Original Article

The efficacy of ^{99m}Tc-rituximab as a tracer for sentinel lymph node biopsy in cutaneous melanoma patients

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Background: The sentinel lymph node (SLN) status is a vital prognostic factor for malignant melanoma (MM) patients. There is increasing evidence that a radioactive agent, rather than its combination with blue dye, is sufficient for a SLN biopsy (SLNB). Thus, we discussed the efficacy of ^{99m}Tc-rituximab as a tracer in MM patients.

Methods: A total of 502 consecutive patients with MM who underwent SLNB were enrolled in this study. All participants were peritumorally injected with ^{99m}Tc-rituximab before imaging, and scanned with single-photon emission computed tomography-computed tomography (SPECT-CT) to detect the number and location of the SLN. A gamma detection probe was employed to detect radioactive SLNs in operation. Follow up was conducted to observe whether nodal or distant recurrence occurred.

Results: The SLNs were successfully imaged via SPECT-CT and harvested from all 502 participants. No drainage tube was indwelled and 32 (6.3%) participants experienced the following complications: seroma (n=26, 5.2%), wound infections or lymphangitis (n=6, 1.2%), sensory nerve injuries (n=4, 0.8%). There were 380 patients who were diagnosed as SLN-negative and 122 (24.2%) were SLN-positive. A total of 85 SLN-positive patients received complete lymph node dissection, and 28 (32.9%) had additional positive lymph nodes. During a median follow-up of 24 months, 28 participants were found to have a false negative (FN) SLN. The FN rate was 18.7%. A higher T stage was a predictive factor for FN [odds ratio (OR) 1.77; P<0.05]. There was no significant difference in the positive or FN rate between the acral and cutaneous groups.

Conclusions: The radiopharmaceutical ^{99m}Tc-rituximab could be employed as a simple and safe tracer in acral and cutaneous melanoma SLN biopsies.

Keywords: Melanoma; sentinel node biopsy; ^{99m}Tc-rituximab; false negative; radioactive tracer

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Introduction

A sentinel lymph node biopsy (SLNB) is a vital procedure in melanoma patients as recommended by the National Comprehensive Cancer Network (NCCN) guideline (1). It is a key staging procedure for patients with clinical stage I-II melanoma according to the presence or absence of nodal metastasis. The available evidence strongly supports the sentinel lymph node (SLN) status as the most powerful independent factor for predicting survival (2-4). Accurate staging is generally accepted as the basis for counseling, therapeutic decision-making, and prognostication in melanoma. Depending on a variety of factors, 5–40% patients will be detected as SLN-positive (1,2,5-8). The commonly acknowledged risk factors of a positive SLN include the Clark level, mitotic rate, ulceration, lymphovascular invasion, anatomic site, tumor infiltrating lymphocytes, and primary tumor thickness (1,3,9-14). Compared to Caucasian patients, Chinese melanoma patients tend to be associated with a longer delay to diagnosis and a higher proportion of T-stage III–IV status (15,16). Therefore, an accurate SLNB procedure is particularly essential for clinical work.

The NCCN-recommended technique for SLNB consists of preoperative dynamic lymphoscintigraphy, intraoperative identification using isosulfan blue or methylene blue dye, and a gamma probe to detect radiolabeled lymph nodes (1). However, recent studies have increasingly indicated that the use of blue dye is associated with a negative outcome. Ranson *et al.* performed SLNB in 537 patients using both a ^{99m}Tc radiocolloid and blue dye, and reported that if the blue dye was excluded and only hot nodes were harvested, it would only result in a 5% reduction of dissected nodes without any compromise in the sensitivity of the test (17). van der Ploeg *et al.* retrospectively assessed 681 patients, and discovered that a blue, nonradioactive sentinel node was removed in only 0.9% of patients (18). There was a minor reduction in the collected nodes; however, there are other negative impacts of using blue dye, including anaphylaxis [ranging from 0.1% to 2.7% (19-21)], prolonged cutaneous staining (22), and its contraindication in pregnant women. In 2013, the US Food and Drug Administration approved Lymphoseek (^{99m}Tc-tilmanocept) as a radiotracer for detecting SLN in breast and melanoma patients (23). Inspired by this invention, we developed ^{99m}Tc-labeled rituximab as a novel radiotracer. The accuracy and specificity of this tracer has been tested and verified in breast cancer patients in our institution, with a sensitivity 97.4% and specificity of 100% (24,25). But its efficacy in melanoma has not been proved.

