Multidisciplinary treatment for locally advanced breast cancer with internal mammary lymph node metastasis in an elderly patient

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Abstract

Internal mammary lymph node (IMLN) metastasis is one of the important prognostic indicators in breast cancer. However, the management for IMLN metastasis is not established. The dissection for IMLN metastasis is not recommended in the National Comprehensive Cancer Network guidelines version 3. 2015. Furthermore, radiotherapy including IMLN region and biopsy have attendant risks and hence should be performed with caution. Here, we describe our experience of multidisciplinary treatment for locally advanced breast cancer with IMLN metastasis in an elderly patient. Core-needle biopsy of the breast tumor histologically diagnosed the tumor as estrogen receptor positive, progesterone receptor positive, human epidermal growth factor receptor-2 negative, and high Ki-67 labeling index. IMLN swelling was detected by ultrasonography and breast cancer metastasis was diagnosed by fine-needle aspiration cytology. The patient underwent mastectomy and axillary lymph node dissection, followed by postmastectomy radiation therapy. Systemic therapy using tegafur plus uracil (UFT®; Taiho Pharmaceutical Co., Ltd, Tokyo, Japan) and letrozole was beneficial treatment for disease control.

Keywords Breast cancer · Internal mammary lymph node metastasis · Multidisciplinary therapy

Introduction

Lymphatic drainage of the breast is an important process of breast cancer metastasis. Intramammary lymphatics flow toward axillary and/or internal mammary lymph nodes (IMLN). Involvement of IMLN is associated with poor prognosis and has been reported in 11.1–23.5% of who underwent internal mammary sentinel lymph node biopsy [1–3]. However, internal mammary sentinel lymph node biopsy for accurate staging or IMLN dissection with IMLN metastasis is controversial [4–7]. The surgical procedure for IMLN sampling carries the risk of pneumothorax or bleeding

caused by inadvertent injury to the internal thoracic vessels. Radiation therapy is reported to reduce the number of local recurrences but may cause adverse effects such as radiation dermatitis, pneumonitis, or cardiac disorders [6, 8]. There are no clear recommendations about IMLN metastasis. According to the National Comprehensive Cancer guidelines version 3. 2015, the dissection for IMLN metastasis has much more disadvantages than merits. At least, systemic or local management without resection of metastatic IMLN might benefit patient prognosis.

On the other hand, safety is not always guaranteed for chemotherapy prescribed to elderly people aged over 80 with locally advanced breast cancer.

Herein, an elderly case with IMLN metastatic breast cancer who underwent multidisciplinary therapy is presented the characteristics of breast cancer with IMLN metastasis were reviewed in our institute. This report focus on the therapy of elderly breast cancer patient with IMLN metastatic, locally advanced disease.

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Case report

An 82-year-old woman presented to the outpatient clinic of the Department of Breast Surgery in Shiga General Hospital (Moriyama, Shiga, Japan) with a history of a lump in the right breast for a month. On physical examination, she had a mass measuring 3.5 cm without skin invasion in the upper medial region in her right breast.

Ultrasonography, computed tomography (CT), and breast magnetic resonance imaging (MRI) showed IMLN swelling in right lateral side of her sternum (Fig. 1a). Core-needle biopsy of the right tumor diagnosed the tumor was high histological grade invasive ductal carcinoma with IMLN metastasis, as estrogen receptor (ER) positive (20%), progesterone receptor (PgR) positive (10%), human epidermal growth factor receptor 2 (HER2) negative (score 1+), and Ki-67 labeling index 50% histologically (Fig. 2).

Fine-needle aspiration of IMLN revealed metastasis from breast tumor. Radiological study classified she was in cT2N2bM0, stage IIIA disease (UICC-TNM classification 8th edition). Bone scintigraphy using ^{99m}Tc -Methylene diphosphonate (555 MBq) showed there was no evidence of bone metastasis.

Disadvantage of intravenous chemotherapy was concerned due to the age of the patient in stratifying the treatment. Thus, preoperative chemotherapy was not administered; she underwent right mastectomy and axillary lymph node dissection. A metastatic IMLN was not resected. The final histological analysis diagnosed she was in pt2n2b(1/24, and non-removed IMLN)M0, stage IIIA disease.

