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Original Article

Clinicopathological predictors of finding additional inguinal lymph node metastases in penile cancer patients after positive dynamic sentinel node biopsy: a European multicentre evaluation

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Objective

To develop a predictive model for additional inguinal lymph node metastases (LNM) at inguinal lymph node dissection (ILND) after positive dynamic sentinel node biopsy (DSNB) using DSNB characteristics to identify a patient group in which ILND might be omitted.

Patients and Methods

We conducted a retrospective study of 407 inguinal basins with a positive DSNB in penile cancer patients who underwent subsequent ILND from seven European centres. From the histopathology reports, the number of positive and negative lymph nodes, presence of extranodal extension and size of the metastasis were recorded. Using bootstrapped logistic regression, variables were selected for the clinical prediction model based on the optimization of Akaike's information criterion. The area under the curve (AUC) of the receiver-operating characteristic curve was calculated for the resulting model. Decision curve analysis (DCA) was used to evaluate the clinical utility of the model.

Results

Of the positive DSNBs, 64 (16%) harboured additional LNM at ILND. Number of positive nodes at positive DSNB (odds ratio [OR] 2.19, 95% confidence interval (CI) 1.17–4.00; $P = 0.01$) and largest metastasis size in mm (OR 1.06, 95% CI 1.03–1.10; $P = 0.001$) were selected for the clinical prediction model. The AUC was 0.67 (95% CI 0.60–0.74). The DCA showed no clinical benefit of using the clinical prediction model.

Conclusion

A small but clinically important group of basins harbour additional LNM at completion ILND after positive DSNB. While DSNB characteristics were associated with additional LNM, they did not improve the selection of basins in which ILND could be omitted. Thus, completion ILND remains necessary in all basins with a positive DSNB.

Keywords

penile cancer, dynamic sentinel node biopsy, inguinal lymph node dissection, clinical prediction model, lymph node metastasis, #PenileCancer, #uroonc

Introduction

The 5-year cancer-specific survival of patients with penile cancer (PeCa) is generally good (81%) [1]. However, the average 5-year cancer-specific survival is 56% for patients with lymph node metastases (LNM) [1,2]. Delayed detection and treatment of potential LNM are detrimental for survival [3,4]. When no inguinal nodes are palpated (cN0), there is still a 25% chance of nodal metastases [5]. Since current imaging strategies are not accurate enough to detect these LNM, invasive nodal staging is required in cN0 basins to detect these metastases at the earliest possible moment in order to improve survival [5].

Currently, dynamic sentinel node biopsy (DSNB) is the preferred staging method for cN0 basins, with primary tumour pathology ≥T1G2 in PeCA in most European high-volume centres [5]. When DSNB is tumour-positive (positive DSNB), a completion inguinal lymph node dissection (ILND) is indicated, according to the current European guidelines [5]. Yet, in 84%–89% of basins with a positive DSNB, no further LNM are found at ILND, while surgical complications occur in as many as 58% of cases [6–10]. Thus, routine ILND after a positive DSNB might result in overtreatment in a subset of patients.

In PeCa, there are limited parameters available to accurately predict the presence of any or additional LNM [5]. In patients with cN0 PeCa, pT stage and differentiation grade are used to identify patients at risk for LNM [5]. Sentinel node metastasis size has previously been used to predict additional inguinal LNM after a positive DSNB in PeCa and other malignancies [11–13]. Additionally, a contralateral positive basin could also increase the risk of additional ipsilateral LNM after positive DSNB as bilateral metastasis could be a surrogate marker of a more biologically aggressive tumour [5,14,15]. Therefore, in addition to sentinel node metastasis size, other variables might improve this prediction. If we can identify and combine these histopathological variables into a model with sufficient accuracy, we may be able to reduce the number of unnecessary completion ILNDs performed after positive DSNB.

The primary aim of this study was to create a clinical prediction model that accurately estimates the risk of ipsilateral additional inguinal LNM at ILND after a positive DSNB based on the histopathological characteristics of the DSNB procedure. Subsequently, we explored whether the inclusion of contralateral basin status could improve prediction.

