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Surgical Resection and Outcome of Synchronous and Metachronous Primary Lung Cancer in Breast Cancer Patients

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Abstract. *Background/Aim: Women with breast cancer are at increased risk of subsequent primary malignancies, specifically lung cancer. The aim of this study was to report the frequency of lung cancer in patients with breast cancer, and patients' characteristics and surgical outcomes. Patients and Methods: We investigated 1,066 consecutive female patients undergoing surgical resection for breast cancer and 666 undergoing surgical resection for lung cancer. Results: Lung cancer with breast cancer was observed in 14 patients (1.3% of breast cancer and 2.1% of lung cancer cases; mean age=65 years), and 3/14 (21.4%) patients were smokers. Sixteen lung cancer lesions in 14 patients were adenocarcinomas and one was squamous cell carcinoma. All 14 patients were alive at the time of this report; 4/14 (28.6%) patients had recurrent breast cancer and 1/14 (7.1%) had recurrent lung cancer. In synchronous cases, 5/6 (83.3%) patients received concomitant surgery for both breast cancer and lung cancer. Patients' postoperative courses were uneventful. In metachronous cases, eight patients had lung cancer a mean of 33 months after breast cancer surgery. All eight patients received adjuvant therapies and 4/8 (50%) patients received adjuvant therapies for recurrent breast cancer, including chemotherapy, radiotherapy, hormonal therapy, and anti-HER2 therapy. All patients had early-stage lung adenocarcinoma and underwent surgical resection. Conclusion: Concomitant surgery for synchronous lung and breast cancer was feasible and safe. In metachronous cases, lung cancers tended to be detected within 3 years after surgery for breast cancer. Careful follow-up for postoperative breast cancer may contribute to the detection of early-stage lung cancer.*

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Lung cancer is the leading cause of cancer death in both Japan and worldwide (1). In 2009 in Japan 103 715 patients had tracheal, bronchial, and lung cancers (2); 31,993 of these patients (30.8%) were female. In the same period, 61,232 Japanese female patients had breast cancer (2). Advances in early detection of cancer and cancer treatment have led to decreased mortality and increased numbers of cancer survivors. As a result, increased numbers of female patients with both lung cancer and breast cancer may be expected in the future. In fact, women with breast cancer are at increased risk of subsequent primary malignancies, specifically lung cancer (3-5). However, little is known about the clinical characteristics or surgical outcomes of patients with both lung cancer and breast cancer. Therefore, the aim of this study was to report the frequency of synchronous and metachronous lung cancer in patients with breast cancer and discuss the clinicopathological features and surgical outcomes of patients with both lung cancer and breast cancer.

Materials and Methods

Patients. Written informed consent to access medical records was obtained from each patient, and the institutional review board of our hospital gave approval for this study. A chart review revealed 1066 consecutive breast cancer patients who underwent surgical resection at Kyushu University Hospital from January 2005 to December 2016. During this period, 1619 consecutive patients underwent surgical treatment for lung cancer, and 666 patients (41.1%) were female. Data collected included clinical characteristics, dates of breast cancer and lung cancer diagnosis, cancer stage, pathological type, breast cancer and lung cancer treatments, survival outcome, recurrence, and prognosis. Pathological staging was undertaken according to the 7th edition of the Tumor-Node-Metastasis (TNM) Classification of Malignant Tumors (6). Pathological TNM staging of breast cancer was also evaluated according to the International Union Against Cancer (UICC) classification system (7). Follow-up examination was performed from 0-135 months (median=39.5

months) following surgery. Blood tests, including tumor markers and chest X-ray, were evaluate at 3- or 4-month intervals during the first year and at 6-month intervals thereafter. Postoperative follow-up also consisted of chest computed tomography (CT), abdominal CT, bone scintigraphy, brain magnetic resonance imaging, and positron emission tomography at 6-month intervals during the first year and yearly thereafter. Multiple primary malignancies defined as separate cancers present a definite picture of malignancy when the possibility of one being a metastasis or recurrence is excluded (8). Based on the timing of diagnosis of a separate malignancy, multiple primary malignancies are classed as synchronous or metachronous malignancies. As described by Moertel *et al*., synchronous malignancies are those that occur within 6 months of the diagnosis of a previous type of cancer. In contrast, metachronous malignancies are those that occur more than 6 months later (9). In the current study, preoperative thin-section CT scan findings including tumor size and radiological features were reviewed by two authors (YK and FS), as previously described (10). Briefly, radiological features were visually classified into three subgroups: pure-ground glass opacity (GGO), part-solid, and pure-solid.

