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Analysis of bevacizumab treatments and metastatic sites of lung cancer

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ABSTRACT

Introduction: Liver metastasis has not been sufficiently evaluated in lung cancer so far. We retrospectively analyzed the distant metastasis of Non-squamous non-small cell lung cancer (NSQ-NSCLC), including liver metastasis, and association between prognosis and therapeutic effect of bevacizumab treatment.

Patients and Methods: Clinical data were collected from 1954 patients with lung cancer admitted in our hospital between 1st April 2011 and 31 March 2019. Information is extracted from the electronic medical record. Main collection data was the age, gender, smoking history, performance status, histology and driver mutation, distant metastasis site. Efficacy data of treatment including treatment duration and survival time were obtained from medical record, image data and local registry.

Results: Total 366 patients receiving any chemotherapy with NSQ-NSCLC were eligible for this study. Most frequent extrathoracic metastasis is bone ($N = 59$) followed by brain (37), liver (18), adrenal gland (23), and OS analysis showed liver metastasis was worse prognosis compared to brain and bone metastasis (median OS: 11.6, 18.9, 15.0, respectively). Bevacizumab treatment was tend to have favorable efficacy in patients with each metastatic sites, especially, induced significant longer OS for patients with liver metastasis.

Conclusion;: Though this study was retrospective study for small sized metastatic patients, the study suggested that liver metastasis was refractory, and that bevacizumab treatment might improve the worse prognosis.

Introduction

Lung cancer is one of the deadliest malignancies. Worldwide, approximately 18 million people develop lung cancer each year, and nearly 10 million die of the disease [1–4]. Although the recent development of molecular-targeted drugs and immune checkpoint inhibitors has extended the survival time of advanced lung cancer, its prognosis remains among the poorest of all cancers.

Lung cancer can be mainly divided into four categories based on the tissue type: adenocarcinoma, squamous cell carcinoma, large cell carcinoma and small cell carcinoma. Initially, maximizing clinical benefit was based only on separating patients with non-small cell lung cancer from those with small cell lung cancer. After the approval of pemetrexed and bevacizumab for NSQ-NSCLC, it became clear that further stratification of NSCLC patients into those with squamous cell carcinoma or non-squamous cell carcinoma consisting mainly of adenocarcinoma was required [5-8].

Many patients have stage IV lung cancer at diagnosis. In fact, according to the National Cancer Institute about 40 percent of patients diagnosed with NSCLC have stage IV disease [9]. Metastatic lung cancers fall into the stage IV category, and multiple organs may be affected. A previous study focusing on bone, brain, and liver metastases [10] defined metastatic factors (M factors), which can be divided into three categories according to the organ that is affected: M1a, intrathoracic metastasis including the ipsilateral lung and the pleura/pericardium with or without effusion; M1b, distant solitary metastasis outside the thorax; M1c, distant multiple metastases, which most often spread to the bones, brain and/or liver. These new groups were categorized according to the difference in survival time.

A recent clinical trial using immune checkpoint inhibitors, chemotherapy and bevacizumab (IMPOWER150) revealed that bevacizumab is effective in the liver metastasis subgroup [11]. Until now, analysis of metastases has mainly focused on brain metastasis, whereas liver metastasis has received little attention. To address this gap in knowledge, we performed a retrospective analysis of distant metastases in patients with NSQ-NSCLC, which also included an evaluation of

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prognosis and treatment efficacy.

Materials and methods

Patients

Clinical data were collected from 1954 consecutive patients with lung cancer who were admitted to our hospital between 1st April 2011 and 31st March 2019. Among them were 1069 patients with lung non-small, non-squamous cell carcinoma (NSQ-NSCLC). This diagnosis was based on 1) cytological examination with the presence of NSQ-NSCLC cells and exclusion of other carcinomas; 2) tumors being histologically diagnosed as primary NSQ-NSCLC of the lung through biopsy.

The present study was conducted based on the principles outlined in the Declaration of Helsinki. Ethical approval was obtained from the Iwate Medical University Ethics Committee (MH2019–134). Because written informed consent for the collection of clinical data from all patients could not be obtained, we selected opt-out recruitment methods in which potential participants were given the opportunity to decline participation in the study and presented information via our institute's homepage.

