Title page

Title
Application of the ACOSOG Z0011 criteria to Chinese patients with breast cancer: A prospective study

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Abstract

Background: Although the ACOSOG Z0011 study showed axillary lymph node dissection (ALND) could be avoided in a specific population of sentinel lymph node positive patients, it’s not widely accepted by Chinese surgeons. We conducted a prospective single-arm study to confirm whether or not the results of Z0011 are applicable to Chinese patients.

Methods: Patients conforming to the Z0011 criteria were prospectively enrolled at the Peking University People’s Hospital Breast Center from November 2014 to June 2019. Clinicopathological features of the study group were compared with the Z0011 study. Lymphedema after surgery, incidence of local-regional recurrence, and survival were analyzed.

Results: One hundred forty-two patients who met Z0011 eligibility criteria were enrolled in this study; 115 had sentinel lymph node biopsy (SLNB) alone. When comparing with the Z0011 trial, younger patients were included (median age, 52 [26-82] years vs 54 [25-90] years; P = 0.03). Among clinical T stage, tumor histology, hormone status, lymphovascular invasion, and the number of positive sentinel lymph nodes (SLNs), no statistically significant differences were observed. More patients received adjuvant chemotherapy and endocrine therapy (90.85% vs 58.0% and 80.99% vs 46.6% respectively, P < .001). A similar percentage of patients received radiotherapy, but more nodal radiotherapy procedures were carried out in our study (54.5% vs 16.9%). After median follow-up of 29 months, only 1 patient (0.9%) had ipsilateral breast tumor recurrence and no regional recurrence occurred.

Conclusion: Our study showed that it is achievable to avoid ALND in patients eligible for Z0011 in China.

Trial registration: ClinicalTrials Registered Number: NCT03606616. Registered 31 July 2018-Retrospectiverly registered, https://www.clinicaltrials.gov/ct2/show/NCT03606616?term=Wang+shu&draw=4&rank=21.

Keywords
Breast cancer, Sentinel lymph node, ACOSOG Z0011, Chinses
Background

The American College of Surgeons Oncology Group (ACOSOG) Z0011 trial is the largest prospective, randomized controlled study comparing local control rates and overall survival rates between axillary lymph node dissection (ALND) and sentinel lymph node biopsy (SLNB) groups in patients with positive SLNs. The results of the trial showed that local-regional control and overall survival for patients receiving SLNB alone was not inferior to receiving ALND in 10 years [1,3]. And the results of this study showed a major effect on the clinical practice of breast surgery; since 2012, the National Comprehensive Cancer Network guidelines have been continually changed to this day [2].

After the Z0011 trial, America, Australia, Europe, Japan, and other regions have verified the results in their own populations [4-10]. Although several studies using different database revealed that ALND could be omitted based on the Z0011 strategy [11-12], the attitudes of surgeons are controversial. According to a survey in 2018 in America, 49% of surgeons would recommend ALND for 1 SLN metastasis and 63% would recommend ALND for 2 SLN metastases [13]. In China, the attitude is more negative, only 16.6% of hospitals accepted the conclusions of the Z0011 study [14].

In 2014, we led a retrospective analysis and found that the clinicopathological factors were not statistically different between the eligible group in China and the Z0011 cohort. These findings laid the foundation for omitting ALND in Chinese patients according to the Z0011 criteria [15]. However, no prospective clinical trial result has been reported in the Chinese population. The current study is the first to assess whether the Z0011 criteria to avoid ALND after positive SLNs findings are applicable to Chinese patients with breast cancer.

Methods

Beginning in November 2014, we adapted the results of the Z0011 trial to the management of patients with breast cancer at Peking University People’s Hospital (PKUPH) Breast Center. This was a prospective, single-arm study. From November 2014 to June 2019, patients with invasive breast cancer were enrolled if they met the following Z0011 trial criteria: (1) diagnosed with clinical stage T1-2N0 cancer and (2) previously underwent breast-conserving surgery with planned whole-breast irradiation. A waiver of ethic approval was issued by PKUPH’s review board and written informed consent was obtained from all the patients. The trial was registered as NCT03606616 at the following site: https://clinicaltrials.gov.

All patients received routine preoperative axillary nodal ultrasound imaging. Fine-needle biopsy was allowed for suspicious lymph nodes. If the aspiration cytology suggested malignancy, ALND was performed.

