treatment. Comparisons were made between the mastectomy and breast-conserving treatment groups in our cohort, along with the sentinel-alone arm in the ACOSOG Z0011 trial.

**Results:** One hundred and seventy-one patients met the inclusion criteria: 112 underwent mastectomy

and 59 underwent breast-conserving treatment. Our mastectomy group had higher prevalences of T2 tumours ( $P<0.001$ ), lymphovascular invasion ( $P<0.001$ ), and SLN macrometastases ( $P=0.004$ ) compared with the ACOSOG Z0011 cohort. However, in our patient population, mean pathological size slightly differed between the mastectomy and breast-conserving treatment groups (2.2 cm vs 1.8 cm;  $P=0.005$ ). Other histopathological features were similar.

**Conclusion:** This study demonstrated that clinicopathological features were comparable between SLN-positive breast cancer patients undergoing mastectomy and those undergoing breast-conserving treatment. Low-risk SLN-positive mastectomy patients may safely avoid completion axillary lymph node dissection.

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### New knowledge added by this study

- Despite the high rate of mastectomy in Hong Kong, a small proportion of node-positive breast cancer patients met the American College of Surgeons Oncology Group (ACOSOG) Z0011 eligibility criteria to forgo axillary lymph node dissection.
- Sentinel lymph node–positive breast cancer patients undergoing mastectomy displayed clinicopathological features similar to those undergoing breast-conserving treatment in Hong Kong.

### Implications for clinical practice or policy

- By expanding the AMAROS trial (After Mapping of the Axilla: Radiotherapy Or Surgery?) eligibility to include ACOSOG Z0011–ineligible mastectomy patients, more patients could avoid axillary lymph node dissection with adjuvant radiotherapy, potentially reducing morbidity.
- Further studies are necessary to explore when adjuvant axillary radiotherapy is indicated among mastectomy patients with low axillary nodal burden.

## Introduction

The evolution of optimal axillary management for breast cancer patients has led to emphasis on the de-escalation of axillary surgery and minimisation of surgical morbidity. Favourable results from the American College of Surgeons Oncology

Group (ACOSOG) Z0011 phase 3 randomised clinical trials have redefined the indications for completion axillary lymph node dissection (ALND) in patients with positive sentinel lymph nodes (SLNs). Early-stage breast cancer patients who undergo upfront breast-conserving surgery and

## 接受全乳切除手術及乳房保留治療的香港前哨淋巴結陽性乳癌患者與ACOSOG Z0011隊列特質比較

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**引言：**美國ACOSOG Z0011試驗顯示，早期乳癌患者在接受乳房保留治療後，在前哨淋巴結只有少量轉移情況下只要配合術後電療及藥物治療，可無須接受腋下淋巴手術。然而在中國人社會，選擇全乳切除手術較為普遍。本研究旨在比較香港前哨淋巴結陽性的全乳切除乳癌患者和符合ACOSOG Z0011條件的患者的臨床腫瘤數據。

**方法：**本研究回顧了香港一間教學醫院於2014年6月至2019年5月期間的乳癌患者紀錄。臨床T1或T2腫瘤分期、觸診未發現腋下淋巴腫脹、組織學檢查發現一至兩粒前哨淋巴結有癌症轉移，及未接受前置化療的入侵性乳癌患者均符合研究要求。本研究比較了紀錄中接受全乳切除手術及乳房保留治療的患者的腫瘤特質，亦與ACOSOG Z0011的西方數據比較。

**結果：**本研究有171位患者符合研究要求，當中112位接受全乳切除手術，59位接受乳房保留治療。與ACOSOG Z0011隊列比較，本研究中接受全乳切除的香港患者其T2期腫瘤 ( $P<0.001$ )、脈管癌栓陽性 ( $P<0.001$ ) 和前哨淋巴結大型轉移 ( $P=0.004$ ) 的患病率更高。然而，當與香港數據中接受乳房保留治療的患者比較，全乳切除患者的腫瘤病理切片平均稍大 (2.2厘米與1.8厘米； $P=0.005$ )，在其他方面的臨床比較則相約。