Data collection

Information was extracted from electronic medical records, and data collected included age, gender, smoking history, performance status and histology. From the medical records we obtained driver mutations including epidermal growth factor receptor (EGFR) mutation, anaplastic lymphoma kinase (ALK) fusion gene, expression rate of programmed death-ligand 1, distant metastasis site, and treatment efficacy (including response rate, treatment period, and survival time). Response rate, one of the indicators of efficacy, was determined by measuring the tumor diameter with contrast-enhanced CT and chest X-ray. We utilized survival data from the cancer registry of our hospital in addition to electronic medical record information.

Information regarding metastasis was retrieved from medical records. If the assessment of metastasis was ambiguous, CT and PET scan findings were reviewed and re-evaluated. We use FDG-PET scans routinely to detect metastases. Most patients received FDG-PET scans in this study. Bone scans were just performed, when patients have contraindication including severe diabetes. In retrospective studies, irregular intervals between tumor assessments in each case make it difficult to determine progression-free survival (PFS). Consequently, we evaluated duration of first-line treatment as a substitute for PFS. Generally, the treatment duration for patients with EGFR mutant tumors on EGFR-TKI therapy was significantly longer that of patients with EGFR wild type tumors on chemotherapy. Generally, overall survival is significantly affected by whether tumors harbored EGFR or ALK driver mutations, or neither. We excluded patients with tumors containing driver mutations from the evaluation of both treatment duration and OS.

Bevacizumab treatment

Bevacizumab treatment history was defined as chemotherapy containing bevacizumab in any line of treatment. The decision to use bevacizumab brezimen depended on the choice of the physician. The presence of pleural effusion and brain metastases with edema often influenced the decision. OS was evaluated in patients who received any lines of bevacizumab treatments and evaluation of treatment duration was limited to the first-line therapy. Cases with driver mutations (EGFR and ALK) were excluded from all evaluation due to longer survival. Given that bevacizumab treatment was more effective than chemotherapy alone in patients with metastases, we analyzed whether bevacizumab treatment might prolong OS and treatment duration in patients with pleural lesions, brain metastases, and liver metastases.

Statistical analysis

We compared patients with brain metastasis, liver metastasis and pleural effusion with and without bevacizumab. Survival curves were constructed by estimating the median OS using the Kaplan-Meier method. Statistical significance was defined as a p value less than 0.05. Hazard ratios were calculated using a stratified Cox proportional hazards regression model. All statistical analyses were performed with Easy R (EZR, Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, this is a modified version of R Commander designed to add statistical functions frequently used in biostatistics.

Results

Patient characteristics

Excluding patients with small cells, squamous cell carcinoma, and driver mutations, and patients who were untreated or did not experience recurrence after surgery and radiation therapy, a total of 207 patients were eligible in this study. (Supplementary figure. 1).

The baseline characteristics of all patients are shown in Table 1. Of the 207 patients who received treatment, 153 (73.9%) were male, and the median age was 69 (30–93). The main histologic type was adenocarcinoma (170, 82.1%); 7 (3.4%) patients had large cell carcinoma, and 26 (12.6%) patients had non-small cell carcinoma. The main characteristics were well balanced across the groups with or without bevacizumab treatment.

Table. 1
Patient Characteristics.

	All	BEV (+)	BEV (-)
	N = 207	41(19.8%)	166(80.2%)
Age			
Median(range)	69 (30–93)	69 (44–91)	68 (33–92)
Sex			
Male	153	30(73.2%)	123(74.1%)
Female	54	11(26.8%)	43(25.9%)
ECOG PS*			
0	78	13(31.7%)	65(39.2%)
1	56	13(31.7%)	43(25.9%)
2	56	13(31.7%)	43(25.9%)
3	14	1(2.4%)	13(7.8%)
4	3	1(2.4%)	2(1.2%)
Smoking status			
Current or former	173	33(80.5%)	140(84.3%)
Never	34	8(19.5%)	26(15.7%)
Histologic features			
Adeno	170	37(90.2%)	133(80.1%)
Adeno-squamous	2	0(0%)	2(1.2%)
Undetermined NSCLC	26	4(9.8%)	22(13.3%)
Large cell	7	0(0%)	7(4.2%)
Pleomorphic	2	0(0%)	2(1.2%)
PD-L1 tumor proportion score			
<1%	16	6(14.6%)	10(6.0%)
1−49%	13	5(12.2%)	8(4.8%)
≥50%	18	2(4.9%)	16(9.6%)
Not inspected	160	28(68.3%)	132(79.5%)
Staging¶			
I	11	0(0.0%)	11(6.6%)
II	4	1(2.4%)	3(1.8%)
III	40	13(31.7%)	27(16.3%)
IV	152	27(65.9%)	125(75.3%)
Post-operative recurrence¶	20	5(12.2%)	15(9.0%)

