# Evaluation of Sentinel Lymph Node Biopsy for Eccrine Porocarcinoma

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Eccrine porocarcinoma (EPC) is a sweat gland carcinoma thought to arise from the lower portion of intraepidermal eccrine ducts. This tumour is rare (0.005–0.01% of all malignant skin tumours) (1) and information about its biological behaviour is limited, although it is known to be aggressive. Previous studies have reported that the local recurrence rate is 17–20% (2), the regional lymph node (RLN) metastasis rate 20%, and the distant metastasis rate 11% (3). In patients who have RLN metastasis, the prognosis is poor, with a mortality rate of 65% (4). In EPC, the lymphogenous route is thought to be the main initial metastatic pathway, and therefore it can be reasonably expected that the prognosis would be improved by sentinel lymph node (SLN) biopsy, discovery of early lymph node metastasis, and RLN dissection. However, few case reports have documented the use of SLN biopsy in patients with EPC, and no large-scale studies have been conducted.

Our department has been conducting SLN biopsy for EPC since 2009, and during this period we have accumulated 13 surgical cases of EPC. This paper reviews these cases, together with previous reports of EPC, and discusses the use of SLN biopsy for this malignancy and future issues.

## PATIENTS, METHODS AND RESULTS

Between 2009 and 2017, 13 patients were diagnosed as having EPC at the Department of Dermatology, Iwate Medical University, Iwate, Japan. Pathologically, the tumours showed malignant characteristics, such as irregular structures, invasive growth and unclear borders. They consisted of atypical poroid cells with dark basaloid staining and cuticular cells with eosinophilic staining. Duct structures were also evident. The tumour cells were immunopositive for carcinoembryonic antigen (CEA) and/or epithelial membrane antigen (EMA). SLN biopsy was performed for cases in which lymph node/distant metastasis was not recognized by imaging (computed tomography (CT) and/or positron emission tomography – computed tomography (PET – CT)) before surgery. On the other hand, SLN biopsy was not performed for cases in which metastasis to RLN was clear or obvious based on preoperative imaging examination; instead, immediate RLN dissection was performed in all such cases.

For identification of SLN, the radioisotope (RI) method and indocyanine green (ICG) fluorescence method were used together. A detailed description of the SLN is shown in Appendix S1[1].

Among the 13 cases, only one was treated by simple wide resection of the primary tumour. The patient was elderly and did not wish to undergo SLN biopsy, opting for minimally invasive surgery. Clinical and imaging findings before surgery demonstrated no lymph node metastasis, and SLN biopsy was performed in 8 cases. Among them, 3 cases were positive for SLN metastasis (positivity rate 37.5%). In 4 cases where clinical and/or imaging examinations revealed RLN metastasis, dissection of the affected nodes was performed at initial surgery (Fig. S1[1]). The characteristics of each treatment group are shown in Table SI[1]. The clinicopathological features of SLN biopsy metastasis-negative cases are shown in Table SII[1] and those of positive cases in Table SIII[1]. RLN dissection was performed in all 3 patients who were positive for SLN metastasis. The mean observation period was 28.7 months and, at time of writing, all of the 3 patients are currently alive. In one patient (Case 1 in Table SIII[1]), recurrence was observed in the parotid gland at 22 months, and resection was performed. The mean Ki-67 labelling index in the SLN metastasis-negative group ($n=5$) was 16.6% (Table SI[1]), and none of the patients in this group had vascular or lymphatic invasion (Table SII[1]). On the other hand, the mean Ki-67 labelling index in the SLN metastasis-positive group ($n=3$) was high (21.0%) (Table SI[1]), and vascular and lymphatic invasion was observed in 2 of the 3 patients in this group (Table SIII[1]). For all SLN metastasis-positive cases, postoperative chemotherapy was administered. The regimen for postoperative chemotherapy was cisplatin (60 mg/m$^2$) and doxorubicin (Adriamycin) (30 mg/m$^2$) once a month. The regimen was based on that used for advanced squamous cell carcinoma (SCC). However, continuation of this regimen is likely to cause bone marrow suppression, kidney damage, and cardiotoxicity. Therefore, it can be administered for only 3 cycles. There were no serious side-effects, however. In case number 2 (Table SIII[1]), the patient requested to be administered only one cycle. Table SIV[1] shows the clinicopathological features of the RLN dissection group. The mean observation period was 30.7 months. All patients in the RLN dissection group had lymphatic invasion. In addition, the mean Ki-67 labelling index was as high as 32.3% (Table SI[1]). Postoperative chemotherapy was administered to all 4 of the patients, but 2 of them died due to multiple distant metastasis. The primary regimen for postoperative chemotherapy was cisplatin and Adriamycin once a month. The dose is described above. For patients showing a poor treatment response, docetaxel (60 mg/m$^2$) was administered monthly, and if this proved ineffective, irinotecan (100 mg/m$^2$) was administered on days 1, 8 and 15, and then every 4–5 weeks.

