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ORIGINAL ARTICLE

Prognosis associated with synchronous or metachronous multiple primary malignancies in patients with completely resected non-small cell lung cancer

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Abstract

Purpose To investigate the influence of multiple primary malignancies (MPMs) on the prognosis of patients with completely resected non-small cell lung cancer (NSCLC).

Methods The subjects of this retrospective study were 521 patients who underwent complete curative pulmonary resection for NSCLC. Patients were divided into two groups: those with and those without MPMs.

Results The 521 NSCLC patients included 184 patients (35.3%) with MPMs and 337 patients without MPMs. The overall 5-year survival rates for patients with vs those without MPMs were 66.1 and 75.6%, respectively ($p=0.0061$). According to multivariate analysis, MPMs, age, gender, pathological stage, and interstitial pneumonia were independent predictors of prognosis. The 47 patients with synchronous MPMs and the 82 patients with metachronous MPMs found within the last 5 years had significantly poorer prognoses than patients without MPMs ($p=0.0048$ and $p=0.0051$, respectively). However, the prognoses of the 55 patients with metachronous MPMs that had been present for over 5 years did not differ from those of the patients without MPMs.

Conclusions NSCLC patients with synchronous MPMs or metachronous MPMs diagnosed within the last 5 years had poor prognoses. Decisions about the best therapeutic strategies require comprehensive consideration of the organ location, malignant potential, recurrence, and prognosis of the MPMs. In contrast, decisions about the best therapeutic strategies for NSCLC patients with metachronous MPMs present for over 5 years should be based solely on the NSCLC.

Keywords Non-small cell lung cancer · Surgery · Multiple primary malignancies

Introduction

Multiple primary malignancies (MPMs) are defined by the presence of two or more independent primary malignancies in the same or different organs in a patient [1]. In a literature review of 1,104,269 cancer patients, the prevalence of MPMs ranged from 0.73 to 11.7%, with an increased incidence in recent years [2]. Improvements in diagnostic tools and treatment modalities, including molecularly targeted therapy, have prolonged the survival of cancer patients; hence, more multiple primary cancers are being detected [3].

Primary lung cancer is often detected on chest computed tomography (CT) or fluorodeoxyglucose-positron emission tomography (FDG-PET) before and after treatment for MPMs in either the same or different organs. When we consider the surgical strategy for lung cancer patients who have synchronous or metachronous MPMs in either the same or different organs, the prognosis associated with the MPMs should be noted. The aim of this study was to investigate the influence of MPMs on the prognosis of patients with completely resected non-small cell lung cancer (NSCLC).

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Methods

We analyzed, retrospectively, 521 NSCLC patients (332 men and 189 women; median age, 68 years) who underwent complete curative pulmonary resection at Osaka City University Hospital between January, 2008 and December, 2014. To evaluate the prognosis of completely resected NSCLC, patients who underwent wedge resection and those without hilar lymph node dissection were excluded from the analysis. Informed consent to use data from their examinations and clinical courses for this clinical study was obtained from all patients preoperatively. The local institutional ethics committee approved this study.

Preoperative chest and abdominal CT, brain magnetic resonance imaging (MRI), and FDG-PET were performed to look for distant metastases. The pathological diagnosis of lung cancer was made by at least two pathologists at our hospital according to the criteria of the World Health Organization, and stages were classified according to the 7th edition of the International Union Against Cancer (UICC) TNM classification of lung cancer. MPMs were defined as two or more tumors detected at different locations, which were histologically malignant with confirmation that one tumor was not a metastasis of the other, according to Warren and Gate's criteria [4]. Synchronous MPMs were defined as those occurring simultaneously or within 6 months of each other, whereas metachronous MPMs were defined as those occurring more than 6 months apart, according to Moertel's criteria [5]. Patients were divided into a group with MPMs in either the same or different organs, and a group without MPMs at the time of lung cancer diagnosis. We investigated the clinical characteristics and surgical outcomes of all patients in detail and then analyzed the differences between each group statistically. The significance of the associations between patient characteristics and the presence of MPMs was evaluated using Fisher's exact and Chi square tests. Survival curves were calculated from the day of lung cancer surgery to death or final follow-up, using the Kaplan–Meier method, and differences in survival curves were assessed with the log-rank test. Multivariate analyses were calculated according to the Cox regression model to look for associations between patient characteristics and postoperative overall survival. Patient characteristics with a p value of <0.1 in the univariate analysis were entered into the multivariate Cox regression model. p values <0.05 were considered significant. All statistical analyses were performed using JMP, version 9 (SAS Institute, Cary, NC, USA).