Table I. *Patients' characteristics*.

Variables	Number of patients
Total assessable patients	14
Age, years	
Mean, range	65, 45-81
Smoking history	
Never	11
Current/former	3
Histological type of breast cancer	
Invasive ductal carcinoma	11
Ductal carcinoma in situ	3
Pathological stage of breast cancer (Tumor-Node-Metastasis stage)	
T1N0M0	7
T2N0M0	1
T1N1M0	1
T2N1M0	4
T1N3M0	1

Results

Frequency of lung cancer in patients with breast cancer. Lung cancer with breast cancer was observed in 14 patients (1.3% of breast cancer and 2.1% of female lung cancer cases) (Table I). Patients were aged 45-81 years (mean age=65 years), three patients were smokers, and the average Brinkman index was 1,307 (range=300-3,000). Seven patients had T1N0M0 breast cancer, one had T1N1M0, one had T2N0M0, four had T2N1M0, and one had T1N3M0. Eleven patients had invasive ductal carcinomas and three patients had ductal carcinoma *in situ*. All lung cancers were discovered by screening CT. Fifteen lung cancer lesions in 13 patients were diagnosed as lung adenocarcinoma and one as lung squamous cell carcinoma. TNM classifications of the lung cancers (7th edition) were as follows: TisN0M0 in one patient, T1aN0M0 in 11, T1bN0M0 in one, and T3N0M0 in one. The median follow-up was 15 months (range=1-88 months), and four patients had postoperative recurrence of breast cancers; however, all patients were still alive at the most recent follow-up, at the time of this report.

Distribution of patients based on breast cancer and lung cancer detection. Six patients (42.9%) had synchronous breast cancer and lung cancer, and breast cancer and lung cancer were metachronously detected in eight patients (57.1%).

CT imaging and pathological features in lung cancer patients. Pulmonary tumor size and radiological features on CT and the pathological features of lung cancers are shown in Table II. A total of 16 lesions were recognized in 14 patients, with an average tumor size of 14.8 mm (range=4-28 mm). Radiological features included seven (43.75%) pure-GGO lesions, five part-solid (31.25%) lesions, and four pure-solid (25.0%) lesions. Fifteen lesions were adenocarcinomas and one lesion was squamous cell carcinoma. Among the adenocarcinoma lesions, 10 were papillary predominant, three were lepidic predominant, one was acinar predominant, and one was colloid predominant.

Patients with synchronous breast cancer and lung cancer. Table III shows the characteristics and treatment of the six patients with synchronous breast cancer and lung cancer. Five patients had stage IA non-small cell lung cancer (NSCLC) (T1aN0M0 in four patients and T1bN0M0 in one). The remaining patient had stage IIB NSCLC (T3N0M0). Pathological examination revealed adenocarcinoma in five patients and squamous cell carcinoma in one patient. Four of these five patients were synchronously diagnosed with both breast cancer and lung cancer and underwent concurrent surgery for both cancers. Breast cancer operations consisted of three mastectomy with axillary lymph node dissection and three partial breast resection (one with axillary lymph node dissection). Pulmonary resections comprised of lobectomy in all six patients. Lobectomy consisted of two right upper lobectomies (one combined with wedge resection of the right lower lobe), one right middle lobectomy, two right lower lobectomies, and one left lower lobectomy. There were no serious perioperative events, and all patients were discharged.