**結論：**本研究發現接受全乳切除術與乳房保留治療的前哨淋巴結陽性乳癌患者的腫瘤特質相近。接受全乳切除的前哨淋巴結陽性乳癌患者如復發風險低，亦有可能避免淋巴清除手術。

have one or two positive SLNs can safely forgo ALND while maintaining good overall survival and disease-free survival.<sup>1,2</sup> Consequently, the ASCO (American Society of Clinical Oncology)<sup>3</sup> and the NCCN (National Comprehensive Cancer Network)<sup>4</sup> have revised their clinical practice guidelines to recommend against completion ALND in this subset of patients. Although this guidance has led to a significant decline in the rate of completion ALND among ACOSOG Z0011-eligible patients,<sup>5-7</sup> a similar reduction was observed among patients undergoing mastectomy.<sup>8,9</sup> This reduction was particularly pronounced among patients with SLN micrometastases.<sup>8</sup> Further evidence was obtained in the phase 3 IBCSG (International Breast Cancer Study Group) 23-01 randomised controlled trials, where approximately 10% of patients with SLN micrometastases underwent mastectomy; subgroup analysis demonstrated that disease-free survival among patients without axillary dissection was non-inferior to those with axillary dissection after 10 years of follow-up.<sup>10,11</sup> Similarly, in the AMAROS trial (After Mapping of the Axilla: Radiotherapy Or Surgery?), 17% of patients with tumour (T) staging T1 to T2 primary breast cancer underwent mastectomy.<sup>12</sup> Axillary radiotherapy led to an

oncological outcome comparable to completion ALND but was associated with a lower rate of lymphoedema.

In Hong Kong, factors such as the relatively small breast sizes among Chinese women<sup>13</sup> and more conservative cultural attitudes<sup>13,14</sup> have contributed to a higher rate of mastectomy. The decision to perform mastectomy has prevented a substantial number of breast cancer patients from meeting the ACOSOG Z0011 criteria. Our previous study evaluated the applicability of ACOSOG Z0011 criteria in Hong Kong.<sup>15</sup> Patients with clinical nodal (N) staging N0 breast cancer and one or more positive SLNs were stratified into eligible and ineligible groups according to the ACOSOG Z0011 criteria, with 93% of patients in the ineligible group undergoing mastectomy.<sup>15</sup> Importantly, only 24% of patients in that study met the ACOSOG Z0011 criteria and could potentially avoid ALND.<sup>15</sup> Therefore, it is important to identify a low-risk subset of SLN-positive mastectomy patients who could benefit from this non-ALND approach. This retrospective study was conducted to compare the clinical characteristics of SLN-positive breast cancer patients in Hong Kong with the ACOSOG Z0011-eligible cohort.

## Methods

### Patient recruitment

This retrospective analysis of a prospectively maintained database was conducted at Queen Mary Hospital, a university-affiliated tertiary breast cancer centre in Hong Kong, from June 2014 to May 2019. Potentially eligible patients in the database were identified by an independent research assistant according to whether they met the ACOSOG Z0011 criteria, irrespective of breast surgery type. Patients were excluded if they had positive non-SLNs or positive SLNs only detected by immunohistochemical staining. Relevant data were extracted in July 2020 and missing information was verified using the Clinical Management System, a central computer system for medical records across public hospitals in Hong Kong. Recruited patients were divided into two groups, namely, the mastectomy group and the breast-conserving treatment (ie, ACOSOG Z0011-eligible) group.

### Clinical management and pathological assessment

All breast cancer patients underwent mammography and ultrasound of the breasts and axillae for clinical tumour and nodal staging. Sentinel lymph node biopsy (SLNB), offered to patients with clinically node-negative disease, was performed with a dual tracer of radioisotope and patent blue dye. Sentinel lymph nodes were defined as lymph nodes with ex vivo gamma probe counts exceeding 10% of

the highest ex vivo reading or lymph nodes that displayed blue staining. Non-SLNs were defined as suspicious nodes that were neither hot (high gamma probe counts) nor blue-stained during SLNB, or nodes that were removed during completion ALND. During the study period, intraoperative frozen sections of SLNs or suspicious non-SLNs were routinely collected; these were analysed by standard haematoxylin and eosin staining. Immunohistochemistry was performed in cases of suspected nodal metastasis. Completion ALND was conducted if frozen or paraffin sections showed evidence of nodal metastasis. All final pathological results were reviewed in multidisciplinary meetings. The pathologies of SLNs were considered normal or containing one of the following: macrometastases (>2 mm), micrometastases (>0.2 to ≤2 mm), or isolated tumour cells (≤0.2 mm). For patients undergoing breast-conserving surgery, 'no ink on tumour' was regarded as an adequate resection margin<sup>16</sup>; alternatively, a second operation was performed to ensure a clear resection margin. Adjuvant treatment was administered by breast oncology specialists according to decisions made in multidisciplinary meetings.