Results

The 521 NSCLC patients included 184 (35.3%) with MPMs and 337 (64.7%) without MPMs. The median follow-up period was 44.5 months. Table 1 summarizes the patients' clinical characteristics according to the presence of MPMs. The patients with MPMs (median age 70 years) were significantly older than those without MPMs (median age 67 years; $p=0.0090$; Mann–Whitney U test). The patients with MPMs underwent more segmentectomies and had fewer mediastinal lymph node dissections than those without MPMs ($p=0.0299$, $p=0.0165$, respectively). There were no significant differences in gender, smoking history, performance status (PS), Hugh–Jones (H–J) classification, interstitial pneumonia (IP), tumor side, tumor location, histology of the resected tumor, or pathological stage between the patients with and those without MPMs.

The overall 5-year survival rates for the NSCLC patients with vs those without MPM were 66.1% and 75.6%, respectively ($p=0.0061$; Fig. 1). According to univariate survival analysis, age (≥ 68), gender (male), smoking, PS, IP, mediastinal lymph node dissection, histology, and pathological stage were also significant predictors of poor prognosis (Table 2). There were no significances between the groups in H–J classification, surgical procedure, tumor side, or location. Multivariate analysis results revealed that the presence of MPMs, age, gender, pathological stage, and IP were independent predictors of prognosis for patients with completely resected NSCLC (Table 2). Multivariate analysis of only patients with MPMs revealed that age (≥ 68) and IP were independent predictors of poor prognosis ($p=0.0076$, $p=0,0050$, respectively).

Table 3 shows the organ locations of the MPMs and surgical outcomes of the MPM patients by organ compared with those of patients without MPMs. Regarding organ location, malignancies of the upper digestive tract, laryngopharynx, hepatobiliary-pancreas, and urological system were significant predictors of poor prognosis. Among 17 patients with multiple lung cancers, 5 had different histological types. The other 12 patients had two adenocarcinomas with different predominant components, such as micropapillary and lepidic components, respectively.

Among the 184 NSCLC patients with MPMs, 47 had synchronous MPMs, and 137 had metachronous MPMs. The patients with synchronous MPM had significantly poorer prognoses than the NSCLC patients without MPM (5-year survival rate 56.6%, $p=0.0048$; Fig. 2). Among the 137 NSCLC patients with metachronous MPMs, 82 had metachronous MPMs diagnosed within the last 5 years, and their prognosis was significantly poorer than that of patients without MPMs (5-year survival rate 64.3%; $p=0.0051$; Fig. 3). The prognosis of the other 55 patients

Table 1 Clinical characteristics of patients with non-small cell lung cancer according to the presence of multiple primary malignancies

Characteristics	All	MPMs		*p* value
		Yes	No	
Age (years)				
Median (range)	68 (20–90)	70 (41, 85)	67 (20, 90)	0.0090
Gender				
Male	332	120	212	0.5998
Female	189	64	125	
Smoking history				
Yes	377	141	236	0.1044
No	144	43	101	
PS				
0	463	158	305	0.1131
1–2	58	26	32	
H–J classification				
1	438	149	289	0.1585
2–3	83	35	48	
IP				
Yes	46	17	29	0.8080
No	475	167	308	
Tumor side				
Right	322	108	214	0.2815
Left	199	76	123	
Tumor location				
Upper/middle	334	116	218	0.7086
Lower	187	68	119	
Surgical procedure				
Lobectomy/pneumonectomy	480	163	317	0.0299
Segmentectomy	41	21	20	
MLND				
Yes	428	141	287	0.0165
No	93	43	50	
Histology				
Adenocarcinoma	372	128	244	0.7197
Squamous cell carcinoma	128	49	79	
Others	21	7	14	
Pathological stage				
1	345	131	214	0.1864
2	107	31	76	
3	69	22	47	