NSCLC: non-small cell lung cancer.
* ECOG: Eastern Cooperative Oncology Group Performance Status.
¶ In post-operative recurrence and staging, duplicated cases existed.

Frequency of metastasis at each metastatic site

We calculated the frequency of metastases at several sites in NSCLC patients at diagnosis. The most frequent extra-thoracic metastasis was to bone (59) followed by brain (37), the adrenal gland (23), and liver (18) (Table 2), whereas the main thoracic metastases were pleura including effusion and dissemination (96) and pulmonary metastasis (71). Metastasis to a single organ was prevalent in bone and brain metastasis, whereas three or more organs were frequently co-involved in cases with liver metastasis. This shows that lung cancer metastasizes to the liver during the advanced phase of metastasis.

Overall survival in patients based on the involved metastatic site

We categorized metastatic sites into a "pleural + pulmonary" metastasis group (equivalent to the M1a classification in RECIST), as well as 'bone', 'brain' and 'liver' metastasis groups. To avoid assigning the same case in multiple groups, both brain and liver metastasis observed concomitantly with bone metastasis were excluded from the bone metastasis group, and liver metastasis was excluded from cases in the brain metastasis group. Kaplan-Meier analysis showed pleural + pulmonary metastasis (M1a) was associated with better survival (median OS: 30.7 month), whereas liver metastasis was related to worse prognosis compared to brain and bone metastasis (median OS: 11.6, 18.9, 15.0, respectively). Our finding that patients in the pleural + pulmonary metastasis group had a better prognosis compared to distal (extra-thoracic) metastasis (M1b, M1c) is consistent with the RECIST classification. The frequency of NSQ-NSCLC patients with metastases detected solely in the liver was low, and we note that patients with liver metastasis generally have a poor prognosis in terms of survival. (Fig. 1)

Bevacizumab treatment in patients with pleural, brain, or liver metastasis

Bevacizumab is the most popular anti-angiogenic agent, and is particularly effective in pleural effusion and in brain metastasis with edema. Recently, the efficacy of bevacizumab in refractory liver metastasis has also been evaluated [11]. Given these observations, we evaluated retrospectively efficacy of bevacizumab in metastatic NSQ-NSCLC. Before evaluating pleural, brain, and liver metastases, we checked influence of bevacizumab on overall survival in total eligible patients, survival benefit of bevacizumab in entire patients was lower than in groups of these three metastasis (Supplementary Fig. 2). The reason is bevacizumab had low efficacy in bone metastases compared to pleural, brain, and liver metastasis (Supplementary Fig. 3). Comparing overall survival, it was known that second-line or more therapies can influence OS. Therefore, we reported the frequency of each second-line or more treatment regimen in Supplementary Table 1. Although immunotherapy was more common in the bevacizumab group and was suspected of being a confounding factor, the forest plots using multivariate analysis showed bevacizumab treatment had a significant effect on OS as well as immunotherapy, age, and performance status (Supplementary Table 1 and Fig. 4).

Pleural metastasis

Duration of first line treatment was compared in all pleural metastasis cases with the exception of pulmonary metastasis. In our retrospective study, treatment duration was considered a surrogate of PFS and we also excluded patients whose tumors harbored driver mutations. Treatment duration was evaluated between 17 patients treated with bevacizumab and 34 patients who did not receive the drug. Bevacizumab-containing regimens had a longer duration than those that did not include this treatment (10.5 vs 4.0 months, respectively;Fig. 2A). OS was evaluated in patients with pleural involvement without driver mutations; for this comparison we selected 18 patients treated with bevacizumab (one case received bevacizumab in the second-line) and 33 patients who did not receive the drug. Bevacizumab treatment yielded a longer median survival time when compared with non-bevacizumab patients (27.2 vs 16.1, respectively), although it was not statistically significant ($p = 0.09$) (Fig. 2B).