Patients and Methods

In this multicentre collaboration of seven European expert centres*, 359 patients with intermediate- to high-risk PeCa (425 cN0 basins), with at least one tumour-positive node at DSNB (between 2001 and 2020), were retrospectively evaluated. Despite not (yet) being strictly recommended in European Association of Urology guidelines, preoperative ultrasonography is routinely performed at all participating centres. As such, a cN0 basin was defined as 'non-palpable lymph nodes', 'no suspicious lymph nodes on ultrasonography' or 'negative fine-needle biopsy of the basin'. After positive DSNB, all patients underwent open ipsilateral completion ILND. The study was approved by the respective institutional review boards of the involved institutions.

The DSNB techniques in the different centres were identical except in the following two aspects. In one centre, fine-needle aspiration results were not usually available prior to DSNB as the ultrasound scan was performed on the day of surgery [8]. Another two centres perform preoperative single-photon emission CT combined with CT in addition to lymphoscintigraphy, and one of these centres also uses indocyanine green fluorescent guidance intra-operatively [9,16].

Primary tumour characteristics were not recorded, as these are known to be weak predictors of any LNM in general, and were not expected to improve the prediction of additional LNM [17–19]. From the patients' pathology reports, we registered the DSNB results: the number of positive and negative resected lymph nodes, the largest LNM size in mm, the presence of extranodal extension (ENE), contralateral basin status, and the subsequent ILND results. Micrometastases were defined as ≤ 2 mm [20]. The size of metastasis in lymph nodes with only isolated tumour cells was recorded as 0.01 mm in three lymph nodes. The median sentinel node (SN) metastasis size was imputed for one lymph node where the pathology report only described 'macrometastasis'. In patients with missing ENE status, ENE status was recorded as 'absent', based on the notion that ENE historically has been explicitly mentioned in pathology reports only when present. The contralateral basin status was reported for all patients in one centre and in the other six centres only if the DSNB was bilaterally positive. The outcome status of ipsilateral ILND was defined as 'positive', when containing additional nodal metastasis, or 'negative', when no additional tumour-harbouring nodes were found.

We performed a complete case analysis; basins with missing data were deleted listwise. Counts with percentages were used to describe categorical variables and median with interquartile range (IQR) to describe non-normally distributed continuous variables. Normality was judged using QQ-plots and histograms. Univariable and multivariable logistic regression was used to predict additional LNM at ILND. Before the final analysis, linearity in the logit was examined and confirmed for the largest metastasis size. The number of positive and

negative resected lymph nodes were categorized, taking into account clinically sensible grouping and avoiding categories with few observations. Thus, we categorized the number of positive nodes at positive DSNB as 1 or ≥ 2 and the number of negative nodes at DSNB as 0, 1–2 or ≥ 3. As there are currently no known variables predicting additional LNM at ILND after positive DSNB, variable selection was performed using repeated backward step-down selection in 600 bootstrap samples. Within bootstrap samples, the variable selection was based on optimization of the Aikake information criterion. The variables selected most frequently in the bootstrap samples were selected for the final model. Discrimination was plotted in a receiver-operating curve, and the area under the curve (AUC) was calculated. The calibration curve was plotted to evaluate how the model predictions correspond to the observed original data. To correct for overfitting, shrinkage of the final model's coefficients was applied using a uniform shrinkage factor estimated from a bootstrap validation (n = 600) of a model including all tested variables [21]. After that, decision curve analysis (DCA) was performed to evaluate the created model's clinical utility [22]. A DCA shows the added benefit the prediction model would have at different risk threshold values if the model were used in clinical practice.

Using the same methodology, in a subgroup of patients, we evaluated if adding the contralateral basin status could improve the prediction of additional LNM at ILND. Models with and without contralateral basins status were compared using the likelihood ratio test. All statistics were performed using R (version 4.0.3) using the following packages: Hmisc, mosaic, scales, lme4, rms, pROC. The DCA was also performed in R using statistical code from www.decisioncurveanalysis.org.