NSCLC non-small cell lung cancer, *MPMs* multiple primary malignancies, *PS* performance status, *H–J classification* Hugh–Jones classification, *IP* interstitial pneumonia, *MLND* mediastinal lymph node dissection

with metachronous MPMs that had been present for more than 5 years did not differ from that of the NSCLC patients without MPMs (5-year survival rate 77.0%; $p = 0.9523$; Fig. 3). The prognosis of patients with metachronous MPMs diagnosed within the last 5 years tended to be poorer than that of patients with metachronous MPMs present for more than 5 years, but the difference was not significant ($p = 0.0877$).

Regarding the number of MPMs, 145 patients had double primary malignancies (including NSCLC), 33 had triple primary malignancies, and six had quadruple primary malignancies. There were no significant differences among the prognoses of these three groups. Regarding the pathological stage of MPMs, 96 MPMs were stage 1, 46 were stage 2, 31 were stage 3, 13 were stage 4, and 43 were unknown or not applicable. There were no significant

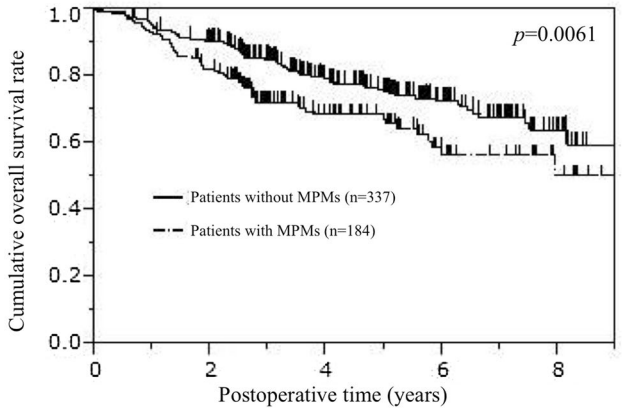

Fig. 1 Kaplan–Meier curves for the postoperative overall survival of 184 non-small cell lung cancer (NSCLC) patients with multiple primary malignancies (MPMs) and 337 NSCLC patients without MPMs. The prognoses of the patients with MPMs were significantly poorer than those of the patients without MPMs ($p=0.0061$)

differences among the prognoses of these four pathological stage groups.

Regarding therapeutic modalities for the MPMs, 199 were treated with surgery and 30 were treated with chemotherapy ($n=11$), radiation therapy ($n=8$), or both ($n=11$). The prognosis of patients treated with chemotherapy or radiation therapy was significantly poorer than that of patients treated with surgery (5-year survival 38.7 vs 71.8%, respectively; $p=0.0007$; Table 4). Surgery was performed for 95.3% of the MPMs that had been present for more than 5 years and 87.3% of the MPMs diagnosed within the last 5 years ($p=0.0102$).

Significantly more of the MPM patients died of other cancers than did the NSCLC patients without MPMs ($p=0.0001$, Table 5). There were no significant differences in NSCLC-related deaths between the groups.

Table 2 Univariate and multivariate analyses of the prognosis of non-small cell lung cancer patients