Rituximab is an antibody that specifically targets the CD20 molecules expressed in B lymphocytes. Theoretically, ^{99m}Tc-rituximab can combine with B lymphocytes in the first lymph node on the lymph circulating route, which is the precise definition of "sentinel lymph node", and avoids imaging of second-tier lymph nodes. Because this radio tracer can be detected within at least 6–8 h post-injection, surgeons are guaranteed to have sufficient time during the operation. Besides, the side effects of blue dye, such as anaphylaxis and skin staining, can be avoided. In this study, we aimed to report the feasibility, effectiveness, and safety of using ^{99m}Tc-rituximab for the clinical testing of SLN in melanoma.

We present the following article in accordance with the STROBE reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-21-6890/rc).

Methods

Patients

From February 2009 to March 2019, a total of 502 consecutive patients with melanoma underwent a biopsy at the Department of Bone and Soft Tissue Sarcoma of Peking University Cancer Hospital. The indications for SLNB included: (I) primary melanoma, Breslow thickness ≥1 mm, or Breslow thickness <1 mm and with other adverse features (e.g., ulceration, high mitotic rate, and lymphovascular invasion); (II) clinically negative lymph nodal basin (examined by palpation and ultrasound); (III) absence of distant metastasis [confirmed by routine physical examination, chest and abdominal computed tomography (CT) scan, or positron emission tomography (PET)-CT]; and (IV) feasibility for anesthesia. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional ethics committee of Peking University Cancer Hospital and informed consent was taken from all the patients.

SLNB

The radiotracer was prepared as described in a previous study (24). The radiotracer solution was approximately 74 MBq/mL with saline. All participants were administered with peritumoral intradermal injections of ^{99m}Tc-rituximab

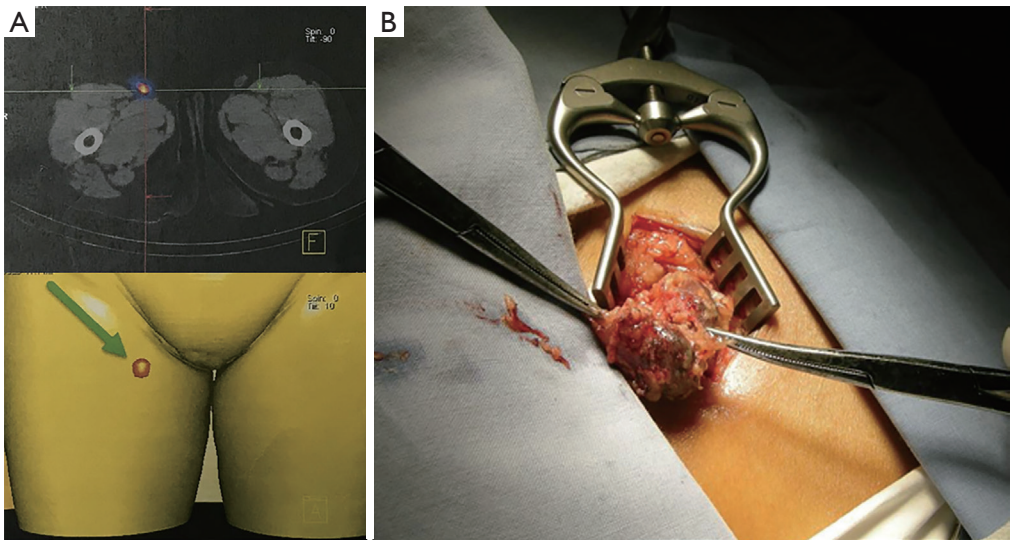

Figure 1 Detecting and harvesting the ^{99m}Tc-rituximab marked SLN. (A) The lymphoscintigraphy of location (arrow) and number of SLN; (B) a minimal incision was made to acquire the SLN. SLN, sentinel lymph node.