Results

After excluding 18 basins with missing data, 407 basins (347 patients) with a positive DSNB were included. The DSNB characteristics in relation to histological ILND outcome are described in Table 1. Additional LNM were found at ILND in 64 basins (16%, 52 patients). The median (IQR) number of positive nodes at a positive DSNB was 1 (1–1), the median (IQR) number of negative nodes at a positive DSNB was 1 (0–2). At ILND, a median of 7 (IQR 5–9) lymph nodes per basin were resected after DSNB, resulting in a median of 9 (IQR 7–12) lymph nodes resected at positive DSNB and ILND combined. The median (IQR) SN metastasis size was 5 (2–10) mm. In 78 basins (19%), the largest metastasis size was above 1 cm. ENE in the SN was found in 50 basins (12%). Additional positive nodes at ILND were identified in 51 basins with macrometastasis (18%) and 13 (10%) with micrometastasis. All predictors under consideration were statistically significantly related to the risk of positive nodes at ILND (odds ratio [OR] range 0.22 to 2.32), except ENE, which was nonsignificantly associated with increased risk in the sample (OR 1.40, 95% CI 0.63–2.88; P = 0.4 [Table 2]).

Table 1 Dynamic sentinel node biopsy (DSNB) characteristics per inguinal lymph node dissection outcome of 407 basins with a positive DSNB.

	Positive ILND	Negative ILND
Number of basins (%)	64 (16)	343 (84)
Number of positive LNs at DSNB, *n* (%)		
1	44 (13)	287 (87)
≥ 2	20 (26)	56 (74)
Number of negative LNs at DSNB, *n* (%)		
0	33 (21)	122 (79)
1 or 2	29 (13)	188 (87)
≥ 3	2 (5.7)	33 (94)
Extranodal extension at DSNB, *n* (%)		
Absent	54 (15)	303 (85)
Present	10 (20)	40 (80)
Largest metastasis size, *n* (%)		
Micrometastasis	13 (10)	114 (90)
Macrometastasis	51 (18)	229 (82)
Contralateral basin status, *n* (%)		
pN0	10 (11)	83 (89)
pN+	29 (20)	119 (80)
Missing	25 (15)	141 (85)
Number of LNs at ILND, median (IQR)	8 (6–10)	7 (5–9)
Number of LNs total, median (IQR)	10 (8–12)	9 (7–12)

DSNB, dynamic sentinel node biopsy; ILND, inguinal lymph node dissection; IQR, interquartile range; LN, lymph node.

Prediction Model

No significant difference in the incidence of additional LNM at ILND was found among the different centres (P = 0.21). Accordingly, adding a random intercept per centre to account for clustering did not improve the model, and further modelling steps were performed using ordinary logistic regression. Multivariable associations of all the variables without missing data are shown in Table 2. The AUC of the prediction model with all variables was 0.67 (95% CI 0.60–0.74). Number of positive lymph nodes at positive DSNB (OR 2.19, 95% CI 1.17–4.00; P = 0.01) and largest metastasis size in mm (OR 1.06, 95% CI 1.03–1.10; P = 0.001) were selected for the prediction model. The calibration plot of the prediction model is shown in Fig. 1. The AUC of the prediction model with only selected variables was 0.67 (95% CI 0.60–0.74).

Decision Curve Analysis

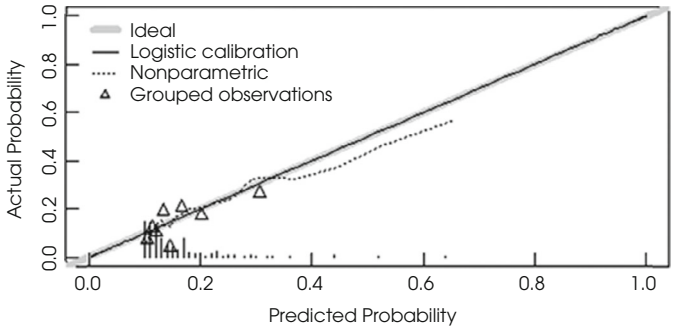
After uniform shrinkage of the model coefficients, we performed a DCA in which we plotted the reduction in ILNDs per 100 patients against the threshold probabilities of missing basins with additional LNM at ILND (Fig. 2; see Fig. S1 for net benefit). If only basins with a predicted probability of harbouring additional LNM at ILND of more

Table 2 Logistic regression of dynamic sentinel node biopsy (DSNB) characteristics of additional positive lymph nodes at inguinal lymph node dissection in 407 basins with a positive DSNB.