Characteristics	Univariate			Multivariate		
	Hazard ratio	95% CI	*p* value	Hazard ratio	95% CI	*p* value
Age						
≥68 vs < 68	1.71	1.22, 2.42	0.0017	1.57	1.10, 2.25	0.0121
Gender						
Male vs female	4.31	2.75, 7.12	< 0.0001	4.64	2.60, 8.64	< 0.0001
Smoking						
Yes vs no	2.43	1.58, 3.93	< 0.0001	1.58	0.86, 2.78	0.1355
PS						
0 vs 1–2	1.93	1.19, 2.97	0.0042	1.56	0.86, 2.74	0.1370
H–J classification						
1 vs 2–3	1.46	0.94, 2.19	0.0742	1.09	0.64, 1.80	0.7336
IP						
Yes vs no	3.98	2.61, 5.89	< 0.0001	2.90	1.84, 4.46	< 0.0001
Surgical procedure						
Lobectomy/pneumonectomy vs segmentectomy	1.57	0.88, 2.59	0.0978	1.44	0.76, 2.62	0.2499
MLND						
Yes vs no	1.80	1.23, 2.58	0.0015	1.49	0.96, 2.26	0.0730
Histology						
Adenocarcinoma vs others	2.23	1.59, 3.11	< 0.0001	1.14	0.78, 1.67	0.4929
Pathological stage						
1 vs 2–3	2.13	1.53, 2.96	< 0.0001	1.88	1.32, 2.67	0.0004
MPMs						
Yes vs no	1.59	1.13, 2.22	0.0061	1.41	1.00, 1.99	0.0475

NSCLC non-small cell lung cancer, *MPMs* multiple primary malignancies, *PS* performance status, *H–J classification* Hugh–Jones classification, *IP* interstitial pneumonia, *MLND* mediastinal lymph node dissection

Table 3 Organ location of multiple primary malignancies and surgical outcomes of the non-small cell lung cancer patients by organ compared with those of non-small cell lung cancer patients without multiple primary malignancies

Organ location of MPMs	Number of patients	5-year survival rate (%)	*p* value
Upper digestive tract	56	65.2	0.0032
Esophagus	27		
Stomach	33		
Colorectum	33	84.5	0.7642
Colon	22		
Rectum	11		
Laryngopharynx	19	47.3	0.0056
Tongue	2		
Pharynx	7		
Larynx	10		
Hepatobiliary-pancreas	9	14.8	< 0.0001
Liver	4		
Bile duct	3		
Pancreas	2		
Breast	23	91.3	0.4105
Urological system	34	53.0	0.0103
Kidney	6		
Urinary tract	2		
Bladder	13		
Prostate	15		
Gynecologic system	15	73.3	0.5477
Uterus	13		
Ovary	2		
Lung	17	66.5	0.5220
Others	15	72.2	0.8787

NSCLC non-small cell lung cancer, *MPMs* multiple primary malignancies

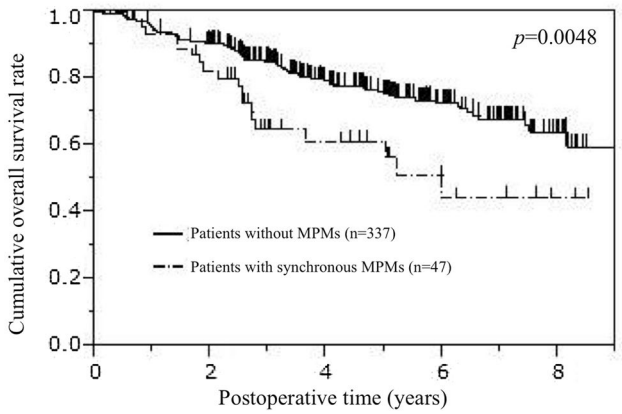

Fig. 2 Kaplan–Meier curves for the postoperative overall survival of 47 non-small cell lung cancer (NSCLC) patients with synchronous multiple primary malignancies (MPMs) and 337 NSCLC patients without MPMs. The prognoses of the patients with synchronous MPMs were significantly poorer than those of the patients without MPMs ($p=0.0048$)