(10.0 MBq, 0.2 mL) on the same day or the day prior to the operation. Planar lymphoscintigraphy was then acquired by a single-photon emission computed tomography-computed tomography (SPECT-CT) system (E. Cam; Siemens, Erlangen, Germany) to determine the location and number of SLNs (*Figure 1A*). During the operation, the precise position of the SLNs was located using a handled gamma detection probe (Neoprobe, Dublin, OH, USA or Crystal Photonics, Berlin, Germany) before the surgical incision, after which a minimal incision (2–4 cm) was performed (*Figure 1B*). All radioactive nodes with a counting rate ≥10% of the hottest node were removed.

Pathology

During routine pathologic examination, SLNs were cut along the major axis, formalin-fixed, embedded in paraffin, and stained with hematoxylin and eosin (H&E). Intraoperative frozen section investigations were not performed. Paraffin-embedded specimens were examined by light microscopy at magnifications of ×40 and ×200. Additional immunohistochemical (IHC) staining (S100, HMB-45 and Melan-A) was used for suspicious cases identified with H&E. All negative SLNs with local nodal recurrence were retrospectively reviewed by an experienced pathologist (Lai). Additional serial sectioning (at a 2-mm interval) was performed on all of the reviewed SLN biopsy specimens, and doubtful cases were stained for IHC.

Statistical analysis

For the statistical analysis of the data, contingency tables were analyzed using a χ^2 test. For the survival analysis, a Kaplan-Meier estimator was used with generalized Wilcoxon and log-rank tests for bivariate comparisons. In the analysis of risk factors, binary logistic regression was deployed. The disease-free survival (DFS) time was calculated from the time of the primary diagnosis to the time point of disease recurrence or death due to any reason. The overall survival (OS) time was calculated from the time of primary diagnosis to the time point of death for any reason. All statistical analyses were performed using SPSS 25.0 (SPSS Inc., Chicago, IL, USA). The differences between groups were considered to be significant for P values <0.05.

Results

A total of 502 patients were enrolled in this study, among whom 239 were men and 263 were women. Acral malignant melanoma (MM) and T3–4 stage patients comprised the majority, accounting for 74.5% (374 patients) and 59.4% (298 patients), respectively (*Table 1*). The SPECT-CT scanning was omitted in 3 participants due to patient rejection or an operation being pressed for time. We detected SLNs in the remaining 499 participants (100%). The imaging time ranged from 0.33 to 16 h (median: 1 h).

Table 1 Characteristics of patients undergoing SLN biopsy

Characteristics	Total patients	Number of SLN-positive patients (%)
Patient (n)	502	122 (24.3)
Male	239	58 (24.3)
Female	263	64 (24.3)
Age [median]	58.0 [8–86]	60.0 [8–80]
Location		
Acral MM	374	87 (23.3)
Upper limb	91	15 (16.5)
Lower limb	283	72 (25.4)
Cutaneous MM	128	35 (27.3)
Upper limb	21	5 (23.8)
Lower limb	58	13 (22.4)
Trunk	45	16 (35.6)
Others (perineum, head, etc.)	4	1 (25.0)
T stage		
Tis	5	0 (0.0)
1	65	9 (13.8)
1a	46	6 (13.0)
1b	18	3 (16.7)
1x	1	0 (0.0)
2	95	15 (15.8)
2a	63	10 (15.9)
2b	28	5 (17.9)
2x	4	0 (0.0)
3	137	37 (27.0)
3a	70	21 (30.0)
3b	63	15 (23.8)
3x	4	1 (25.0)
4	161	52 (32.3)
4a	47	12 (25.5)
4b	108	37 (34.3)
4x	6	3 (50.0)
NA	33	9 (27.3)
Ulceration		
Positive	216	58 (26.9)
Negative	255	53 (20.8)
NA	31	11 (35.5)
Lymphovascular invasion		
Positive	27	9 (33.3)
Negative	365	91 (25.2)
NA	110	22 (20.0)
Clark		
I	3	0 (0.0)
II	11	3 (27.3)
III	41	6 (14.6)
IV	157	35 (22.3)
V	53	16 (30.2)
NA	237	62 (26.2)

SLN, sentinel lymph node; NA, not available; MM, malignant melanoma.