Brain metastasis

In patients with brain metastasis, we compared treatment duration in 5 patients treated with bevacizumab to that of 32 patients without bevacizumab, and found a significant difference (13.3 vs 3.1 months, respectively; $p < 0.05$ Fig. 3A). We also evaluated OS in patients with brain metastasis without driver mutations. There was no significant difference between 8 patients treated with bevacizumab and 29 patients who did not receive the drug (31.1 vs 17.0 months, respectively) (Fig. 3B).

Liver metastasis

As patients with liver metastasis present at the advanced stage of disease, about half of them are not fit enough to receive chemotherapy. Consequently we only had 18 patients available for analysis in this group. Out of four patients receiving bevacizumab treatment, only two of them received it as first-line therapy. We therefore concluded that analysis of treatment duration would not be meaningful, and performed an OS analysis only. The Kaplan-Meier curve revealed that 4 patients treated with bevacizumab had significantly longer OS than 14 patients who did not receive the drug (47.5 vs 9.5, respectively, $p < 0.05$; Fig. 4). Because there were very few patients with liver metastases received treatments with bevacizumab, individual cases were showed in Supplementary Table 2. All 4 cases responded good to bevacizumab treatment despite their advanced state.

Discussion

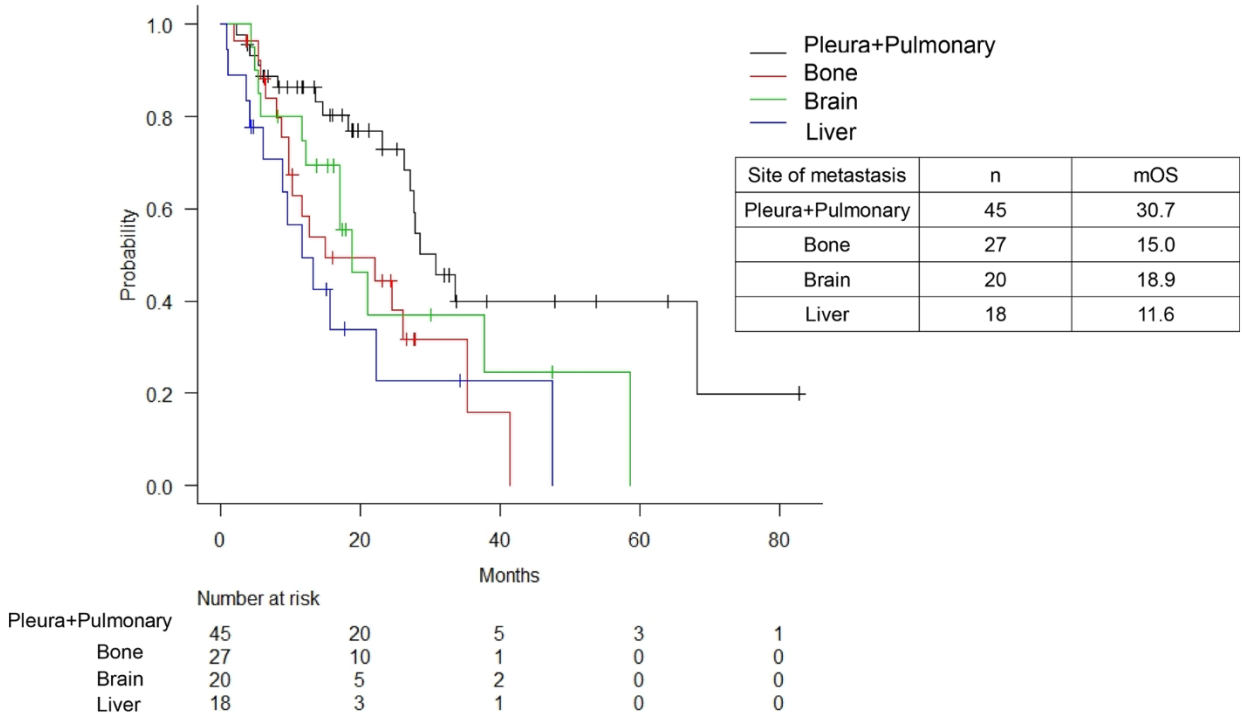
Herein, we have shown that patients with liver metastasis have shorter survival times compared to patients with pleural, bone or brain metastases. Although the number of cases available for analysis was relatively small, we suggest that bevacizumab treatment might improve the survival of patients with liver metastasis.

