Ablative Procedures and Additional Anticancer Therapy Prolong the Survival in Patients With Endoluminal or Mixed-type Malignant Central Airway Obstruction: A Single-institution Retrospective Study

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Research Article

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Abstract

Background

In patients with malignant central airway obstruction (MCAO) receiving transbronchial interventions (TBIs), it remains unclear if the prognosis after the intervention might differ according to the bronchoscopic appearance of the airway obstruction.

Methods

TBIs were undertaken in MCAO patients with endoluminal obstruction (TM group, n = 19), extraluminal obstruction (EX group, n = 19) and mixed-type obstruction (MX group, n = 23), under moderate sedation and high fractions of inspired oxygen (FiO_2). We evaluated the differences in the overall survival period (OS) after the TBIs among the 3 groups.

Results

Regarding the TBIs, the initial procedure was transbronchial microwave ablation (TMA) in the TM group and MX group and stent placement in the EX group. However, 7 patients in the MX group received stent placement as the second-line procedure, after failure of TMA. The OS tended to be longer in the TM/MX group as compared to that in the EX group, both in the subgroups of patients who received post-TBI anticancer therapy (27.2 months/32.9 months vs. 6.0 months, $p = 0.011$) and in the subgroups of patients who received best supportive care alone (3.2 months/3.1 months vs. 1.4 months, $p = 0.072$). Multivariate analysis identified adoption of TMA as the initial procedure, successful airway patency restoration following the TBI, and post-TBI anticancer therapy as independent factors associated with a reduced risk of death in patients with MCAO.

Conclusion

It is beneficial to administer post-TBI anticancer therapy to MCAO patients with endoluminal or mixed-type obstruction following ablative procedures.

Introduction

Malignant central airway obstruction (MCAO) is a complication sometimes in patients with advanced non-small cell lung cancer (NSCLC) or with lung metastases from primary malignant tumors at other sites; it is a serious and life-threatening complication, and can cause death from suffocation, if left untreated. MCAO is generally defined as >50% obstruction of the trachea or mainstem bronchi and is classified as endoluminal obstruction, extraluminal obstruction or mixed-type obstruction [1] [2] [3].

Transbronchial interventions (TBIs) can relieve respiratory distress and additional anticancer therapy after TBIs has been reported to improve the quality of life in patients with MCAO [4] [5] [6] [7]. Laser ablation, electrocautery and argon plasma coagulation are commonly used ablative procedures in MCAO

patients with endoluminal obstruction caused by ingrowing tumors into the lumen of the airway, and stent placement is employed in patients with extraluminal obstruction caused by tumors growing adjacent to the airway. In patients with mixed-type obstruction, an ablative procedure followed by stent placement is usually adopted.

Some authors have reported that the overall survival period (OS) after TBIs in MCAO patients is longer in patients with endoluminal obstruction than in those with extraluminal obstruction or mixed-type obstruction [6] [8] [9], presumably because patients with endoluminal obstruction have less severe airway obstruction or lesions that are more amenable to treatment by ablation (e.g., polypoid lesions). There are also some reports of the efficacy of ablative procedures in MCAO patients with endoluminal obstruction and respiratory failure (severe airway obstruction) [10] [11].

We speculated that there might be more reasons for the better prognosis after TBIs in MCAO patients with endoluminal obstruction than that these patients tend to have less severe air obstruction and that the lesions tend to be more amenable to treatment by ablative procedures. Therefore, we conducted this retrospective study to evaluate the difference in the OS after TBIs among the MCAO patients with endoluminal obstruction, extraluminal obstruction and mixed-type obstruction, and to investigate the prognostic factors in MCAO patients treated by TBIs.

Patients And Methods

This retrospective, single-institution study was conducted with the approval of the Institutional Review Board of Kumamoto Regional Medical Center (approval date, June 16, 2021; approval number, 21-003). The data of 65 patients with advanced NSCLC or lung metastases from other primaries with symptomatic MCAO were retrieved from our medical records database for the period between October 1, 2013, and December 31, 2020. Some of the patients who underwent ablative procedures have been included in previously published data [11].