### Statistical analysis

Patient demographic characteristics and tumour characteristics were retrieved from database records; percentages were calculated. Missing information was evaluated and managed by pairwise deletion. Comparisons were made between the mastectomy and breast-conserving treatment groups in our cohort, along with the sentinel-alone arm in the ACOSOG Z0011 trial (n=436, in intention to treat).<sup>1,2</sup> Analyses followed the per-protocol approach and calculations were performed with SPSS software (Windows version 24.0; IBM Corp, Armonk [NY], United States). Comparisons between cohorts were conducted with Student's *t* test or the Chi squared test, as appropriate. Human epidermal growth factor receptor 2 (HER2) status was not assessed in the ACOSOG Z0011 study; therefore, HER2 statuses were only compared within our cohort. The Memorial Sloan Kettering Cancer Center (MSKCC) breast cancer nomogram,<sup>17</sup> a well-validated prediction tool to assess the likelihood of non-sentinel node metastases<sup>18-20</sup> (including external validation in the Chinese population<sup>19,20</sup>), was used to calculate probability through an online calculator that considered nine variables; comparisons were made between the breast-conserving treatment and mastectomy groups. P values <0.05 were considered statistically significant.

## Results

In our centre, the ACOSOG Z0011 criteria have

been used to manage patients undergoing breast-conserving surgery since June 2019. From June 2014 to May 2019, 1249 breast cancer patients underwent SLNB in our institution; 171 patients (13.7%) met the study inclusion criteria of clinical T1 or T2 invasive breast cancer and one or two positive SLNs. One hundred and twelve patients (65.5%) underwent mastectomy and 59 patients (34.5%) underwent breast-conserving treatment. The median follow-up period was 58 months (range, 25-84).

### Our mastectomy group versus the sentinel-alone arm in the ACOSOG Z0011 trial

Patient demographic characteristics and tumour characteristics of our mastectomy group and the sentinel-alone arm in the ACOSOG Z0011 trial are presented in Table 1. Invasive ductal carcinoma was more common in our patient population than in the ACOSOG Z0011 group. A higher prevalence of clinical T2 breast cancers (~50%) was observed in our mastectomy group (P<0.001). There were also significantly more patients with lymphovascular invasion in our cohort than in the sentinel-alone arm in the ACOSOG Z0011 trial (P<0.001). Although nearly half of the original ACOSOG Z0011 cohort had micrometastatic SLNs, approximately 70% of mastectomy patients had macrometastatic SLNs (P=0.004). These findings suggested that the clinicopathological profile was more aggressive in patients requiring mastectomy.

### Our mastectomy group versus our breast-conserving treatment group

In our patient cohort, the mastectomy group exhibited many clinicopathological characteristics similar to the breast-conserving treatment group (Table 2). There were no statistically significant differences in terms of age, tumour grade, lymphovascular invasion status, oestrogen receptor/progesterone receptor status, or HER2 status. The mastectomy group had relatively larger tumours than the breast-conserving treatment group (mean: 2.2 cm vs 1.8 cm; P=0.005). Although the difference was not statistically significant, the mastectomy group tended to have larger proportions of patients with two metastatic SLNs (24.1% vs 13.6%; P=0.1) and SLN macrometastases (70.5% vs 57.6%; P=0.11) than the breast-conserving treatment group. Furthermore, the MSKCC probability for additional metastatic non-SLNs was slightly higher in the mastectomy group than in the breast-conserving treatment group (37.1% vs 31.4%; P=0.03) [Table 2].