Several reports have investigated the frequency with which multiple organs are affected by metastasis in lung cancer. Riihimaki et al. reported the frequency of metastatic sites in 17,431 lung cancer patients

Table 2
The frequency of metastases.

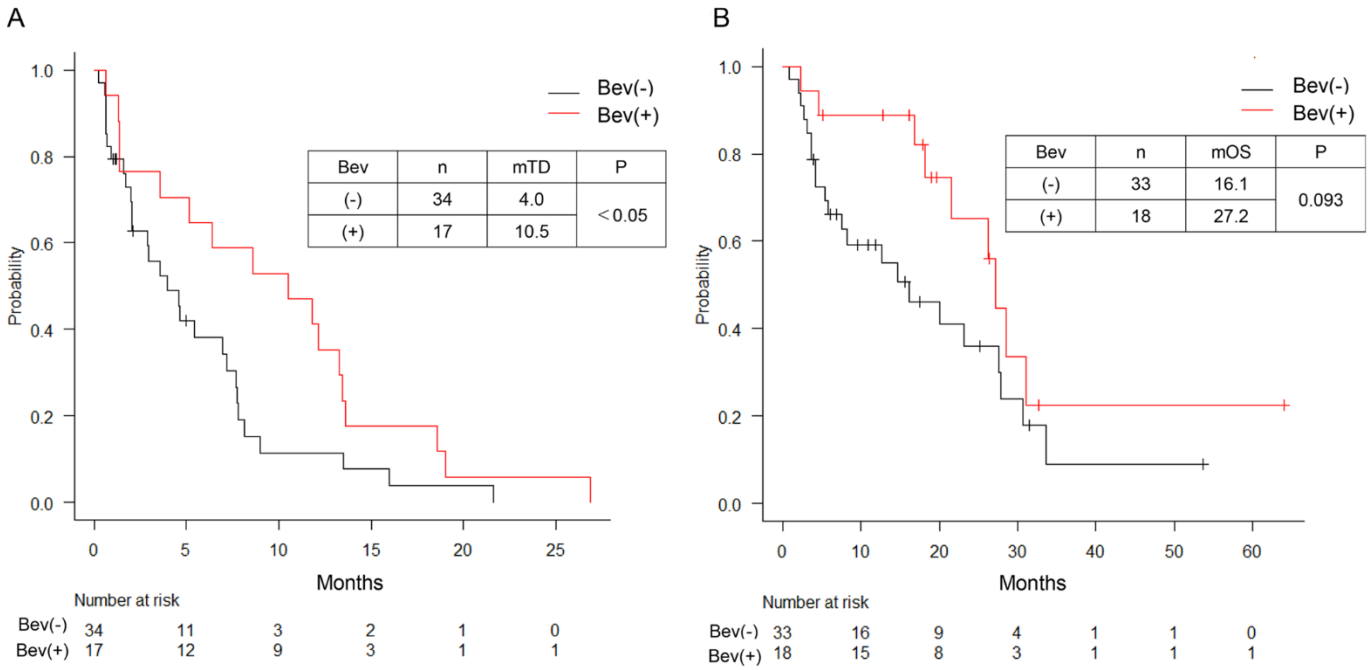
Metastatic site	Total	single metastasis	(%)	double metastasis	(%)	triple or more	(%)
Brain	37	16	(43.2)	14	(37.8)	7	(18.9)
Bone	59	38	(64.4)	15	(25.4)	6	(10.2)
Liver	18	4	(22.2)	2	(11.1)	12	(66.7)
Adrenal	23	7	(30.4)	12	(52.2)	4	(17.4)
Other	9	4	(44.4)	5	(55.6)	0	(0.0)

*Other: distal lymph,skin,muscle,intestine.