	Univariable		Multivariable: all variables		Multivariable: selected variables	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Number of positive LNs at DSNB, ≥2 (Reference: 1 LN)	2.32 (1.25–4.21)	0.006	2.06 (1.08–3.83)	0.02	2.19 (1.17–4.00)	0.01
Number of negative LNS at DSNB (Reference: 0 LNs)						
1 or 2	0.57 (0.33–0.99)	0.045	0.65 (0.37–1.16)	0.15	–	–
≥ 3	0.22 (0.04–0.79)	0.047	0.24 (0.04–0.88)	0.06	–	–
Extranodal extension at DSNB (Reference: absent)	1.40 (0.63–2.88)	0.4	0.71 (0.29–1.61)	0.4	–	–
Largest metastasis size, mm	1.07 (1.03–1.11)	<0.001	1.07 (1.03–1.11)	0.001	1.06 (1.03–1.10)	0.001

DSNB, dynamic sentinel node biopsy; ILND, inguinal lymph node dissection; LN, lymph node; OR, odds ratio; pT, pathological T-stage.

Fig. 1 Calibration plot of the final model.



than 10% were subjected to ILND, a net reduction of 10 ILNDs per 100 basins would be achieved.

Contralateral Basin Status

In 179 patients (241 basins), the contralateral basin status was known. Within this subset, contralateral LNMs were reported in 86 patients (148 basins). Of these, 24 patients had a direct ILND and the remaining 62 had completion ILND after positive DSNB. Additional LNM were found in 29/148 basins (20%) in patients with contralateral LNM, and in 10/93 basins (11%) in patients without contralateral LNM (OR 2.02, 95% CI 0.96–4.57; $P = 0.07$). Contralateral basin status did not give added value to the prediction models with only selected variables (likelihood ratio test $P = 0.6$) or all investigated variables (likelihood ratio test $P = 0.18$) and was also not retained in the bootstrap selection.

Discussion

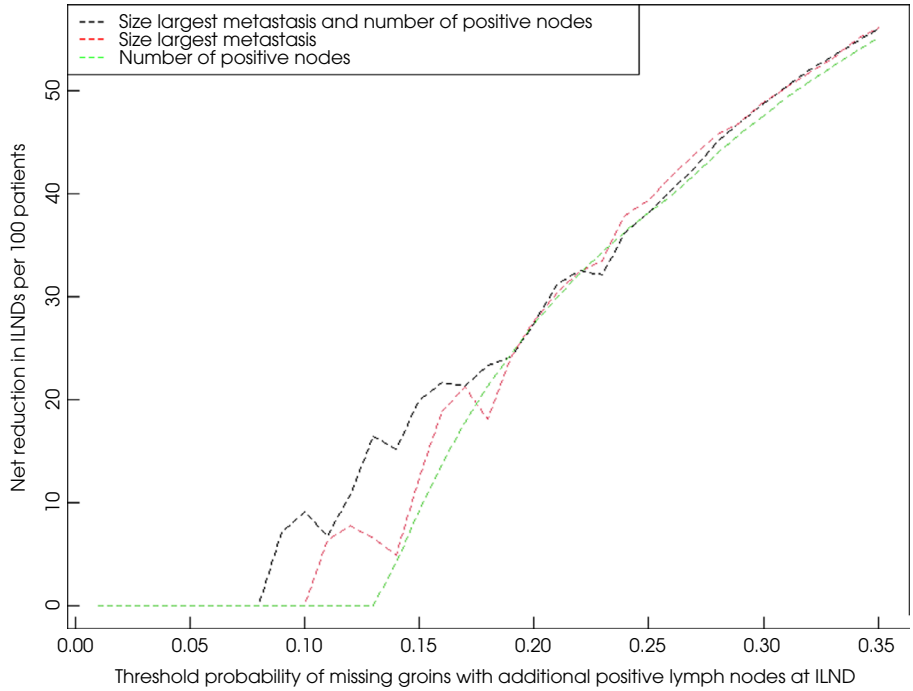
In the present study, the incidence of additional LNM at ILND after a positive DSNB was 16%. Number of positive and negative lymph nodes and largest metastasis size at positive DSNB were significantly associated with finding additional LNM at ILND. A prediction model including these variables would achieve a reduction of 10 ILNDs per 100 patients, if a threshold of a 10% chance of missing additional LNM at ILND were to be accepted. Since delayed surgical treatment of occult LNM results in a substantially decreased survival and the 10% threshold would also result in up to 10 basins with untreated LNM per 100 patients, the prediction model is not suitable to identify a substantial subgroup of positive DSNB basins in which subsequent ILND could be omitted safely [4].