We performed transbronchial microwave ablation (TMA) as the ablative procedure in MCAO patients. Microwave induces polar molecules (mainly H_2O) in the tissue to rotate and produce dielectric heat in an electrical magnetic field at a frequency of 2450 MHz around the monopolar antenna (electrode). TMA therapy can be performed more safely in MCAO patients with respiratory failure with high fractions of inspired oxygen (FiO_2) without increased risk of airway fire or accidental penetrating injury, as compared to other ablative therapies, because the tissue temperature rarely exceeds 100℃ (boiling point of water) during TMA [12].

In the patients enrolled in our study, TMA therapy was performed using a Microwave Tissue Coagulator (Microtaze® OT-110M or AFM-712, Alfresa Pharma Co., Osaka, Japan) and stent placement was performed using an Ultraflex™ Tracheobronchial Stent System (Boston Scientific Co., Tokyo, Japan), under moderate sedation (intravenous administration with midazolam at the starting dose of 3-4 mg) and high FiO_2 values (supplemental oxygen via an oxygen mask at a flow rate of 5-10 L/min). In patients with

MCAO with life-threatening respiratory failure, TBIs performed under moderate sedation could save time for general anesthesia in the operating room [11]. TMA therapy and stent placement are considered successful if at least 50% airway patency is restored [1] [2] [3] within an hour of initiation of the first session of the TBI.

We stratified the total of 61 MCAO patients who underwent TBIs into 3 groups according to bronchoscopic appearance of the MCAO, as follows: patients with endoluminal obstruction (TM group, n = 19), patients with extraluminal obstruction (EX group, n = 19), and patients with mixed-type obstruction (MX group, n = 23) (Figure 1). The endpoint of the study was the differences in the median OS among the TM group, EX group, and MX group. OS was defined as the period from the initiation of the TBIs until patient death. Comorbidities at the time of the initiation of TBIs were evaluated according to the Charlson comorbidity index [13]. Presence of respiratory failure was defined as a ratio of the partial pressure of oxygen in the arterial blood (PaO_2) to the FiO_2 (PaO_2/FiO_2) of <300.

Statistical analysis was performed using the Stat View J 5.0 statistical program (SAS, Institute Inc., Berkeley, CA, USA). One-way factorial analysis of variance and multiple comparison tests were used to compare three independent parameters. Analysis of categorical data was performed with the $\chi 2$ test. The log-rank test was performed to identify the clinical variables potentially associated with the OS. Variables identified as being significant with *p* values of < 0.10 were entered into a Cox proportional-hazards model for multivariate analysis. The hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) were determined. OS was estimated by the Kaplan-Meier method. A two-tailed *p*-value of less than 0.05 was considered as being indicative of a statistically significant differences.

Results

Patient and disease characteristics

There were no significant differences in the median age of the patients, percentages of patients with an Eastern Cooperative Oncology Group performance status (PS) score of 3-4, proportions of patients with respiratory failure, distributions of patients with different pathological types of lung cancer or different sites of origin of the metastatic lung tumors, or proportions of patients with a previous history of anticancer therapy among the 3 groups. The symptoms of dyspnea on exertion, cough/bloody sputum, and stridor were the main indications for TBI (Table 1).

Efficacy and complications of TBIs

The most common site of MCAO was the trachea/tracheal bifurcation in all the 3 groups. The initial TBI procedure was TMA therapy in the TM and MX groups, and stent placement in the EX group. The successful airway patency restoration rate (95% vs. 74% or 89%) as well as the percentage of patients in whom the symptoms/PS improved after the TBIs (84% vs. 65%/74%) was higher in the TM group than in the MX group/EX group. Seven (32%) of the patients in the MX group received stent placement as second-line therapy, because of failure of TMA to successfully restore the airway patency (Table 2).

There were no differences in the frequencies of complications during the TBIs among the 3 groups. Three patients required tracheal intubation during the TBIs due to hypoxemia, and 2 patients developed airway re-occlusion because of bronchial epithelial detachment within 24 hours of the TMA therapy, as a result of the normal bronchial mucosa having been accidentally coagulated during the TMA procedure. The frequency of complications after the TBI (>24 hours) was statistically significantly higher in the EX group than in the TM group/MX group (37% vs. 0%/13%, $p = 0.008$) (Table 2). Regarding the frequency of complications after stent placement as the TBIs, complications occurred in 9 (35%) of the 26 patients who received stent placement and 1 (3%) of the 35 patients who did not receive stent placement.