Site of metastasis	n	mOS
Pleura+Pulmonary	45	30.7
Bone	27	15.0
Brain	20	18.9
Liver	18	11.6

Fig. 1. Overall survival among metastatic sites Shown is Kaplan-Meier curve of overall survival among metastatic sites. Due to avoid duplication, Pleura + Pulmonary (Black line) includes malignant pleural effusion and pulmonary metastases without other metastasis. Bone (Red line) excludes brain and liver metastasis. Brain (Green line) excludes bone and liver metastasis. Liver (Blue line) includes all metastatic sites other than liver metastasis. *n= Number of cases. mOS=Median overall survival.



Bev	n	mTD	P
(-)	34	4.0	<0.05
(+)	17	10.5	

Bev	n	mOS	P
(-)	33	16.1	0.093
(+)	18	27.2	

Fig. 2. (A) Duration of first line treatments with and without bevacizumab in patients with pleura metastasis. This Kaplan-Meier curve compares the duration of first line treatment with or without bevacizumab in patients with pleural effusion. The red line indicates treatment with bevacizumab. The black line indicates treatment without bevacizumab. Pleural metastasis cases includes metastases other than pleural metastasis. *mTD=Median treatment duration. Bev=Bevacizumab. $P = p$ value. Fig. 2 (B) Overall survival of pleural effusion patients with and without bevacizumab treatments. This Kaplan-Meier curve represents the overall survival between patients who received at least one bevacizumab treatments and who never received bevacizumab treatments. The red line represents cases receiving treatment with bevacizumab. The black line represents cases treated without bevacizumab.