Ninety-seven patients (86.6%) in the mastectomy group and 45 patients (76.3%) in the breast-conserving treatment group underwent completion ALND. Among patients who underwent mastectomy and completion ALND, 26 patients

TABLE 1. Clinical characteristics of patients with mastectomy in this study and the sentinel-alone arm in the ACOSOG (American College of Surgeons Oncology Group) Z0011 trial\*

	Mastectomy group in this study (n=112)	Sentinel-alone arm in the ACOSOG Z0011 trial (n=436) <sup>1,2</sup>	P value
Age, y	54 (29-85)	54 (25-90)	
Age-group			0.48
≤50 y	38 (33.9%)	160 (37.6%)	
>50 y	74 (66.1%)	266 (62.4%)	
Missing	0	10	
Clinical tumour (T) stage			<0.001
T1	49 (48.5%)	303 (70.6%)	
T2	52 (51.5%)	126 (29.4%)	
Missing	11	7	
Tumour size, cm	2.2 (0.3-4.9)	1.6 (0.0-5.0)	
Receptor status			0.38
ER+/PR+	86 (76.8%)	270 (68.9%)	
ER+/PR-	13 (11.6%)	54 (13.8%)	
ER-/PR+	1 (0.9%)	4 (1.0%)	
ER-/PR-	12 (10.7%)	64 (16.3%)	
Missing	0	44	
Lymphovascular invasion			<0.001
Yes	67 (61.5%)	113 (35.2%)	
No	42 (38.5%)	208 (64.8%)	
Missing	3	115	
Modified Bloom-Richardson score			0.47
1	24 (21.8%)	81 (25.6%)	
2	59 (53.6%)	148 (46.8%)	
3	27 (24.6%)	87 (27.5%)	
Missing	2	120	
Tumour type			0.005
Invasive ductal	108 (96.4%)	356 (84.0%)	
Invasive lobular	4 (3.6%)	36 (8.5%)	
Mixed ductal and lobular	0	10 (2.4%)	
Other	0	22 (5.2%)	
Missing	0	12	
Size of SLN metastasis			0.004
Micrometastasis	33 (29.5%)	164 (44.8%)	
Macrometastasis	79 (70.5%)	202 (55.2%)	

Abbreviations: ER = oestrogen receptor; PR = progesterone receptor; SLN = sentinel lymph node

\* Data are shown as No. (%) or median (range), unless otherwise specified

(26.8%) had additional non-SLN metastases (range, 1-18). In contrast, eight patients (17.8%) in the breast-conserving treatment group had additional non-SLN metastases (range, 1-8). There was no

statistically significant difference in the rate of non-SLN metastases between the two treatment arms (P=0.24). Twenty-nine patients (17.9%) underwent SLNB alone; 15 of these patients were in the mastectomy group. Most patients with SLNB alone had micrometastatic SLNs (89.7%) and one patient had isolated tumour cells. None of the patients with SLNB alone experienced recurrence.

### Adjuvant treatment

In the mastectomy group, 97 patients (86.6%) underwent post-mastectomy irradiation targeting the chest wall and third field regional nodes. Third field regional nodes refer to level III axillary and supraclavicular lymph node regions. None of these patients developed chest wall or axillary recurrence during the follow-up period. Among the 15 patients who did not undergo post-mastectomy irradiation, eight (53.3%) had micrometastatic SLNs and six (40.0%) had macrometastatic SLNs. There were two recurrences (13.3%). First, a 38-year-old patient with one macrometastatic SLN developed ipsilateral chest wall recurrence 4 years after the index operation; this recurrence was managed by a second operation. Second, a patient with two macrometastatic SLNs refused adjuvant systemic treatment and died of breast cancer-related distant metastases. One hundred and ten patients in the mastectomy group (98.2%) received adjuvant systemic treatment: 10 patients (8.9%) required chemotherapy only, 22 patients (19.6%) required hormonal treatment only, and 78 patients (69.6%) required both of these treatments. Seven patients (6.3%) in the mastectomy group developed distant recurrence, and there were three (2.7%) breast cancer-related deaths.

In the breast-conserving treatment group, 58 of the 59 patients underwent adjuvant whole-breast irradiation; 61.0% of these patients underwent additional third field nodal irradiation. Fifty-eight patients (98.3%) in the breast-conserving treatment group received adjuvant systemic treatment involving hormonal therapy and/or chemotherapy. Three patients (5.1%) had distant recurrence; among them, one (1.7%) died at 39 months after the initial diagnosis. One patient experienced ipsilateral breast recurrence at 30 months and underwent completion mastectomy.