SLNs were detected using blue dye and indocyanine green. All blue staining or fluorescent-labeled lymph nodes were removed. Any patients with negative SLNs or isolated tumor cells within the SLNs were excluded from further analysis. ALND was performed if 3 or more positive nodes were detected or within nodes with gross extracapsular extension. Adjuvant treatment for each patient was based on national guidelines and physicians’ choices. Whole-breast radiation therapy had to be included,
in addition to other radiotherapy fields depending on treatment specified by the radiation oncologists.

We collected the clinical and pathological data, including the adjuvant therapies. Local-regional recurrence, distant metastasis, and survival were closely monitored. The presence of lymphedema was reported in one of 2 ways: (1) self-report by the patient or (2) physician diagnosis and use of the Breast Cancer and Lymphedema Symptom Experience Index (BCLE-SEI)

All data were analyzed using SPSS, version 20.0 statistical software. The clinicopathological features of the study group and the Z0011 trial SLNB cohort were compared. The characteristics of the eligible group and the Z0011 SLNB alone group were compared using chi-square and t tests. A P value < .05 was considered significant. The survival data were analyzed with descriptive statistics.

Results

In the current study, 828 patients with invasive breast cancer were enrolled from November 2014 to June 2019. The patient flow chart is shown in Figure 1. Six hundred eighty-six patients with (1) negative SLNs, (2) isolated tumor cells, (3) 3 or more positive SLNs, or (4) nodes with gross extracapsular extension were excluded from the study and underwent ALND. One hundred forty-two patients were eligible and therefore remained in the analysis. Twenty-seven patients otherwise eligible for SLNB alone underwent ALND as a result of either surgeon or patient preference.

Table 1 shows the baseline characteristics of the 142 eligible patients. The median age of the patients was 52 (range, 26-82) years old, and 112 (78.87%) patients presented with clinical T1 tumors. Patients who were hormone receptor positive accounted for 82.39%. In 76.76% of patients, only 1 metastatic lymph node was found among SLNs. Adjuvant chemotherapy was given to 129 (90.85%) patients and adjuvant endocrine therapy to 115 (80.99%). In the 27 patients who underwent ALND, 7 (25.93%) had additional positive nodes (range, 1-9). Among 115 patients treated with SLNB alone, 101 (87.8%) received radiotherapy. Detailed radiotherapy records were obtained for 99 patients. Of these, 54 (54.55%) patients received breast and nodal radiotherapy (nodal radiotherapy included the level III axillary and supraclavicular nodes) and 23 (23.23%) patients received high-tangent radiotherapy. The features of each group of patients are shown in Table 2.

The pathological and clinical characteristics of patients in the Z0011 trial SLNB-alone arm were compared to our patients in the current study; these comparisons are shown in Table 3. Among clinical T stage, tumor histology, hormone status, lymphovascular invasion, and the number of positive SLNs, no statistically significant differences were observed. Our eligible patients were younger than those in the Z0011 trial, and most patients received chemotherapy and endocrine therapy (P < .001).

No axillary recurrences have occurred in our study at a median follow-up of 29 months (range, 5-60 months). One patient had ipsilateral breast tumor recurrence 56 months after operation.

We administered a questionnaire using BCLE-SEI in all patients. Sixteen patients were at risk of lymphedema (symptom score, 2-8 points). The scores in the ALND
group were higher than those in the SLN-alone group (Table 4). In patients from the SLN-alone group, 2 (1.7%) were either self-reported cases of lymphedema or had a physician diagnosis of lymphedema. Three (11.1%) patients who had ALND reported lymphedema.

Discussion

In recent years, the clinical practice of breast surgery has been greatly influenced by the ACOSOG Z0011 trial. In Europe and Australia, the rate of ALND decreased obviously after the Z0011 study published [16-17]. And in China, ALND has been the standard treatment for patients with positive SLNs until the guidelines of Breast Cancer Committee affiliated with the Chinese Anti-Cancer Association were revised in 2019 [18]. The reason why the Z0011 trial results have not been accepted by most Chinese surgeons in the past few years may be because of the lack of Chinese patients' own data. It is unknown if Chinese patients with breast cancer and patients from the West with breast cancer share clinical characteristics similar to those of the Z0011 trial. It is also unclear if results similar to those of the Z0011 trial can be achieved in a population of Chinese patients under the current adjuvant treatment pattern in China, especially the excellent local-regional control. In our study, we prospectively investigated whether or not the Z0011 criteria could feasibly be applied to Chinese patients.