In the final model, number of positive nodes and largest metastasis size at DSNB were selected using bootstrapping. The risk of additional LNM increased when more than two positive inguinal nodes at positive DSNB were detected (OR 2.32). This relationship is similar to the increased risk of pelvic metastases observed in patients with ≥2 positive inguinal lymph nodes [18]. We also report that every 1-mm increase in the largest metastasis size also increases the risk of additional LNM by a factor of 1.07.

In contrast to Kroon et al. [13], who, after serial sectioning of all lymph nodes, found no additional LNM at ILND in basins with micrometastasis, we found additional LNM in 10% of basins with micrometastasis without serial sectioning. These differences can probably be explained by the small sample size and possible incomplete representation of the population with positive DSNB in the study by Kroon et al. Surprisingly, ENE was not associated with additional inguinal LNM, while inguinal ENE predicts pelvic LNM [5,18]. The number of resected negative lymph nodes at DSNB was inversely associated with additional inguinal LNM at completion ILND, although number of negative lymph nodes was not selected for the prediction model. Moreover, the AUCs of the model with all variables and selected variables were the same after rounding. Thus, number of resected negative lymph nodes and presence of ENE are, in our opinion, unlikely to improve selection in an even larger sample. While there were protocol differences among centres, this did not change the predictive relationship between the histopathological variables and additional LNM at ILND, as the correction for clustering did not improve model selection.

With only cN0 basins included, the fact that 19% of basins harboured metastases larger than 10 mm is surprising. The

Fig. 2 Net reduction curves from the decision curve analysis, including two models with largest metastasis size and number of positive lymph nodes at dynamic sentinel node biopsy and the final model of a combination of these two variables. On the *y*-axis, the net reduction in the number of inguinal lymph node dissections (ILNDs) per 100 basins is reported, and on the *x*-axis, the different threshold probabilities for performing ILND based on the final model's predictions.



presence of these large metastases either indicates understaging by palpation or rapid tumour growth. As we expect that these metastases would be palpable or detected by ultrasonography (with fine-needle aspiration) at the time of surgery, it might be interesting to repeat staging just before DSNB. In the upstaged basins, hypothetically, immediate ILND could then be performed, which could shorten the time to adequate treatment and reduce the number of surgeries.

As developed in the present study, the model was unable accurately to predict additional LNM after positive DSNB using histopathological DSNB characteristics. The risk for metastases is, of course, not the direct result of a causal relationship between metastatic disease and these histopathological characteristics, but rather a result of cancer-cell intrinsic factors and the extrinsic tissue microenviroment at the metastatic site and a temporal component [23]. The currently used variables are all different representations of tumour load at positive DSNB. As expected, when the tumour load at positive DSNB was higher (e.g. larger metastasis size, more positive nodes), the risk of harbouring additional LNM at ILND also increased, and vice versa. Cancer-cell intrinsic factors (e.g. gene signatures) are used to predict breast cancer recurrence and could also be of value in predicting additional metastasis in PeCa [24]. Extrinsic factors that might improve metastasis prediction comprise tumour secretions (e.g. extracellular vesicles, cytokines and chemokines) [25]. Another major risk factor for metastasis formation is treatment delay. The longer a tumour remains untreated, the more tumour cells will have a chance to enter the lymphatic system and seed metastasis. Therefore, time until treatment, including delay caused by doctor- or patient-related reasons, might also aid the prediction of metastasis. Although these variables are not readily available, the prediction model might benefit by incorporating these tumour-intrinsic and -extrinsic factors or a temporal component, which could be further investigated in future prospective studies.