The patient's performance status was worth treating intensively by the evaluation based on comprehensive geriatric assessment [9]. The patient has no serious comorbidities contribute to overall survival other than breast cancer, so the long-term survival was expected if breast

Fig. 1 Radiological images of right IMLN metastases. **a** CT indicated right breast mass and IMLN swelling at diagnosis. **b** CT planning image for post-mastectomy radiation therapy PMRT including IMLN region. **c** After PMRT, during adjuvant therapy. *IMLN* internal mammary lymph node, *CT* computed tomography, *PMRT* post-mastectomy radiation therapy

Fig. 2 Pathological findings of breast cancer by CNB and FNAC at diagnosis. Right breast cancer was defined as (a, b) invasive ductal carcinoma, histological grade 3 (tubular formation; score 3, nuclear atypia; score 3, mitotic figures; score 3), c ER positive: 20%, d PgR positive: 10%, e HER2 negative: score 1+, f Ki-67 labeling index; 50%. g FNAC using 23-gauge Cathelin needle was performed. Atypical ductal cells were collected from IMLN. CNB core-needle biopsy, FNAC fine-needle aspiration cytology, ER estrogen receptor, PgR progesterone receptor, HER2 human epidermal growth factor receptor 2

cancer control would be performed. She underwent post-mastectomy radiation therapy (PMRT) including IMLN region, with the dose of 60 Gy/30 fractions as local control (Fig. 1b). After PMRT, tegafur plus uracil (UFT®; Taiho Pharmaceutical, Co., Ltd, Tokyo, Japan) 600 mg a day with letrozole 2.5 mg a day were administered as systemic therapy. UFT® was reduced to 400 mg due to grade 2 neutropenia and fatigue according to Common Terminology Criteria of Adverse Event (CTCAE) version 4.0. A year after surgery, CT scan described no evidence of IMLN enlargement or other new metastatic regions radiologically (Fig. 1c). To date, she has a good quality of life and has demonstrated stable disease for 18 months.

The medical records of 626 operable breast cancer patients were retrospectively reviewed. Between 2007 and 2017, all the patients who underwent breast surgery at Shiga General Hospital were investigated and χ^2 tests were used to analyze qualitative data. Overall survival

Fig. 3 Kaplan-Meier plot comparing a DFS, b OS, and c BCSS times between the patients with N1–3 lymph node metastasis and IMLN metastasis. DFS disease-free survival, OS overall survival, BCSS breast cancer-specific survival, IMLN internal mammary lymph node, HR hazard ratio, CI confidence interval

(OS) was defined as the period from the date of diagnosis to the date of the last follow-up or death from any cause, and disease-free survival (DFS) was defined as the period from the date of diagnosis to occurrence of any event, such as disease progression, relapse, recurrence or death. Kaplan-Meier estimates were used to calculate OS and DFS using Stat Mate V for Win & Mac Hybrid software (ATMS, Tokyo, Japan).

Figure 3 shows Kaplan-Meier plot comparing DFS, OS, and BCSS between the patients with N1–3 lymph node metastasis and IMLN metastasis. Patients who experienced postoperative axillary lymph nodes or IMLN metastasis were included in this verification. Because most of patients who underwent local recurrence received insufficient local control, as omission of PMRT for patients with skin invasion or lymph node metastases. As shown in Table 2, even patients with N1–2 disease did not receive PMRT. Primary local control was considered to contribute to DFS or BCSS. Compared with patients with axillary lymph node metastasis (N1–3), those with IMLN metastasis had no statistically

Table 1 Patient characteristics with internal mammary lymph node metastasis at diagnosis

Age	Clinical stage	Location	Subtype	Neoadjuvant therapy	Operation	Radiation	Adjuvant therapy	Outcome
42	T3N3bM0	Upper lateral	Luminal-HER2	EC-wPTX + HCPT	Bp + SLNB	60 Gy/30fr	HCPT + TAM	SD
44	T4bN3bM1 (synchronous bilateral)	Upper medi- olateral	Luminal-HER2	TC	Bt		TAM + zometa- DTX + Per + HCPT + zometa	SD
58	T4bN2bM0 (SCC)	Upper medial	Luminal A-like	EC-wPTX-VNR	Bp + Ax	50 Gy/25fr	DTX-TS-1 + ANA- GEM-eribulin	Death due to sepsis
68	T2N3bM0	Lower medial	Luminal B-like	wPTX	Bp + Ax	50 Gy/25fr	LET	SD
82	T2N3bM0	Upper medial	Luminal B-like		Bp + Ax	60 Gy/30fr	UFT + LET	SD