In our prospective study, 142 patients met the ACOSOG Z0011 eligibility criteria and 115 patients no longer underwent ALND. Although our patients were a little bit younger than the patients of the Z0011 trial, the clinical T stage, tumor histology, hormone status, lymphovascular invasion, and the number of positive SLNs showed no remarkable difference between both studies. In our study, 25.94% (7 out of 27) patients had additional positive nodes after ALND, similar to previous studies [5-7, 15,19] (Table 5). Although a 1 out of 4 possibilities of non-SLN metastasis exists, we still achieved very good local-regional control and survival. Only 1 patient experienced ipsilateral breast recurrence, and no regional recurrence or death occurred. This result is consistent with that of the Z0011 trial, which showed that potential residual positive lymph nodes could be successfully controlled by radiotherapy and systemic therapies. Therefore, ALND can be performed to avoid SLN positivity in a large majority of patients following the Z0011 criteria. In our study, ALND was avoided in 73.25% (115 out of 157) of positive SLNs, similar to other retrospective and prospective reports [5,7,10,19-20].

There are differences between patients in the Z0011 trial and those eligible for our analysis. First, most studies used radioisotopes, blue dye, or in the case of Japan, indocyanine green and technetium tin colloids for SLNB [5-6, 8]. Our study used blue dye and indocyanine green. According to previous research reports, indocyanine green in conjunction with blue dye is an efficient method [21-22] to detect SLNs without affecting the results.

Second, we conducted a rigorous preoperative assessment. The Z0011 trial applied no specific requirements for preoperative axillary lymph node imaging assessment, unless the enlarged axillary lymph nodes were palpable, according to United States
guidelines. However, in our opinion, imaging assessment of axillary lymph nodes before surgery may be useful. If a lymph node is found to be positive on ultrasound-guided fine-needle biopsy, a higher nodal burden is predicted than on a positive SLNB [19,23-24]. Under the European guidelines [25-26], in patients with or without palpable lymph nodes, axillary ultrasound is a routine diagnostic procedure. This is true according to the Chinese guidelines as well [18]. According to the guidelines in China, our study required the preoperative assessment of the axillary nodal status of all patients using ultrasound. If fine-needle aspiration cytology for suspicious lymph nodes was positive, then the patients were ineligible to enroll. However, in Morrow’s study, the researchers excluded routine imaging of the axilla with ultrasound or magnetic resonance imaging [4]. In their opinion, even if the image guided aspiration was positive, there are still some patients with only 1 or 2 positive nodes who were able to avoid ALND; further, the local-regional control was unaffected. Moreover, in our previous study, we assumed that if only one abnormal lymph node is detected on ultrasound, then fine-needle biopsy could be omitted but not for multiple suspicious nodes [27]. Perhaps axillary ultrasound assessment and fine-needle aspiration are not necessary for all patients, but we cannot omit use of either today in China.

Third, in practice, more patients received regional nodal radiotherapy. In the Z0011 trial, among the patients with radiotherapy records, 52.6% were treated by high-tangent radiotherapy, and 16.9% received treatment of the supraclavicular region [28]. In Morrow’s study, 21% of the patients received breast and nodal irradiation, and 58% received supine breast radiotherapy (this method allows patients to receive more axillary I/II radiotherapy than prone breast radiation therapy). Meanwhile, 23.2% of our patients received high-tangent irradiation, and 54.5% included treatment of the nodal radiotherapy (level III axillary and supraclavicular nodes). The radiotherapy field in several prospective studies is shown in Figure 2. The choice of irradiation field is directly related to the understanding of recurrence risks by radiation physicians. Patients with high risks of recurrence, including young age, larger tumor size, hormone receptor negative, and HER2 positive, were more likely to receive nodal RT in our study. The use of nodal RT increased with the number of positive SLNs; this is consistent with the Z0011 and Morrow study. The high-risk patients treated with heavier radiation have also been confirmed in a nomogram-based study [29]. It has been hypothesized that radiation oncologists, who could not be blinded to the surgical treatment of the patients nor to the pathological results after surgery, may have treated patients on the SLN-only arm with high-tangent radiotherapy to include a component of axillary level I/II and even three-field radiation more often than those in the ALND arm, particularly for patients at high risk. Even in America, nearly half of Z0011-eligible patients receive regional nodal irradiation from National Cancer Database study [30]. Close multidisciplinary teamwork between clinical oncologist and radiation physicians are needed to optimize the radiotherapy field. And the optimal radiation therapy for these patients still need further study.