### Discussion

The favourable oncological results of the ACOSOG Z0011 trial<sup>1,2</sup> have challenged the conventional approach of performing completion ALND in patients with SLN metastases. Patients with one or two SLN metastases who underwent breast-conserving surgery, whole-breast irradiation, and adjuvant systemic treatment could safely forgo completion ALND. This paradigm shift has led

to substantial de-escalation of axillary surgery worldwide.<sup>5</sup> A meta-analysis by Schmidt-Hansen et al,<sup>21</sup> which involved 2020 patients and findings from the IBCSG 23-01<sup>10,11</sup> and the AATRM (Agència d'Avaluació de Tecnologia i Recerca Mèdiques) 048/13/2000<sup>22</sup> trials, concluded that SLNB alone was sufficient for locoregional control in early breast cancer, without adverse effects on survival.

### Limitations of the ACOSOG Z0011 study

Despite widespread adoption of the ACOSOG Z0011 criteria, the study has been criticised in several ways. The low locoregional relapse rate of 1.5% indicates that the study was underpowered.<sup>23</sup> Furthermore, significant deviation in the radiotherapy protocol, such that 18.9% of patients received 'high tangents' radiotherapy, has raised questions concerning the oncological safety of SLNB alone in patients without third field nodal irradiation.<sup>24</sup> Combined with the insufficient numbers of mastectomy patients in the IBCSG 23-01,<sup>10,11</sup> AMAROS,<sup>12</sup> and AATRM 048/13/2000<sup>22</sup> trials, it has been unclear whether this non-ALND approach can be extrapolated to SLN-positive breast cancer patients who undergo mastectomy with or without radiotherapy.

### Aggressive tumour characteristics among mastectomy patients and local or regional failure rate

In this study, we compared the clinicopathological characteristics among our mastectomy group, our breast-conserving treatment group, and the sentinel-alone arm in the original ACOSOG Z0011 study. Unsurprisingly, our mastectomy group exhibited more aggressive tumour characteristics than the sentinel-alone arm in the Western population; specifically, it had a larger tumour size, more frequent lymphovascular invasion, and a greater proportion of patients with SLN macrometastases. These differences in clinicopathological features have also been reported in Western populations. For example, Hennigs et al<sup>8</sup> analysed a large German cohort that included 4093 SLN-positive mastectomy patients. Compared with the entire study cohort of 166 074 patients, T2 tumour and lymphovascular invasion were more commonly found in patients requiring mastectomy. Additionally, the study by Milgrom et al<sup>25</sup> included 535 early-stage breast cancer patients with a positive SLNB and no ALND. In their mastectomy group, patients had significantly larger tumours and more frequently displayed multifocal/multicentric disease. However, these adverse pathological features among mastectomy patients did not justify a more aggressive axillary approach. Similarly, the low rates of local and regional failure observed in our cohort were consistent with previous reports, suggesting that axillary-specific treatment can be considered

TABLE 2. Clinical characteristics of patients with mastectomy and breast-conserving treatment in this study\*