The number of imaged SLNs ranged from 1–8 (median 1). During the operation, SLNs were successfully harvested from all participants, including the 3 patients without SPECT-CT results. The average number of harvested SLN was 2.75.

Complications were observed in 32 patients (6.3%): 26 were seroma (5.2%), 6 were wound infections or lymphangitis (1.2%), and 4 were sensory nerve injuries (0.8%). The inguinal region was a high-risk region for SLNB complications compared to the axilla and neck (*Table 2*). There were 19 (73.1%) participants with seroma that did not require any intervention, and the remaining 7 (26.9%) participants recovered well after suctioning fluid with a syringe. Those with a wound infection or lymphangitis were treated with antibiotics. Participants with sensory nerve injures were observed and the symptoms were fully or partially relieved within 6 months. No drainage tube needed to be indwelled, and no second operation was performed.

A total of 112 participants were diagnosed as SLN-

Table 2 Complications after SLNB

Complications	N (%)	P value
Total patients with complications	32/502 (6.3)	
Seroma	26 (5.2)	
Wound infection	6 (1.2)	
Sensory nerve injury	4 (0.8)	
Location		
Inguina	30/387	P<0.05 (χ^2 test)
Axilla	2/112	
Neck	0/3	

SLNB, sentinel lymph node biopsy.

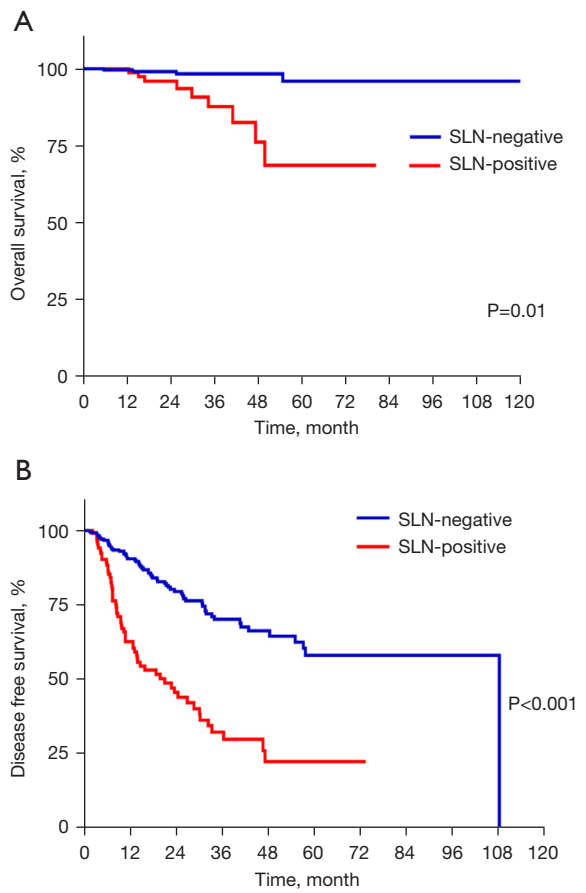

Figure 2 The OS and DFS of SLN-negative and SLN-positive patients. The mean DFS and OS of the SLN-negative group was 74.4 and 106.1 months. The mean DFS and OS of the SLN-positive group was 28.2 and 67.2 months. OS, overall survival; SLN, sentinel lymph node; DFS, disease-free survival.

positive after a pathological examination, in which 74 had only 1 positive SLN, 27 had 2 positive SLNs, and 11 had 3 or more positive SLNs. The SLN positive rates of the acral and cutaneous groups were not significantly different (23.3% *vs.* 27.3%; P=0.40). A total of 85 patients received a complete lymph node dissection. Additional positive lymph nodes (non-SLN positive) were discovered in 28 (32.9%) patients. There were 16 (57.1%) participants who had only 1 non-SLN positive lymph node, 5 (17.9%) had 2 non-SLNs positive lymph nodes, and 7 (25.0%) had 3 nodes or more.