Fourth, more patients in our study received chemotherapy and endocrine therapy compared with the Z0011 trial ($P < .001$). Chemotherapy and endocrine therapy can improve the prognosis of patients with breast cancer, whether in terms of local-
regional control or overall survival. Positive lymph nodes are one of the indications for adjuvant chemotherapy per the Chinese Society of Clinical Oncology guidelines. The use of prognostic multigene signatures such as Oncotype DX or MammaPrint may influence results in the future in China. We believe that reducing chemotherapy in some low risk patients will not affect the prognosis of these patients.

The use of SLNB alone resulted in fewer complications. In the Z0011 trial, lymphedema was reported by 13% of patients after ALND and 2% of patients after SLNB alone at 1 year. Lymphedema diagnosed by arm circumferences (defined as a 2 cm or greater postoperative increase in ipsilateral arm measurements compared with the contralateral arm) was 6% vs 11% in the 2 arms, respectively [31]. Lymphedema evaluation methods varied in different studies. In the IBCSG 23-01 trial, the treating physician reported edema; assessments were based on the National Cancer Institute Common Toxicity Criteria version 2. The incidence of lymphedema was 3% in the SLN group and 13% in the ALND group (median follow-up of 5 years) [32]. Our patients received more nodal RT compared with Z0011 trial, but did not see a significant increase in lymphedema. Lymphedema reported by patients or physicians was 11.1% after ALND and 1.7% after SLNB alone with a median follow-up of 29 months. In a trial comparing radiotherapy and ALND after SLNB, at 5 years, the lymphedema reported by arm circumference was 5% in the radiotherapy arm and 13% in the ALND arm [33]. From the above data, even after receiving axillary radiotherapy after SLNB, the incidence of edema did not increase significantly, and the proportion of edema was significantly reduced compared to ALND. However, a longer follow-up period is required.

This study has several limitations. First, the median follow-up of 29 months was short, and the number of patients was insufficient to draw final conclusions about the incidence of local-regional recurrences. However, thus far, our results demonstrate an extremely low rate of local-regional recurrence in Chinese patients considering the diagnosis and treatment pattern today. Long-term follow-up is suggested to confirm the reliability of our data. Second, our results reflect a single-center experience and the adjuvant treatments are influenced by individual physician’s preferences, such as the use of adjuvant chemotherapy and the irradiation field. The results of this trial should be confirmed by multicenter studies.

To our knowledge, this prospective study is the first to apply the ACOSOG Z0011 criteria to Chinese patients with early stage breast cancer. Our study demonstrates (1) a low risk of local-regional recurrence and (2) a good prognosis in patients with positive SLNs who were treated with SLNB alone. We believe that the results of our pilot study regarding the Chinese patient population will have a great effect on the clinical practice of Chinese surgeons in treating patients with breast cancer.
List of abbreviations
ALND  axillary lymph node dissection
SLNB  sentinel lymph node biopsy
SLN  sentinel lymph node
PKUPH  Peking University People’s Hospital
BCLE-SEI  Breast Cancer and Lymphedema Symptom Experience Index

Declarations

Ethics approval and consent to participate
The study was approved by the Peking University People’s hospital ethics committee. Committee’s reference number: 2018PHB152

Consent for publication
Not applicable

Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests
The authors declare that they have no competing interests.