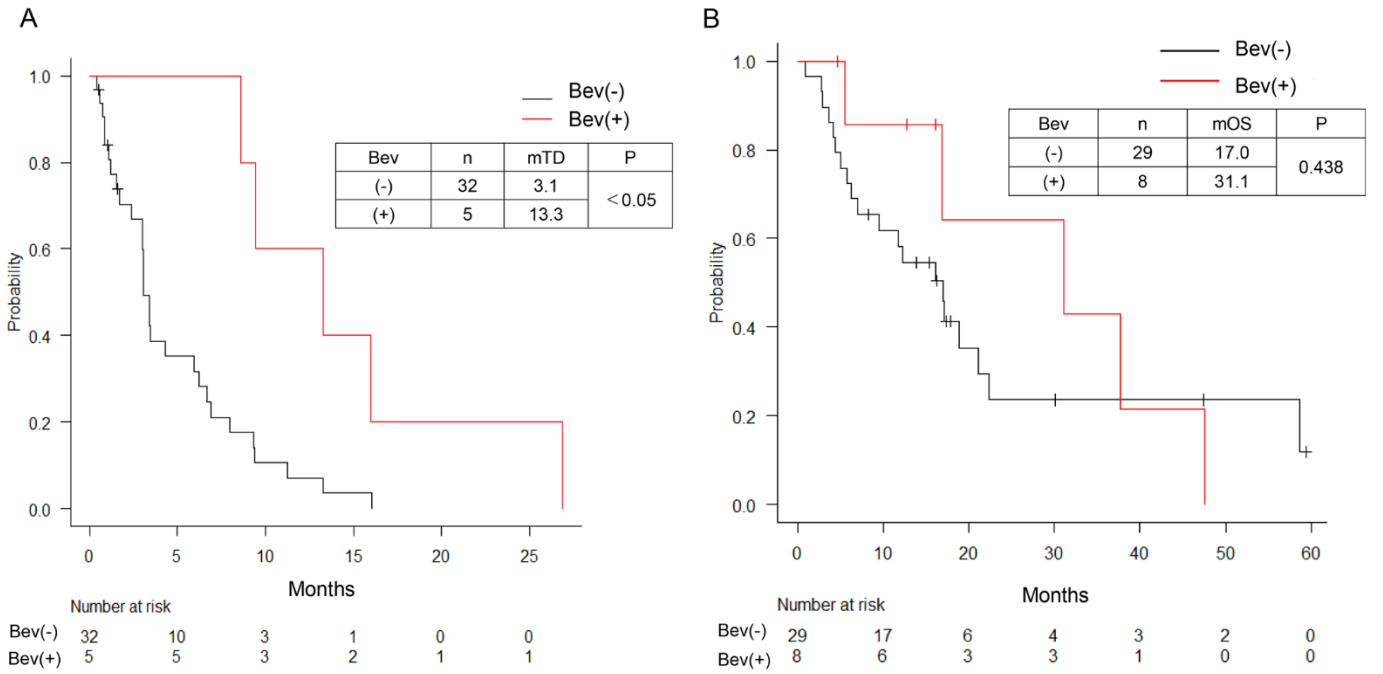


Fig. 3.. (A) Duration of treatment with and without bevacizumab in patients with brain metastasis. This Kaplan-Meier curve compares the duration of first line treatment with or without bevacizumab in patients with brain metastasis. The red line indicates treatment with bevacizumab. The black line indicates treatment without bevacizumab. Brain metastasis case includes metastases other than brain metastasis. *mTD=Median treatment duration. Bev=Bevacizumab. $P = p$ value. Fig. 3 (B) Overall survival of brain metastasis cases with and without bevacizumab treatments. This is a Kaplan-Meier curve of the overall survival of patients with brain metastasis, who have been treated with bevacizumab at least once. The red line represents cases receiving at least one treatment with bevacizumab. The black line represents cases never treated with bevacizumab.

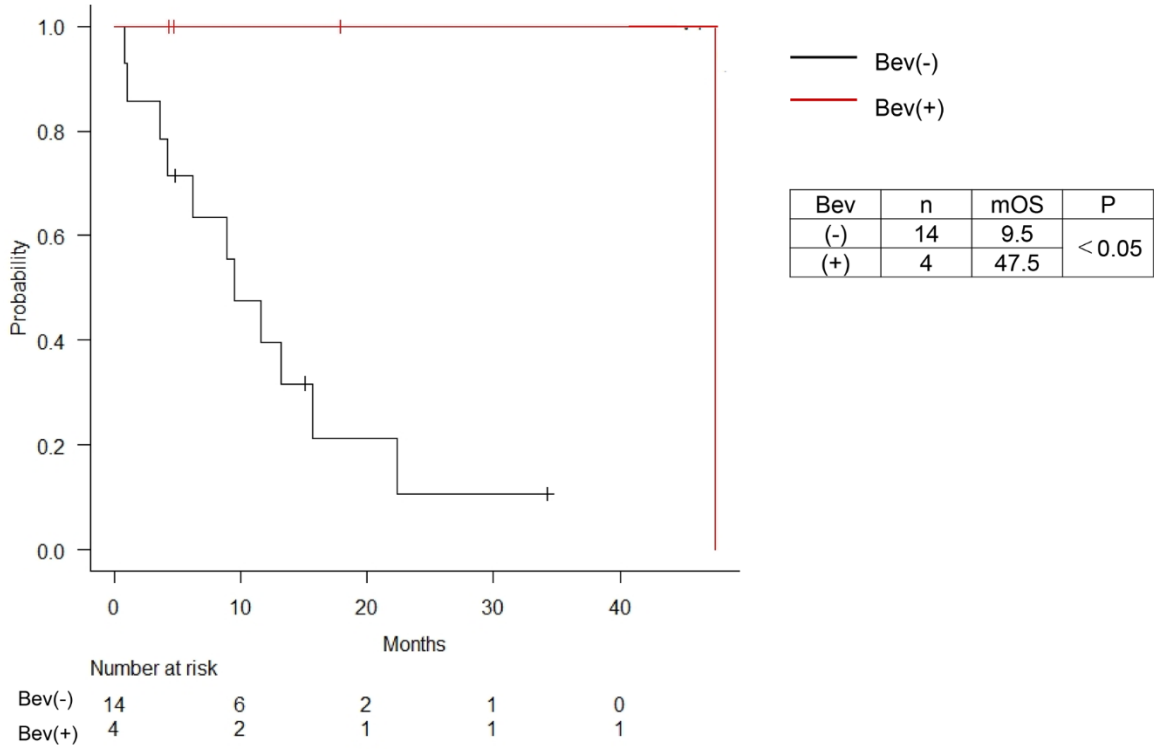


Fig. 4. Overall survival of liver metastasis cases with and without bevacizumab treatments. This Kaplan-Meier curve represents the overall survival between patients who received at least one bevacizumab treatments and who never received bevacizumab treatments. The red line represents cases receiving treatment with bevacizumab. The black line represents cases treated without bevacizumab. *mTD=Median treatment duration. Bev=Bevacizumab. $P = p$ value.