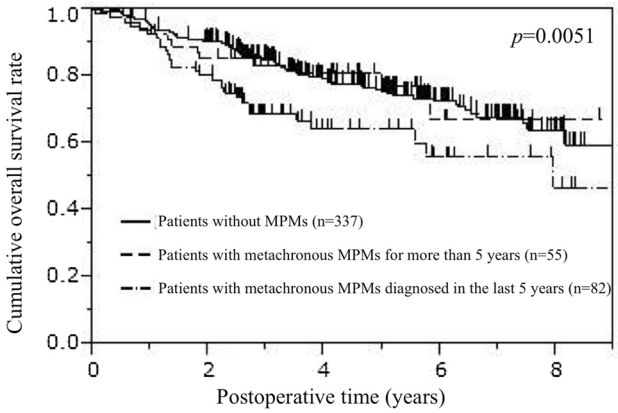

Fig. 3 Kaplan–Meier curves for the postoperative overall survival of 82 non-small cell lung cancer (NSCLC) patients with metachronous multiple primary malignancies (MPMs) found within the last 5 years, 55 NSCLC patients with metachronous MPMs present for more than 5 years, and 337 NSCLC patients without MPMs. The prognoses of the patients with metachronous MPMs found within the last 5 years were significantly poorer than those of the patients without MPMs ($p=0.0051$). The prognoses of patients with metachronous MPMs present for more than 5 years after did not differ from those of the patients without MPMs ($p=0.9523$)

Table 4 The prognosis of non-small cell lung cancer patients with multiple primary malignancies according to therapeutic modality

Therapeutic modality	Number of patients	5-year survival rate (%)	*p* value
Surgery	199	71.8	0.0007
Chemotherapy or radiation	30	38.7	
Chemotherapy	11		
Radiation	8		
Chemotherapy and radiation	11		

NSCLC non-small cell lung cancer, *MPMs* multiple primary malignancies

Table 5 The causes of death of non-small cell lung cancer patients according to the coexistence of multiple primary malignancies

	MPMs		*p* value
	Yes	No	
Died/surviving	60/124	82/255	
Cause of death			
NSCLC	28 (46.7%)	44 (53.7%)	0.4102
Other cancers	20 (33.3%)	4 (4.9%)	< 0.0001

NSCLC non-small cell lung cancer, *MPMs* multiple primary malignancies

Discussion

The incidence of MPMs has increased because cancer patients are now surviving long enough for subsequent primary malignancies to be found [2, 3]. There have been several reports on MPMs involving lung cancer [3, 6–9]. In this study, 184 (35.3%) of 521 NSCLC patients had MPMs, which is a higher MPM prevalence than the 3.4–22.3% reported in previous studies [3, 6–9], and was unique to our institution. One reason for this was that this study was performed very recently, and therefore more patients who survived an initial malignancy had the opportunity for subsequent primary malignancies to develop. Another reason was that many patients were referred to our department from other departments in our hospital during the follow-up period for other malignancies. Moreover, treatments for other malignancies, including chemotherapy and radiation therapy, are associated with an increased risk of subsequent lung cancer [10, 11].

The most frequent accompanying malignancy was cancer of the upper digestive tract, followed by urological malignancies and colorectal cancers, which is consistent with previous studies [3, 6–9]. Upper aerodigestive tract cancers have been found to frequently accompany lung cancer because of the same carcinogenic origins, such as smoking [12, 13]. Head and neck (laryngopharynx) squamous cell carcinoma is also a smoking-associated cancer. Schwartz et al. reported the high probability of diagnosing a synchronous or metachronous second primary lung cancer in patients with head and neck squamous cell carcinoma and the poor prognosis of those patients [14]. Thus, smoking plays an important role in MPMs. In fact, 141 (76.6%) of the 184 NSCLC patients with MPMs in our study had a smoking history.