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Authors’ contributions
Yuan Peng, the acquisition, analysis, and interpretation of data, have drafted the work or substantively revised it.
Miao Liu, Fuzhong Tong, Yingming Cao, Liu Peng, Bo Zhou, Hongjun Liu, Lin Cheng, Jiajia Guo, Fei Xie, Houpu Yang, Siyuan Wang, Chaobin Wang, the acquisition of data.
Shu Wang, substantial contributions to the conception, design of the work, have drafted the work or substantively revised it.
All authors read and approved the final manuscript

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Figures

Fig 1. Flow chart of the study procedures

Fig 2. Radiotherapy field in the prospective studies
| Clinicopathological characteristics | Total (n=142) | SLN alone (n=115) | ALND (n=27) |
|------------------------------------|--------------|-------------------|-------------|
| **Age (median, range)**            | 52 years (26–82) | 52 years (29–82) | 44 years (26–69) |
| **Age group, no. (%)**             |              |                   |             |
| ≤ 50                               | 68 (47.89)   | 51 (44.35)        | 17 (62.96)  |
| > 50                               | 74 (52.11)   | 64 (55.65)        | 10 (37.04)  |
| **Clinical T stage, no. (%)**      |              |                   |             |
| cT1                                | 112 (78.87)  | 90 (78.26)        | 22 (81.48)  |
| cT2                                | 30 (21.13)   | 25 (21.74)        | 5 (18.52)   |
| **Pathological T stage, no. (%)**  |              |                   |             |
| pT1                                | 103 (72.54)  | 81 (70.43)        | 22 (81.48)  |
| pT2                                | 39 (33.91)   | 34 (29.57)        | 5 (18.52)   |
| **Tumor histology, no. (%)**       |              |                   |             |
| Ductal                             | 119 (83.80)  | 95 (82.61)        | 24 (88.89)  |
| Lobular                            | 15 (10.56)   | 13 (11.30)        | 2 (7.41)    |
| Other                              | 8 (5.63)     | 7 (6.09)          | 1 (3.7)     |
| **Lymphovascular invasion, no. (%)** |          |                   |             |
| Present                            | 33 (23.24)   | 26 (22.61)        | 7 (25.93)   |
| Absent                             | 68 (47.89)   | 60 (52.17)        | 8 (29.63)   |
| Missing                            | 41 (28.87)   | 29 (25.22)        | 12 (44.44)  |
| **Hormone status, no. (%)**        |              |                   |             |
| Positive                           | 117 (82.39)  | 92 (80.0)         | 25 (92.59)  |
| Negative                           | 25 (17.61)   | 23 (20.0)         | 2 (7.41)    |
| **HER2 status, no. (%)**           |              |                   |             |
| Negative                           | 118 (83.10)  | 96 (83.48)        | 22 (81.48)  |
| Positive                           | 21 (14.79)   | 17 (14.78)        | 4 (14.81)   |
| Unknown                            | 3 (2.11)     | 2 (1.74)          | 1 (3.70)    |
| **Number of positive SLN, no. (%)**|              |                   |             |
| 1                                  | 109 (76.76)  | 94 (81.74)        | 15 (55.56)  |
| 2                                  | 33 (23.24)   | 21 (18.26)        | 12 (44.44)  |
| **Adjuvant chemotherapy, no. (%)** |              |                   |             |
| Yes                                | 129 (90.45)  | 102 (88.70)       | 27 (100.00) |
| No                                 | 13 (9.15)    | 13 (11.30)        | 0 (0.00)    |
| **Adjuvant endocrine therapy, no. (%)** |        |                   |             |
| Yes                                | 115 (80.99)  | 92 (80.00)        | 23 (85.19)  |
| No                                 | 27 (19.01)   | 23 (20.00)        | 4 (14.81)   |
Table 2. Comparison of characteristics between patients treated with whole-breast irradiation alone, high-tangent radiotherapy and treated with nodal radiotherapy

| Characteristics                  | Whole-breast alone (n=22) | High tangent (n=23) | Breast+nodes (n=54) |
|----------------------------------|---------------------------|---------------------|---------------------|
| Age, (median) years              | 52.5                      | 55                  | 49.5                |
| Pathological T stage, (cm; mean) | 1.51                      | 1.78                | 1.89                |
| Hormone status, no. (%)          |                           |                     |                     |
| Positive                         | 20 (90.91)                | 20(86.96)           | 43(79.63)           |
| Negative                         | 2 (9.09)                  | 3(13.04)            | 11(20.37)           |
| HER2 status, no. (%)             |                           |                     |                     |
| Negative                         | 20 (95.24)                | 21(91.30)           | 42(79.25)           |
| Positive                         | 1 (4.76)                  | 2(8.70)             | 11(20.75)           |
| Unknown                          | 1                         | 0                   | 1                   |
| Lymphovascular invasion, no. (%) |                           |                     |                     |
| Present                          | 4 (22.22)                 | 7(43.75)            | 14(34.15)           |
| Absent                           | 14 (77.78)                | 9(56.25)            | 27(65.85)           |
| Missing                          | 4                         | 7                   | 13                  |
| Number of positive SLN           |                           |                     |                     |
| one                              | 20(90.91)                 | 20(86.96)           | 41(75.93)           |
| two                              | 2(9.09)                   | 3(13.04)            | 13(24.07)           |