	Mastectomy group (n=112)	Breast-conserving treatment group (n=59)	P value
Age, y (median [range])	54 (29-85)	52 (29-80)	
Age-group, y			0.08
≤50	38 (33.9%)	28 (47.5%)	
>50	74 (66.1%)	31 (52.5%)	
Missing	0	0	
Clinical tumour (T) stage			0.69
T1	49 (48.5%)	27 (51.9%)	
T2	52 (51.5%)	25 (48.1%)	
Missing	11	7	
Size of invasive focus, cm	2.2 ± 0.9	1.8 ± 0.8	0.005
Receptor status			0.54
ER+/PR+	86 (76.8%)	49 (83.1%)	
ER+/PR-	13 (11.6%)	3 (5.1%)	
ER-/PR+	1 (0.9%)	1 (1.7%)	
ER-/PR-	12 (10.7%)	6 (10.2%)	
Missing	0	0	
Lymphovascular invasion			0.33
Yes	67 (61.5%)	30 (53.6%)	
No	42 (38.5%)	26 (46.4%)	
Missing	3	3	
Multifocal disease			0.11
Yes	29 (25.9%)	9 (15.3%)	
No	83 (74.1%)	50 (84.7%)	
Modified Bloom-Richardson score			0.58
1	24 (21.8%)	9 (15.8%)	
2	59 (53.6%)	31 (54.4%)	
3	27 (24.6%)	17 (29.8%)	
Missing	2	2	
Tumour type			0.24
Invasive ductal	108 (96.4%)	54 (91.5%)	
Invasive lobular	4 (3.6%)	4 (6.8%)	
Mixed ductal and lobular	0	1 (1.7%)	
Other	0	0	
Missing	0	0	
Size of SLN metastasis			0.11
Micrometastasis	33 (29.5%)	24 (40.7%)	
Macrometastasis	79 (70.5%)	34 (57.6%)	
Isolated tumour cells	0	1 (1.7%)	
No. of SLN metastases			0.1
1	85 (75.9%)	51 (86.4%)	
2	27 (24.1%)	8 (13.6%)	
HER2 status			0.30
Positive	18 (16.1%)	7 (11.9%)	
Negative	94 (83.9%)	51 (86.4%)	
Equivocal	0	1 (1.7%)	
MSKCC breast cancer nomogram probability, <sup>17</sup> %	37.1 ± 17.2	31.4 ± 15.1	0.03
Third field irradiation			<0.001
Yes	97 (86.6%)	36 (61.0%)	
No	15 (13.4%)	23 (39.0%)	

Abbreviations: ER = oestrogen receptor; HER2 = human epidermal growth factor receptor 2; MSKCC = Memorial Sloan Kettering Cancer Center; PR = progesterone receptor; SLN = sentinel lymph node

\* Data are shown as No. (%) or mean ± standard deviation, unless otherwise specified

in this group of patients with low-volume SLN disease.<sup>25-28</sup> Debate persists regarding the comparatively large proportions of patients with micrometastatic disease in the original ACOSOG Z0011 trial<sup>1,2</sup> and other studies.<sup>25,26</sup> Cowher et al<sup>29</sup> published a retrospective analysis of patients who underwent mastectomy and conservative axillary regional excision (ie, removal of SLNs and other palpable nodes). Among 144 patients with pathological N1 disease, a small proportion (24%) had micrometastatic disease; only three axillary recurrences (2.1%) were reported.<sup>29</sup> Notably, the low locoregional failure rate was not attributed to post-mastectomy irradiation<sup>25-29</sup> or increased use of chemotherapy.<sup>26-28</sup>

### **Intrinsic differences in tumour characteristics between different patient populations**

In our previous study, we demonstrated differences in clinical characteristics between Asian and Western populations.<sup>15</sup> In the present study, our breast-conserving treatment group had a higher rate of clinical T2 tumours and more frequent lymphovascular invasion compared with the Western population. Similar findings were observed in Korean<sup>30</sup> and Japanese<sup>31</sup> studies, which revealed larger and higher-grade tumours, increased lymphovascular permeation, and more frequent SLN macrometastases. Despite these disparities, the Korean<sup>30</sup> and Japanese<sup>31</sup> studies both demonstrated safe application of ACOSOG Z0011 criteria in Asia, with low incidences of disease recurrence. These intrinsic differences in tumour characteristics between Eastern and Western populations have presumably reduced the gap in clinicopathological features between patients undergoing mastectomy and those undergoing breast-conserving surgery. In the head-to-head comparison between our mastectomy cohort and our breast-conserving treatment group, the only notable difference involved the mean pathological size of the invasive focus (2.2 cm vs 1.8 cm;  $P=0.005$ ); the clinical tumour stage distribution did not differ ( $P=0.69$ ) [Table 2]. The small difference in mean MSKCC breast cancer nomogram probability (37.1% vs 31.4%;  $P=0.03$ ) could also be related to the difference in pathological size, which is one of the nine variables considered in the nomogram. Therefore, we believe that a non-ALND approach in this low-risk subset of SLN-positive mastectomy patients is acceptable.