SCC squamous cell carcinoma, *HER2* human epidermal growth factor receptor 2, *EC* epirubicin + cyclophosphamide, *wPTX* weekly paclitaxel, *HCPT* trastuzumab, *TC* docetaxel + cyclophosphamide, *VNR* vinorelbine, *Bp* partial mastectomy or breast-conserving surgery, *Bt* total mastectomy, *SLNB* sentinel lymph node biopsy, *Ax* axillary lymph node dissection, *TAM* tamoxifen, *DTX* docetaxel, *Per* pertuzumab, *TS-1* Tegafur/Gimeracil/Oteracil, *ANA* anastrozole, *GEM* gemcitabine, *LET* letrozole, *UFT* tegafur plus uracil, *SD* stable disease

Table 2 Patient characteristics with internal mammary lymph node metastasis after primary therapy

Age	Clinical stage	Location	Subtype	Neoadjuvant therapy	Operation	Radiation	Adjuvant therapy	DFI (months) first metastatic site
41	T3N2M0	Upper medi- olateral	Luminal- HER2	EC-wPTX	Bt + Ax		HCPT + LHRHa + TAM	26 lung, IMLN meta
44	T2N0M0	Unknown	Luminal A-like		Bt + Ax		5'DFUR + TAM	203 bone, IMLN meta
45	T?N1M0	Unknown	Luminal -HER2		Bt + Ax		EC-TAM-LET-LHRHa	120 SCLN meta
60	T3N2M0	Upper medial	HER2 enriched	EC	Bt + Ax		EC-wPTX	38 IMLN, lung meta Death; liver meta
62	T1cN0M0 (metachro- nous bilat- eral BC)	Lower lateral	TNBC		Bt + SLNB		wPTX + CPA + UFT	24 contralateral BC
64	T1cN0M0 (Metachro- nous bilat- eral BC)	Lower lateral	Luminal A-like		Bt + Ax	50 Gy/25fr	ANA	22 bone, IMLN, SCLN meta
82	T2N0M0	Upper medial	TNBC		Bt + Ax			23 bone, IMLN meta Death; lung meta

HER2 human epidermal growth factor receptor 2, *TNBC* triple-negative breast cancer, *EC* epirubicin + cyclophosphamide, *wPTX* weekly paclitaxel, *Bt* total mastectomy, *Ax* axillary lymph node dissection, *SLNB* sentinel lymph node biopsy, *HCPT* trastuzumab, *LHRHa* luteinizing hormone-releasing hormone-analog, *TAM* tamoxifen, *5'DFUR* doxifluridine, *LET* letrozole, *CPA* cyclophosphamide, *UFT* tegafur plus uracil, *ANA* anastrozole, *DFI* disease-free interval, *IMLN* internal mammary lymph node, *SCLN* subclavicular lymph node, *BC* breast cancer

significant differences in OS, BCSS (Fig. 3a–c); however, the hazard ratios in DFS, OS, and BCSS were worse.

Table 1 shows the characteristics of 5 patients with IMLN metastasis at diagnosis, and Table 2 shows those of 7 patients with IMLN recurrence after primary therapy among 626 patients. Primary breast cancer with IMLN metastasis tended to be locally advanced, located in the medial side of

the breast, and has a luminal-like phenotype. Four patients, except 1 who had stage IV disease, received irradiation. No patients experienced relapse of IMLN metastasis, and 1 patient died from sepsis from a wound infection 33 months after surgery (Table 1).

Seven patients experienced IMLN recurrence after primary therapy, although they had no IMLN metastasis at diagnosis (Table 2). They also tended to have luminal-like

tumors. However, the tumors primarily included those with a small diameter and those located in the lateral side of the breast. Five of them (71.4%) were non-irradiated patients after primary surgery. Two patients died within 2 years after IMLN recurrence with visceral metastases (Table 1).