Table 3. Clinicopathological characteristics between patients in the Z0011 SLNB-alone arm and the current study

| Characteristics                  | Eligible patients (n=142) | Z0011 SLNB alone (n = 436) | P Value |
|----------------------------------|---------------------------|-----------------------------|---------|
| Age, median (range), years       | 52 (26–82)                | 54 (25–90)                  | -       |
| Age group, no. (%)               |                           |                             |         |
| ≤ 50                             | 68 (47.89)                | 160 (37.6)                  | 0.03    |
| > 50                             | 74 (52.11)                | 266 (62.4)                  |         |
| Missing                          | 0                         | 10                          |         |
| Clinical T stage, no. (%)        |                           |                             |         |
| cT1                              | 112 (78.87)               | 303 (70.6)                  | 0.056   |
| cT2                              | 30 (21.13)                | 126 (29.4)                  |         |
| Missing                          | 0                         | 7                           |         |
| Tumor histology, no. (%)         |                           |                             |         |
| Ductal      | 119 (83.80) | 356 (84.0) | 0.589 |
|------------|-------------|------------|-------|
| Lobular    | 15 (10.56)  | 36 (8.5)   |       |
| Other      | 8 (5.63)    | 32 (7.5)   |       |
| Missing    | 0           | 12         |       |

Hormone status, no. (%)

| Positive    | 117 (82.39) | 328 (83.7) | 0.726 |
|-------------|-------------|------------|-------|
| Negative    | 25 (17.61)  | 64 (16.3)  |       |
| Missing     | 0           | 44         |       |

Lymphovascular invasion, no. (%)

| Present     | 33 (32.67)  | 113 (35.2) | 0.641 |
|-------------|-------------|------------|-------|
| Absent      | 68 (67.33)  | 208 (64.8) |       |
| Missing     | 41          | 115        |       |

Number of positive SLN, no. (%)

| 0–1         | 109 (76.76) | 324 (78.1) | 0.746 |
|-------------|-------------|------------|-------|
| ≥ 2         | 33 (23.24)  | 91 (21.9)  |       |
| Missing     | 0           | 21         |       |

Adjuvant chemotherapy, no. (%)

| Yes         | 129 (90.85) | 253 (58.0) | < 0.001 |
|-------------|-------------|------------|---------|
| No/Missing  | 13 (9.15)   | 183 (42.0) |         |

Adjuvant endocrine therapy, no. (%)

| Yes         | 115 (80.99) | 203 (46.6) | < 0.001 |
|-------------|-------------|------------|---------|
| No/Missing  | 27 (19.01)  | 233 (53.4) |         |

Radiotherapy, no. (%)

| Yes         | 127 (89.44) | 277* (89.64) | 0.947 |
|-------------|-------------|--------------|-------|
| No          | 15 (10.56)  | 32* (10.36)  |       |

| *n=309 |

Table 4. The BCLE-SEI symptom score among the eligible patients

| Symptom score | SLNB-alone (n=115) | ALND (n=27) | P Value |
|---------------|---------------------|-------------|---------|
| 0, n (%)      | 104 (90.43)         | 22 (81.48)  | <0.001  |
| 2-8, n (%)    | 11 (9.57)           | 5 (18.52)   |         |
| ≥9, n (%)     | 0                   | 0           |         |
Table 5. Additional positive nodes after ALND in eligible patients based on the Z0011 criteria

| Author          | Number of patients | Non-SLN positive |
|-----------------|--------------------|-------------------|
| Giuliano [1]    | 355                | 27.3%             |
| Aigner [6]      | 132                | 39%               |
| Delpech [5]     | 87                 | 29%               |
| Miao Liu [15]   | 151                | 25.2%             |
| Verheuvel [19]  | 625                | 26%               |
| Ngui [7]        | 22                 | 27.3%             |
| Present study   | 27                 | 25.94%            |