Our data demonstrated that NSCLC patients with synchronous or metachronous MPMs diagnosed within the last 5 years had significantly poorer prognoses than NSCLC patients without MPMs. The poor prognosis of patients with synchronous MPMs in this study was consistent with previous studies [3, 8]. However, lung cancer patients with metachronous MPMs have been reported to have better survival rates than the general cancer population [15–17]. This may be because of early detection of the second primary cancer at a curable stage with intensive examination and follow-up for the first primary cancer. In fact, some studies found that lung cancer patients with metachronous MPMs were more likely to be diagnosed with early-stage disease than those without metachronous MPMs [7, 9, 17]. There have also been reports that lung cancer survival is associated more strongly with the lung cancer stage than with metachronous MPMs [7, 18, 19], although Kurishima et al. reported that metachronous MPMs were independent prognostic factors for survival of NSCLC patients [20]. Thus, the influence of metachronous MPMs on prognosis varies from study to study because of differences in the sample size and source. The poor prognosis of NSCLC patients with metachronous MPMs in this study can be explained as follows. First, this study consisted of only NSCLC patients who underwent complete resection, whereas most previous reports included patients with inoperable disease treated with chemotherapy or radiotherapy. This selection bias resulted in significantly more deaths of the patients with MPMs from their other cancers than of the patients without MPMs, which would account for the poor prognosis of patients with metachronous MPMs. Second, the pathological stages of lung cancer did not differ between the patients with and those without MPMs, as expected. This might be because of the selection bias mentioned above, which would decrease the merit of the metachronous MPMs being a second primary lung cancer detected at a nearly curable stage. Finally, in this study, MPMs were defined at the time of diagnosis of lung cancer, as our goal was to evaluate the influence of MPMs on prognosis to help us decide on the best therapeutic strategies for NSCLC patients. Therefore, patients who had lung cancer as the first detected lesion and were then found to have a second malignancy more than 6 months later, who are known to have better prognoses [6, 7], were defined as patients without a MPM in this study. This led to the better prognoses of patients without MPM. Despite the poor prognosis of NSCLC patients with metachronous MPMs found within the last 5 years, the prognosis of NSCLC patients with metachronous MPMs present for more than 5 years did not differ from that of NSCLC patients without MPMs. Patients with metachronous MPMs for more than 5 years underwent more surgery than patients with metachronous MPMs found within the last 5 years, and the first malignancy might be cured or well controlled by surgery, which could account for the better prognosis of patients with metachronous MPMs for more than 5 years. These results suggest that the surgical assessment of NSCLC patients with metachronous MPMs diagnosed within the last 5 years requires careful attention to the recurrence and prognosis of the MPMs. This is the first report to focus on the prognosis of NSCLC patients with metachronous MPMs, which analyzed two MPM groups: metachronous MPMs found within the last 5 years and MPM present for more than 5 years between diagnoses. Metachronous second primary lung cancer diagnosed more than 5 years after head and neck squamous cell carcinoma has been reported to be associated with better prognosis [21]. Our data confirmed this result in our NSCLC patients with a variety of metachronous MPMs present for more than 5 years between diagnoses.

The prognoses did not differ according to each pathological stage of the MPMs. This is because the malignant potential varies even in the same pathological stages of different organ malignancies. Thus, we evaluated the malignant potential of coexisting MPMs according to the organ origin. There have been few reports focusing on prognosis according to the organ location of MPMs accompanying lung cancer; however, head and neck cancer is reported to be associated with poor prognosis for patients with metachronous MPMs [3, 14]. In this study, the NSCLC patients with malignancies of the upper digestive tract, laryngopharynx, hepatobiliary–pancreas, and urological system had poor prognoses, suggesting that the surgical indications for these patients should be considered more carefully. Age (≥ 68) and IP were also predictors of poor prognosis for patients with MPMs. Among 12 patients with MPMs who died of intercurrent diseases, 3 (25%) died of IP. The poor prognosis of lung cancer patients with interstitial lung disease is well documented [22], so we should consider not only MPMs, but also the coexistence of IP.

This was a single-institution retrospective study conducted in Japan and it had several limitations. First, there was no information about the pathological stage of 43 (18.8%) of the 229 MPMs. Second, the patients with MPMs had background factors other than the analyzed characteristics, such as the pathological types of the MPMs. Therefore, a larger prospective study spanning multiple institutions is needed to confirm the prognostic importance of MPMs in NSCLC patients.

In conclusion, NSCLC patients with synchronous or metachronous MPMs detected within the last 5 years had significantly poorer prognoses than NSCLC patients without MPMs. Deciding on the best therapeutic strategy for these patients requires comprehensive consideration of the organ location, malignant potential, recurrence, and prognosis of the MPMs, and also the coexistence of IP. In contrast, the prognosis of NSCLC patients with metachronous MPMs present for more than 5 years did not differ from that of NSCLC patients without MPMs, and their therapeutic strategy should be based on the NSCLC.

Compliance with ethical standards

Conflict of interest We have no conflicts of interest to declare.

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