Patients with metachronous breast cancer and lung cancer. As shown in Table IV, all eight patients had stage IA NSCLC (T1aN0M0 in seven patients and T1bN0M0 in one); and all had adenocarcinoma. The time from breast cancer surgery to diagnosis of lung cancer ranged from 11-

Table II. *Computed tomographic imaging findings and pathological features of the lung cancers.*

Patient	Detection period	CT findings		Pathological feature	
		Size (mm)	Radiological features	Pathological type	Predominant type
1	Synchronous	22	Part-solid	Ad	Papillary
2	Synchronous	23	Pure-solid	Ad	Acinar
3	Synchronous	14	Part-solid	Ad	Papillary
4	Synchronous	15	Part-solid	Sq	-
5	Synchronous	19	Pure-solid	Ad	Lepidic
		4	Pure-GGO	Ad	Papillary
6	Synchronous	17	Pure-GGO	Ad	Papillary
		6	Pure-GGO	Ad	Lepidic
7	Metachronous	6	Pure-GGO	Ad	Papillary
8	Metachronous	28	Pure-GGO	Ad	Papillary
9	Metachronous	19	Pure-GGO	Ad	Papillary
10	Metachronous	14	Pure-GGO	Ad	Lepidic
11	Metachronous	10	Pure-solid	Ad	Colloid
12	Metachronous	11	Pure-solid	Ad	Papillary
13	Metachronous	12	Part-solid	Ad	Papillary
14	Metachronous	17	Part-solid	Ad	Papillary

Ad: Adenocarcinoma; CT: computed tomography; GGO: ground glass opacity; Sq: squamous cell carcinoma.

Table III. *Patients with lung cancer and synchronously-detected breast cancer.*

Patient characteristics

Patient	Age (years)	Smoking history	Breast cancer stage, pathological type	Lung cancer stage, pathological type	Interval* (months)
1	65	No	T2N1M0 Invasive	T3N0M0 Ad	0
2	81	No	T1N0M0 DCIS	T1bN0M0 Ad	0
3	66	No	T2N1M0 Invasive	T1aN0M0 Ad	0
4	72	Yes	T2N0M0 Invasive	T1aN0M0 Ad	0
5	51	Yes	T1N1M0 Invasive	T1aN0M0/TisN0M0 Ad/AIS	0
6	54	No	T1N0M0 DCIS	T1aN0M0 Ad	3

Treatment and outcome

Patient	Concomitant surgery	BC surgery	LC surgery	BC/LC recurrence	OS (mo)	Prognosis
1	Yes	Bp+Ax	RML	No/Yes	48	Alive
2	Yes	Bp	RLL	No/No	13	Alive
3	Yes	Bt+Ax	RUL	No/No	19	Alive
4	Yes	Bt+Ax	LLL	No/No	14	Alive
5	Yes	Bt+Ax	RUL+wedge resection	No/No	9	Alive
6	No	Bp	RLL	No/No	13	Alive

*Interval between detection of breast cancer and lung cancer. Ad: Adenocarcinoma; AIS: adenocarcinoma in situ; Ax: axillary lymph node dissection; BC: breast cancer; BI: Brinkman index; Bp: partial mastectomy; Bt: total mastectomy; DCIS: ductal carcinoma in situ; Invasive: invasive ductal carcinoma; LC: lung cancer; LLL: left lower lobectomy; OS (mo): overall survival (months); RLL: right lower lobectomy; RML: right middle lobectomy; RUL: right upper lobectomy.