A total of 390 patients were initially diagnosed to be SLN-negative. We followed these patients for up to 140 months (3–40 months; median: 24.0 months). There were 44 patients who exhibited local nodal basin recurrence. After a pathological and medical history review, 10 participants were found to be initially misdiagnosed as SLN-negative, and 6 participants had in-transit recurrence before nodal basin metastasis. After these 16 participants had been excluded, 28 participants were confirmed to be false-negative (FN). The FN rate was defined as the proportion of patients with nodal recurrences after negative SLNB in the patients with nodal involvement. The failure rate was defined as the number of FN patients divided by the total number of SLN-negative patients. Based on this definition, the FN rate of our tracer was 18.7%, and the failure rate was 7.2%.

After pathological review, we increased the number of SLN-positive patients from 112 (22.3%) to 122 (24.2%), and the number of SLN-negative patients was amended to 380. We then compared the survival rate between the 2 groups. The mean DFS and OS of the SLN-negative group was 74.4 months [95% confidence interval (CI): 67.0 to 81.9] and 106.1 months (95% CI: 103.2 to 109.0), respectively. The mean DFS and OS of the SLN-positive group was 28.2 months (95% CI: 22.8 to 33.7) and 67.2 (95% CI: 59.2 to 75.1). Statistical differences were identified between the 2 groups regarding both DFS and OS rates (P<0.05) (*Figure 2*). These results confirmed that the SLN status was a strong predictor of survival.

We further explored the risk factors of FN status. age, gender, T stage, ulceration, Clark stage, mitosis rate, lymphovascular invasion, and primary lesion location (acral or non-acral) were taken into account in the analysis. The FN group was compared with SLN-negative group and SLN-positive group. The results showed that T stage was the only predicting factor for the FN group compared with

Table 3 Analysis of predicting factors of FN

	FN	SLN-negative	SLN-positive	P value (FN *vs.* SLN-negative)	P value (FN *vs.* SLN-positive)
Patient(n)	28	352	122		
Male	14	167	58	0.79	0.81
Female	14	185	64		
Age [median]	60.0 [27–84]	58.0 [20–86]	60.0 [8–80]	0.91	0.95
Location				0.33	0.72
Acral MM	19	268	87		
Cutaneous MM	9	84	35		
T stage				0.01	0.75
Tis	0	5	0		
1	0	56	9		
2	5	76	15		
3	8	92	37		
4	12	97	52		
NA	3	26	9		
Ulceration				0.64	0.70
Positive	13	145	58		
Negative	14	188	53		
NA	1	19	11		
Lymphovascular invasion				0.32	0.84
Positive	3	15	9		
Negative	20	254	91		
NA	5	83	22		
Clark				0.42	0.98
I	0	3	0		
II	0	8	3		
III	0	31	6		
IV	6	110	35		
V	1	33	16		
NA	21	164	62		

FN, false negative; SLN, sentinel lymph node; MM, malignant melanoma; NA, not available.

the SLN-negative group (OR: 1.77; 95% CI: 1.12 to 2.78; P=0.01). Acral or cutaneous subtype was not a risk factor in either comparison (FN *vs.* SLN-negative, P=0.33; FN *vs.* SLN-positive, P=0.72). There were no differences between the FN group and SLN-positive group in the listed risk factors (*Table 3*). The median time to nodal basin recurrence in the FN group was 10.6 months. Although misdiagnosed, the OS of FN group (mean: 94.9 months; 95% CI: 84.8 to 104.9) was not statistically different from the OS of the SLN-positive group (P=0.17) (*Figure 3*).

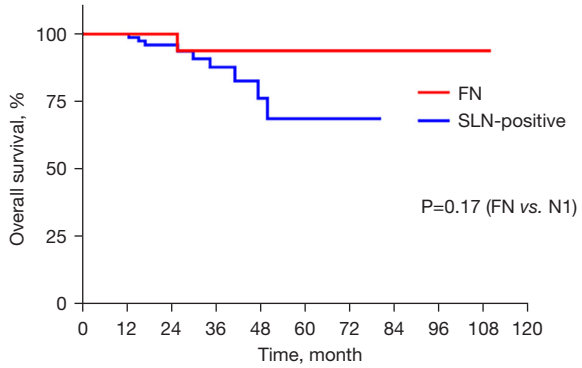

Figure 3 The OS of FN and SLN-positive patients. The OS of FN group was not statistically different from the OS of the SLN-positive group. OS, overall survival; FN, false negative; SLN, sentinel lymph node; DFS, disease-free survival.