from a national Swedish cancer registry. The authors found that metastasis to the nervous system was most frequent, followed by metastases to the bone, respiratory system, liver, and adrenal gland. Other smaller studies have shown that the frequency of metastasis to the bone is highest, followed by the lung, brain, liver, and adrenal glands [12-14]. Our data are concordant with the order reported in the latter study. We have also added key information in our present study that reveals liver metastases are likely to be present is cases with multiple organ metastases. Indeed, the liver was the 4thmost frequent site of metastasis during the course of the disease, closely following bone and brain, which was in accordance with previous reports.

Liver metastasis has been reported as a poor prognostic factor in several reports [15-18], and we confirmed this in our current study. One reason for this association is that liver metastasis occurs after metastasis to other organs, and it is well known that multiple metastasis has a worse prognosis than oligo-metastasis in which cancer cells form a small number of new tumors in one or two other parts of the body. [15-18]. When we consider why metastasis to the liver may lead to poorer outcomes in comparison to other organs, one has to take into account the cellular composition and role of each organ. The liver consists of a unique cell population, including hepatocytes, liver sinusoidal endothelial cells (LSEC), hepatic stellate cells (HSC), Kupffer cells (KC), dendritic cells, liver-associated lymphocytes, and portal vein fibroblasts. Immune cells, including NK cells, resident KCs, and host immune T cells, also play a key role in preventing liver metastases [19]. Conversely, immune suppressive microenvironments including regulatory T cells (T reg), and myeloid-derived suppressor cells (MDSC) in the liver promote metastatic progression. Bevacizumab can suppress the activities of both T regs and MDSCs, which likely contribute to the benefits for patients with liver metastases who are treated with this drug. Angiogenic factors suppress immunity by directly suppressing antigen-presenting cells and immune effector cells, or by enhancing the effects of T regs, MDSCs, and tumor-associated macrophages (TAMs). These suppressive immune cells also promote angiogenesis and trigger a vicious cycle of pro-tumorigenic immune activation. Treatment with bevacizumab normalizes vasculature [20], restores DC maturation, reduces T regs in cancer patients [21, 22], and can reduce MDSC numbers in a mouse model [23]. Together, these effects of bevacizumab might explain its potential success in overcoming refractory liver metastasis.

In fact, for the liver metastases subgroup, combination chemotherapy with bevacizumab and atezolizumab (a humanized PD-L1 antibody) achieved longer PFS than chemotherapy alone. This efficacy was not seen following combination chemotherapy with atezolizumab excluding bevacizumab. This has suggested that bevacizumab was a key agent in treatment of liver metastases. Recently, it was proven that atezolizumab combined with bevacizumab resulted in significant better OS and PFS outcomes than sorafenib in patients with unresectable hepatocellular carcinoma [24]. Taken together, these data suggest that the serious threat of liver metastases in non-squamous NSCLC might be mitigated by bevacizumab treatment.

The current study has some limitations. First, these data were collected and analyzed retrospectively in a single institute. Although there was a collection of consecutive cases (Supplementary Figure 1), this may have led to a bias in case selection. Second, the duration of first-line treatment had to be employed instead of PFS, because we had no control over how regularly the tumors were evaluated. Duration of treatment is not a sufficient criterion upon which to analyze treatment efficacy. Despite these shortcomings, we consider that the survival data we analyzed are robust due to a rigorous registry system in place in our hospital.

Conclusion

This retrospective study reports the frequency of metastasis to various organ sites in patients with primary non-squamous NSCLC. In the extrathoracic metastasis class, bone and the brain were more frequent than the liver or the adrenal glands. Patients with liver metastases had more metastases to other sites and have a poor prognosis. Bevacizumab treatment appears to be effective in patients with pleural, brain, and liver metastases, and this drug may play an effective role in treating refractory liver metastases. Further analyses are needed to understand metastasis during NSCLC in order to improve outcomes for lung cancer patients.

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Declaration of Competing Interests

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Makoto Maemondo received lecture fees from Chugai pharma.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ctarc.2020.100290.

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