Table IV. *Patients with metachronous lung cancer after treatment for breast cancer.*

Patients' characteristics

Patient	Age (years), smoking history	BC stage, pathological type	Adjuvant therapy treatment	BC recurrence, pathological type	LC stage, (months)	Interval*
7	55	T2N1M0	CTx	No	T1aN0M0	119
	No	Invasive		-	Ad	
8	74	T1N0M0	HTx	Yes	T1bN0M0	34
	No	Invasive		HTx	Ad	
9	77	T1N0M0	HTx	Yes	T1aN0M0	72
	No	Invasive		HTx	Ad	
10	69	T1N3M0	Anti-HER2	Yes	T1aN0M0	105
	Yes	Invasive			CTx	Ad
11	77	T1N0M0	RTx, HTx	No	T1aN0M0	13
	No	Invasive		-	Ad	
12	76	T1N0M0	RTx	No	T1aN0M0	17
	No	DCIS		-	Ad	
13	52	T1N0M0	HTx	No	T1aN0M0	11
	No	Invasive		-	Ad	
14	80	T2N1M0	CTx, RTx,	Yes	T1aN0M0	32
	No	Invasive	Anti-HER2	Anti-HER2	Ad	

Treatment and outcome

Patient	BC surgery	LC surgery	LC recurrence	BC OS (mo)	LC OS (mo)	Prognosis
7	Bt+Ax	RLL	No	135	14	Alive
8	Bt+Ax	Rt. basal seg	No	123	89	Alive
9	Bt+Ax	Lt. upper seg	No	123	50	Alive
10	Bt+Ax	RUL	No	107	1	Alive
11	Bp	Wedge resection	No	54	41	Alive
12	Bt	LUL	No	49	32	Alive
13	Bp	LLL	No	42	30	Alive
14	Bt+Ax	RML	No	39	7	Alive

*Interval between detection of breast cancer and lung cancer. Ad: Adenocarcinoma; Ax: axillary lymph node dissection; BC: breast cancer; BI: Brinkman index; Bp: partial mastectomy; Bt: total mastectomy; CTx: chemotherapy; DCIS: ductal carcinoma in situ; HTx: hormonal therapy; Invasive: invasive ductal carcinoma; LC: lung cancer; LLL: left lower lobectomy; LUL: left upper lobectomy; OS (mo): overall survival (months); RLL: right lower lobectomy; RML: right middle lobectomy; RUL: right upper lobectomy; RTx: radiotherapy; Seg: segmentectomy.

119 months, with a mean of 33 months. All eight patients received adjuvant therapies including chemotherapy, radiotherapy, hormonal therapy, anti-HER2 therapy, or a combination of these modalities. Four of eight (50%) patients with breast cancer recurrence received chemotherapy, hormonal therapy, and anti-HER2 therapy. Surgery comprised lobectomy in five patients, segmentectomy in two, and wedge resection in one. Lobectomy consisted of one right upper lobectomy, one right middle lobectomy, one right lower lobectomy, one left upper lobectomy, and one left lower lobectomy. One patient underwent segmentectomy of the left upper division and one received right basal segmentectomy; one patient underwent wedge resection. There were no serious events during patients' perioperative courses.

Discussion

In this study, we reported the frequency of synchronous and metachronous surgically-resected lung cancer and breast cancer (total, 14 patients; 1.3% with breast cancer and 2.1% with lung cancer).

In Europe, several large cancer registry-based studies have reported the risk of lung cancer in breast cancer patients (11-14); however, few similar studies have been conducted in Asia (3, 4). In particular, no study has reported both incidence and surgical outcome of second primary lung cancer in women with breast cancer. Therefore, we described a series of female patients with breast cancer undergoing surgical resection for synchronous or metachronous lung cancer in a single institution. Evans *et al*. (11) summarized five cancer

registry-reported studies of female breast cancer patients and showed an increased risk for lung cancer after breast cancer (relative risk, 1.4-1.7), although the reasons for the association are unknown. In contrast, Kwast *et al*. (14) suggested that chemotherapy for breast cancer was associated with a decreased risk of second primary cancers including lung cancer, although radiotherapy and endocrine therapy were not associated with a decreased risk. Also, some studies suggest that radiotherapy for breast cancer is a risk factor for developing a second primary lung cancer (15, 16). In our series, all eight (100%) metachronous patients received adjuvant therapies including chemotherapy, radiotherapy, hormonal therapy, anti-HER2 therapy, or a combination of these modalities. In addition, 4/8 (50%) metachronous patients with postoperative recurrence of breast cancer in our study received chemotherapy, hormonal therapy, or anti-HER2 therapy. However, the sample size in our series was too small to detect differences between these therapies and the risk of lung cancer. According to the histological type, 16 lung cancer lesions in 14 patients (94.1%) were adenocarcinomas and one (5.9%) was squamous cell carcinoma, which is similar to a previous report stating that the most common pathological lung cancer subtype (27/38 patients) was adenocarcinoma in breast cancer patients (17).