Discussion

Management of IMLN metastasis is controversial. Surgical resection of metastatic site is harmful more than benefit [4, 6]. Although PMRT including supraclavicular and IMLN region might be effective for local control, it causes unavoidable radiation to healthy tissues and organs [6, 8]. And systemic therapy is another option for disease control.

The resected breast tumor was diagnosed as high histological grade, ER positive (20%), PgR positive (10%), HER2 negative (score 1+), and 50% of Ki-67 labeling index. For young patients with such locally advanced, high-grade luminal B-like breast cancer, preoperative chemotherapy including anthracycline and taxane will be administered to evaluate the effect of preoperative chemotherapy [10]. Intensive systemic therapy also is usually performed after surgery since IMLN dissection is not recommended [1–7].

In the meta-analysis, PMRT reduced locoregional recurrence, overall recurrence, and BCSS for patients with one to three positive nodes (N1 stage) [11]. And some reports showed PMRT could improve locoregional recurrence, DFS, OS for patients with even T1-2 and N1 stage breast cancer especially with high-risk disease such as age, lymph node ratio, molecular subtype, and lymphovascular invasion [12, 13]. That is, most patients with lymph node metastasis are considered to have good indications of PMRT. In addition, efficacy of PMRT for patients with IMLN metastasis is also indicated in DFS and BSCC [14].

For such an elderly patient as in this case, disadvantage of intravenous chemotherapy sometimes causes severe adverse effects. According to the comprehensive geriatric assessment for this patient, the long-term survival was expected if breast cancer control was provided [9]. The prognosis varies considerably depending on many factors in elderly patients. Therapeutic strategy becomes sometimes overtreatment or undertreatment if the risk–benefit balance is misdiagnosed. Radiotherapy for elderly patients is sometimes omitted to avoid adverse events. Fortunately, for this case, PMRT was especially effective in local control without any severe radiation-related events such as pneumonitis or pericarditis.

Although endocrine therapy is relatively harmless therapy, endocrine sensitivity may be low in this case (Fig. 2). To maintain her quality of life, UFT® was considered to be a useful option instead of intensive chemotherapy [15, 16]. Previous clinical trials in Japan as NSASBC-01 and CUBC

showed UFT® had similar effect on DFS and OS to those with classical CMF, and higher quality of life scores to the patients [15, 16]. She has been stable with no recurrence and continuing adjuvant systemic therapy with good quality of life for 18 months postoperatively. UFT® and letrozole will be administered in 2 years [15, 16], and 5 years after surgery, respectively, if without IMLN relapse.

As shown in Fig. 3, patients with IMLN metastasis have higher risk of distant metastasis or mortality compared to those with axillary lymph node metastasis. Aggressive therapy, in this situation, chemotherapy with radiation therapy would be effective to prevent postoperative relapse even though with IMLN metastasis, for the patient with good performance status. Since IMLN metastasis is not a life-threatening situation, oral chemotherapy such as UFT® is one option to avoid adverse event associated with chemotherapy. Based on the guidelines, chemotherapy should not be used concurrently with endocrine therapy. However, such treatment works effectively and harmlessly in some cases.

The limitation of this study is the small number of patients diagnosed with IMLN metastasis. In Fig. 3, although IMLN metastatic group tended to show lower DFS and BCSS compared to N1–3 stage group, there was no statistical significance. Several percentages of patients with IMLN metastasis were thought to be included in N1–3 stage group in our study, because sentinel lymph node biopsy of IMLN was not performed in our institution. True IMLN metastatic patients and N1–3 stage group should have been compared. However, from this point of view, the influence of IMLN metastasis on the prognosis of breast cancer patients is enormous and the importance of local control is suggested.

Conclusion

Locally advanced breast cancer with IMLN metastasis is controllable by multidisciplinary treatment without resection. For elderly patients, oral chemotherapy as UFT® is a harmless and beneficial option.

Compliance with ethical standards

Conflict of interest No conflicts of interest relevant to this article are reported.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from the patient in this study.

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