Another option to improve early and accurate nodal staging could be the use of tumour-specific tracers for imaging or surgery [26]. The most drastic option to reduce surgical morbidity is omitting lymph node dissection after positive DSNB for all patients. In melanoma, omitting ILND after positive DSNB did not negatively affect cancer-specific survival [27]. Melanoma patients with additional microscopic LNM after positive DSNB have similar survival to patients with clinically diagnosed bulky metastases [27]. However, this is not the case for PeCa [5]. Moreover, melanoma patients' survival has recently increased with the development of effective systematic therapies, whereas the outcome of systemic therapies in PeCa remains poor [28,29]. Therefore, omitting all ILNDs after positive DSNBs in PeCa is, in our opinion, not advisable. Nevertheless, while we know that delayed treatment of occult metastasis is linked to decreased

survival, a direct comparison between immediate treatment and close surveillance after positive DSNB has not been reported. Also, in selected cases (e.g. frail patients with generally short life expectancy and extensive comorbidity), omitting further treatment remains an option when the expected morbidity does not outweigh the expected survival benefit.

While the tumour characteristics that increase the metastatic potential and tumour-specific tracers are currently not clinically available and omitting all ILND is not realistic, non-surgical treatment methods could be considered for selected patients. Oonk et al. [30]prospectively investigated the use of radiotherapy as a replacement for ILND in 322 basins with a positive DSNB in patients with vulva cancer. At an interim analysis, the protocol was amended to only treat basins harbouring micrometastasis without ENE with radiotherapy because an increased risk of recurrence was seen in basins with macrometastasis and ENE [30]. In the 126 patients with micrometastasis who received radiotherapy, only two (1.6%) ipsilateral inguinal basin recurrences were seen with minimal toxicity [30]. A retrospective vulvar cancer study and a randomized breast cancer study found similar results when radiotherapy replaced lymph node dissection [31,32]. Therefore, we could hypothesize that the use of radiotherapy as a replacement for ILND after positive DSNB might also be feasible in a subgroup of PeCa patients.

In addition to its retrospective nature, our study has the following limitations. First, as the lymph nodes after ILND are not processed in the same meticulous fashion as sentinel nodes, it is possible that negatively scored ILND contained metastases. In a similar cohort, two of 398 (0.5%) initially negative lymph nodes at the routine histological evaluation of ILNDs after positive DSNB turned out to contain a metastasis when additional serial sectioning was performed. Still, it is unknown if these positive lymph nodes identified with serial sectioning would have been harvested from basins with an initially negative ILND and if they would be of clinical relevance. Second, this study did not include patients who could not or did not want to undergo ILND, which is, of course, a group in which the prediction model would probably not be used but which could be of interest for further research to investigate the impact of omitting ILND after positive DSNB. Third, due to the limited data on contralateral groin status, uncertainty for this variable for prediction of additional LNM after positive DSNB remains. Finally, although the multicentre nature of the study may have introduced heterogeneity in surgical techniques used, a correction for study centre did not improve the model fit or change the results. We therefore believe that the influence of such heterogeneity on the study outcomes is negligible.

Despite these limitations, to our knowledge, this remains the largest study consisting of only positive PeCa DNSB procedures, which was only possible thanks to a European multicentre collaboration. This study assessed a recurring question in PeCa management: is completion ILND always necessary after positive DSNB? While no clear group of patients could be identified in which completion ILND can be omitted, the results from this study may be useful for shared decision making in some cases in clinical practice (e.g. close monitoring instead of completion ILND in a frail patient with micrometastasis in only one SN, with multiple additional negative nodes at DSNB). However, a prospective study is required to definitively determine if and when completion ILND after positive DNSB can be safely omitted in PeCa patients.

In conclusion, in this large multicentre cohort of cN0 PeCa patients with a tumour-positive DSNB, a small but clinically important group of basins harbour additional LNM at completion ILND after positive DSNB. When micrometastasis were present in the SN, a positive ILND was still found in 10% of cases. While histopathological DSNB characteristics were associated with additional LNM, they did not improve the selection of basins in which ILND could be omitted. Thus, completion ILND remains indicated in all basins with a positive DSNB.

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Disclosure of Interests

None declared.

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Abbreviations: AUC, area under the curve; DCA, decision curve analysis; DSNB, dynamic sentinel node biopsy; ENE, extranodal extension; ILND, inguinal lymph node dissection; IQR, interquartile range; LNM, lymph node metastases; OR, odds ratio; PeCa, penile cancer; SN, sentinel node.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Net benefit curve from the decision curve analysis, including two models with largest metastasis size and number of positive lymph nodes at DSNB and the final model of a combination of these two variables.