Discussion

In the present study, SLN was detected in 100% of patients by SPECT-CT, and none of the participants failed the SLN biopsy. The mean number of harvested SLNs was 2.75. The operation procedure was simplified because the location and number of SLN could be identified based on the SPECT-CT report. ^{99m}Tc-rituximab has been deployed successfully as a tracer in breast cancer patients. In a study about evaluation of ^{99m}Tc-rituximab in breast cancer published in 2016, the success rate of lymphoscintigraphy and SLNB was 98.8% and 99.9% (24). Our result is in accordance with the previous study. In addition, by using the γ-detector to accurately locate the SLN before incision, surgeons could minimalize the surgical wound and shorten the operation time. Without a drainage tube, only 6.3% patients experienced postoperative complications, which was a relatively low rate compared to that of other studies (5–10%) (26-32). Most of the complications were mild and recovered following conservative treatment. Complications were more common in groin SLNB than in the axilla and neck. There results were similar to those of previous studies.

In this study, SLN was a strong predictor of both OS and DFS. These results complied with previous studies, and showed that the tracer, ^{99m}Tc-rituximab, could distinguish the SLN-positive patients from the entire population.

After revision, 122 participants (24.2%) were diagnosed as SLNB-positive, 85 of whom received a complete lymph node dissection (CLND). A total of 28 participants (32.9%) were found to have non-SLN positive lymph nodes. The non-SLN positive rate was much higher compared with the NCCN guidelines and the findings of other studies (12–32%, average 20%) (1,33-37). These differences may be attributed to a higher proportion of acral melanoma and a higher number of T3-4 patients in our group. Previous studies have demonstrated that Asian melanoma patients tend to be affected by the acral subtype, have a more advanced stage at the time of diagnosis, and face a poorer prognosis (16,38-42). These results may imply that CLND is still a necessary procedure for SLNB-positive patients with acral melanoma; thus, further randomized clinical trials are warranted.

A total of 10 participants were found to be SLN-positive following a pathological review. The NCCN guidelines for cutaneous melanoma recommended that large lymph nodes might be bisected or sliced at 2-mm intervals (1). Previously, the routine at our center was to bisect the SLN along the longitudinal axis. In the 10 misdiagnosed participants, 4 had micrometastasis on the marginal sinus of the previous SLN pathology slide; 5 had no metastasis on the primary SLN pathology slide, but after additional sectioning, micrometastasis was discovered on high magnification; and 1 had suspicious metastasis after additional sectioning, which was confirmed by IHC staining. These results prompted that 2-mm interval sectioning, instead of a bisection, may be an essential procedure in melanoma SLN pathology. The IHC staining should be applied when suspicious lesions are observed. We have negotiated with our pathologists and agreed that the 2-mm interval sectioning should be adopted as a standard procedure afterwards. We would like to observe whether the FN rate could be further lowered by additional sectioning.

The FN rate in our study was 18.7%, which was a reasonable level compared with that of previous studies (7–20%) (5,13,35,36,43-47). In our analysis, a higher T stage was a predictive factor for the FN status. These results were in accordance with the findings of a study conducted by Nowecki, who analyzed 1,207 MM patients and found that primary tumor thickness, primary tumor ulceration, Clark stage IV/V, and histological nodular melanoma were strongly associated with FN occurrence (45). The risk factors (e.g., ulceration, Clark stage, and histological type) were not significant in this study. This might have contributed to a relatively small number of FN patients (28 *vs.* 57; Nowecki study). The OS between the FN group and SLN-positive group was not significant, which indicated that despite an initial misdiagnosis, the survival of FN group patients would not be impaired as long as close follow-up was ensured in each patient (48-50).

Conclusions

The findings of this study suggested that ^{99m}Tc-rituximab may be employed as a simple and safe tracer in a melanoma SLN biopsy.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-21-6890/rc

Data Sharing Statement: Available at https://atm.amegroups.com/article/view/10.21037/atm-21-6890/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-21-6890/coif). All authors report that this study was supported by the Science Foundation of Peking University Cancer Hospital. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional ethics committee of Peking University Cancer Hospital and informed consent was taken from all the patients.

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