After surgery, the levels of tumour markers (CEA and CYFRA) were checked monthly and CT imaging examinations performed every 3 months in all patients with EPC. However, if elevation of a tumour marker was evident, imaging was carried out promptly.

## DISCUSSION

The utility of SLN biopsy for staging of malignant melanoma and breast cancer has been well established (5, 6). Recently, SLN biopsy has also been attempted for patients with non-malignant melanoma, such as SCC and extramammary Paget's disease, in which the lymphoid route is thought to be the predominant metastatic pathway. Lymphatic metastasis is also believed to be the main mode of metastasis in EPC. We believe that to improve the prognosis of patients with EPC, it is important to perform SLN biopsy for identification of lymph node metastasis at an early stage and to perform RLN dissection in positive cases. However, few case reports of EPC have documented the use of SLN biopsy.

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Robson et al. (3) reported that 3 factors were indicative of a poor prognosis in EPC: a tumour depth of more than 7 mm, a high mitotic count (> 14 /high-power field), and the presence of vascular invasion. Data for the present series showed that tumours with poor histopathological differentiation had a high rate of lymph node metastasis and lymphovascular invasion. However, lymph node metastasis did not necessarily occur in deeply invasive cases, and SLN metastasis was observed even in cases with a shallow tumour depth of 0.9 mm. Pathologically, the degree of tumour differentiation was poor, and cases with lymphovascular invasion were considered to have a high risk of lymph node metastasis. In our series, SLN biopsy was performed in 8 cases, 3 of which were positive for sentinel node metastasis. Lymph node dissection was performed for these 3 patients, and all of them survived. On the other hand, among 4 patients who already had RLN metastasis at initial surgery, 2 died within 1 year despite immediate local lymph node dissection. Therefore, positive application of SLN biopsy, early discovery of lymph node metastasis, and enforcing dissection of RLN may improve the survival rate. Here, we performed adjuvant chemotherapy for all SLN metastasis-positive cases and all patients in the RLN dissection group. The regimen employed was similar to that used for advanced SCC. However, no accepted adjuvant regimen exists for advanced SCC, and recent guidelines are not helpful (7). Although there have been some reports of chemoradiation as adjuvant treatment for advanced SCC (8, 9), there is no accepted consensus regarding adjuvant therapy, because the existing data are based only on retrospective case series. We conclude that, not only RLN dissection, but also postoperative chemotherapy, were effective for prevention of metastasis in patients with EPC. However, this remains unproven on the basis of this limited case series; further research is needed into the effectiveness of postoperative chemotherapy for EPC.

In the series reported here, the positivity rate of SLN metastasis in EPC was 37.5%. This rate was higher than that for malignant melanoma (13.9–23.0%) (10, 11). The proportion of patients positive for SLN metastasis and those found to have lymph node metastasis on the basis of clinical and/or imaging examinations at initial surgery was also very high, at 53.8% (7/13). Since, to date, EPC has been considered a subtype of SCC in a broad sense, it has been treated as SCC. However, while the positivity rate for SLN metastasis in SCC has been reported to be 7.4–23.1% (12–15), taking into account that SLN biopsy is performed actively for high-risk cases of SCC in many instances, the positivity rate for SLN metastasis appears to be considerably higher in EPC.

Currently, the standard treatment of EPC is total surgical resection of the tumour (16), and application of regional lymphadenectomy is common when clinical metastasis is confirmed. However, in patients with advanced EPC associated with lymph node metastasis or distant metastasis, the effectiveness of chemotherapy and radiotherapy has not been established. From this viewpoint, treatment of advanced EPC is often difficult, and therefore early discovery of lymph node metastasis is considered important for improving the prognosis. For this reason, we believe that SLN biopsy should be considered first-line management for EPC when staging scans do not reveal clear or obvious metastases. To clarify whether the dissection of enlarged lymph nodes improves the prognosis of SLN metastasis-positive patients, it will be necessary to compare the prognosis of patients who do and who do not undergo RLN dissection. In order to specifically clarify the utility of SLN biopsy, a randomized controlled trial involving an adequate number of cases will be required; however, because EPC is a rare skin cancer, it is difficult to conduct a randomized controlled trial at a single facility. Therefore, it is hoped that international multi-centre randomized controlled trials of SLN biopsy in patients with EPC will be possible in future.

*The authors have no conflicts of interest to declare.*

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