In our five synchronous cases, all patients had both lung and breast cancers detected at the same time and underwent concurrent surgery for both cancers. Breast cancer surgery consisted of partial or total mastectomy with/without axillary lymph node dissection. Lung cancer surgery consisted of pulmonary lobectomy with lymph node dissection. There were no serious postoperative complications, and the perioperative course was uneventful in all patients undergoing concomitant surgery. Therefore, concomitant surgical resection of both lung cancer and breast cancer may be feasible and safe.

At the time of this report, as of the most recent follow-up, all 14 patients were alive. In our series, 4/14 (28.6%) patients had recurrent breast cancer and 1/14 (7.1%) patients had recurrent lung cancer. In synchronous cases, no patients had postoperative breast cancer recurrence, although 1/5 (20%) patients had postoperative recurrence of lung cancer. In metachronous cases, 4/8 (50%) patients had postoperative breast cancer, although none had postoperative recurrence of lung cancer. Kim *et al*. (4) studied metachronous primary cancers after treatment for breast cancer, and reported that lung cancer was the fifth leading second primary organ cancer detected with breast cancer (0.19%, 5/2657). The study also showed that the mean time to diagnosis of a second primary lung cancer was 89.1±45.9 months. Four of five second primary lung cancer patients were diagnosed 5 years after diagnosis of breast cancer. However, the 5-year survival rate after diagnosis of the second primary lung cancer was 22.2%, although the lung cancer stages were not shown. In a review of lung cancer risk and time elapsed since breast cancer treatment (15), several lung cancers were coincidentally found within 5 years from breast cancer treatment, with many studies showing that the risk of lung cancer after breast cancer treatment increases with time. In the present study, all metachronous lung cancers tended to be detected within 3 years after surgery for breast cancer, and the pathological stage for all lung cancer was early. The reason for the early detection may be the result of routine CT screening after surgery for breast cancer. As a result, careful follow-up for postoperative breast cancer may contribute to the early detection of lung cancer.

Finally, based on the imaging features of preoperative CT, we presented the radiological features of lung cancer in breast cancer. It is important to distinguish primary lung cancer and metastatic lung tumor from breast cancer. It is well known that pure-GGO pathological findings highly suggest that the tumor is primary lung cancer. A previous study demonstrated that no metastatic lung tumor from breast cancer was identified as pure-GGO (18). Our series showed that pure-GGO was seen in approximately 44% of primary lung cancer cases with the remaining 56% of lung cancers classed as part- or pure-solid, similar to a previous study showing that most primary lung cancers demonstrated part- or pure-solid features (18). Therefore, it may be difficult to diagnose exactly whether a tumor is primary or metastatic lung cancer based solely on preoperative CT imaging features. Some investigations of mammary carcinogenesis or metastasis using animal models have been demonstrated (19, 20). In addition, several studies that genotype/phenotype can be used for novel diagnostic markers have been reported, which may provide the best strategies and targets in early detection and prediction the susceptibility and outcomes in breast cancer patients (21-24). Thus, further basic researches are also necessary.

In conclusion, we report a series of patients with synchronous or metachronous lung cancer and breast cancer in a single institution. Concomitant surgery for synchronous lung and breast cancer was safe. In metachronous cases, lung cancer tended to be detected within 3 years after surgery for breast cancer, and the pathological stage of all lung cancers was early. Careful follow-up for postoperative breast cancer may contribute to the detection of early-stage lung cancer.

Conflicts of Interest

All Authors disclose no financial and personal relationships with other people or organizations that could have inappropriately influenced our work.

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