### **Residual non-sentinel lymph node metastasis in non-axillary lymph node dissection approach**

The primary concern regarding extrapolation of this non-ALND approach is the risk of undertreatment for patients with an extensive nodal burden. The

original ACOSOG Z0011 trial revealed a non-SLN macrometastasis rate of 27.3% in the ALND group.<sup>1,2</sup> The AMAROS trial also showed that 33% of patients in the ALND group had additional positive lymph nodes.<sup>12</sup> Importantly, the axillary recurrence rate remained low in both of these studies. In our SLN-positive mastectomy and breast-conserving treatment groups, the proportions of patients with additional non-SLN metastases were 26.8% and 17.8%, respectively. Among patients undergoing adjuvant irradiation and adjuvant systemic treatment, it is likely that some non-SLN metastases do not progress to clinically detectable disease.

### **Limitations of this study**

This study had several limitations. First, its retrospective design could result in recall bias and the potential for missing clinical information. Although data from the ACOSOG Z0011 trial were limited with respect to HER2 status, extracapsular extension, and multifocality, we attempted to mitigate this issue by including some of the affected variables in the comparison of our mastectomy and breast-conserving treatment groups. Second, we could not address the need for post-mastectomy irradiation among patients in this study. The value of such irradiation for breast cancer patients with <4 positive lymph nodes remains controversial. The meta-analysis by the Early Breast Cancer Trialists' Collaborative Group,<sup>32</sup> which included 1314 breast cancer patients with one to three positive nodes after mastectomy and ALND, suggested that radiotherapy provided oncological benefit in terms of locoregional recurrence, overall recurrence, and breast cancer mortality. However, this meta-analysis has been criticised for including some very early studies from the 1970s, in which the reported recurrence rates were much higher than rates in later studies. In 2016, a focused update by the American Society of Clinical Oncology, American Society for Radiation Oncology, and Society of Surgical Oncology acknowledged the use of post-mastectomy radiotherapy for this group of patients but recommended clinical judgement for patients with a low risk of locoregional recurrence.<sup>33</sup> In our centre, post-mastectomy irradiation was generally administered to patients with pathological N1 disease during the study period; 86.6% of patients in the present study underwent adjuvant radiotherapy. Considering the similarities in clinicopathological features and adjuvant systemic treatment use between our SLN-positive mastectomy and breast-conserving treatment groups, we suspect that it is safe for selected low-risk SLN-positive mastectomy patients to forgo ALND through the expansion of AMAROS eligibility<sup>12</sup> to ACOSOG Z0011-ineligible patients. Several ongoing randomised studies, such as the English POSNOC (POSitive Sentinel NOde:

adjuvant therapy alone versus adjuvant therapy plus Clearance or axillary radiotherapy)<sup>34</sup> and the Dutch BOOG 2013-07,<sup>35</sup> are recruiting breast cancer patients who undergo mastectomy and have a maximum of two to three positive SLNs; these studies aim to compare completion axillary treatment (ALND or axillary radiotherapy) and the lack of completion axillary treatment. Additionally, the SINODAR-ONE trial<sup>36</sup> recently published their subgroup analysis and found non-inferior overall survival and recurrence-free survival among mastectomy patients receiving SLNB and ALND. The ongoing studies are expected to provide more robust evidence concerning the optimal treatment for SLN-positive mastectomy patients.

## Conclusion

This study demonstrated the clinicopathological similarities between SLN-positive mastectomy and breast-conserving treatment groups among breast cancer patients in Hong Kong. Cautious application of the non-ALND approach in mastectomy patients with low-volume SLN disease is reasonable, considering the low locoregional recurrence rate. However, additional research is needed to standardise the adjuvant post-mastectomy radiotherapy protocol, especially among patients who forego ALND.

## Author contributions

Concept or design: V Man.  
Acquisition of data: V Man.  
Analysis or interpretation of data: V Man.  
Drafting of the manuscript: Both authors.  
Critical revision of the manuscript for important intellectual content: A Kwong.

Both authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

## Conflicts of interest

Both authors have disclosed no conflicts of interest.

## Declaration

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## Ethics approval

This study was approved by the Institutional Review Board of The University of Hong Kong/Hospital Authority Hong Kong West Cluster, Hong Kong (Ref No.: HKU/HA HKW UW 09-

045). Written informed consent was obtained from patients for all treatments, procedures, and publication.

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