Post-TBI anticancer therapy

The percentage of patients who received post-TBI anticancer therapy (79% vs. 30%/58%) and the median number of anticancer therapy regimens (2 regimens vs. 1 regimen/1 regimen) was higher in the TM group than in the MX group/EX group. The reasons for not administering post-TBI anticancer therapy were that the patients refused to receive post-TBI anticancer therapy or their PS was poor, precluding post-TBI anticancer therapy (Table 3). In the TM group, 2 patients (11%) with lesions that were amenable to treatment by ablation alone did not need post-TBI anticancer therapy; a 72-year-old woman with a single endoluminal metastatic tumor from postoperative colon cancer, and a 56-year-old man with an endobronchial carcinoid in the left main bronchus.

Survival

During the median follow-up period of 5.6 months (range, 0.4 to 95.6 months) after the TBI, 63% of patients in the TM group, 83% in the MX group, and 89% in the EX group died (Table 3). The OS was longer in the TM group than in the MX group/EX group (18.5 months vs. 3.8 months/4.5 months, $p = 0.001$) (Figure 2-a). Multivariate analysis identified adoption of TMA as the initial procedure (HR 0.294, 95%CI 0.113-0.770, $p = 0.013$), successful airway patency restoration after the TBI (HR 0.239, 95%CI 0.106-0.538, $p = 0.005$) and post-TBI anticancer therapy (HR 0.194, 95% CI 0.087-0.431, $p < 0.001$) as significant factors associated with a reduced risk of death (Table 4).

Among the patients who received post-TBI anticancer therapy, the OS was longer in the TM group/MX group than in the EX group (27.2 months/32.9 months vs. 6.0 months, $p = 0.011$) (Figure 3-b). Among the patients who received best supportive care (BSC) alone, the OS tended to be longer in the TM group/MX group than in the EX group (3.2 months/3.1 months vs. 1.4 months, $p = 0.072$) (Figure 3-c).

Discussion

Our results showed that adoption of the TMA procedure as the initial procedure, successful airway patency restoration following the TBI and post-TBI anticancer therapy were factors that were independently associated with a reduced risk of death in MCAO patients, and that the OS tended to be longer in the TM group and MX group than that in the EX group both in the subgroups of patients that received post-TBI anticancer therapy and in the subgroups of patients that received BSC alone.

Many studies have already reported that additional anticancer therapy after TBI such as chemotherapy or radiotherapy, improves the quality of life in patients with MCAO [4] [5] [6] [7]. In the present study, the percentage of patients who received post-TBI anticancer therapy was lower in the MX group and EX group than that in the TM group; the reason was the patient refusal or poor PS. This could explain the high frequency of complications after TBI in the EX group (Table 2). Complications after the TBI occurred in 35% of the patients who received stent placement and 3% of the patients who did not receive stent placement. Although stent placement can be performed more quickly and safely as compared to ablative procedures, long-term complications associated with an airway foreign body, including bacterial pneumonia, mucus plugging of the stent, stent migration, or massive hemoptysis caused by a tracheo-arterial fistula have also been reported after stent placement [14] [15].

In our study, the median OS time was 18.5 months in the TM group, 3.8 months in the MX group and 4.5 months in the EX group, consistent with previous reports [8] [9] [14] [16]. In addition, in the TM group, 30% of the patients had respiratory failure (severe airway obstruction), and 89% of the patients needed post-TBI anticancer therapy. We suggest that TMA therapy itself decreases the risk of death in the TM group, because ablative procedures can directly decrease the volume of the ingrowing tumors into the lumen of the airway without placement of an airway foreign body. Stent placement is the best procedure for MCAO patients with extraluminal obstruction. However, as Ost et al [17] points out, stent placement for its barrier effect should be undertaken after airway patency restoration by ablative procedures in those with endoluminal or mixed-type obstruction.

Our study had certain limitations. Firstly, the sample size was small because this was a retrospective study conducted at a single institution. Secondly, we performed TMA therapy as the initial ablative procedure in all the patients of the TM group and MX group, even though laser ablation, electrocautery and argon plasma coagulation are also commonly used ablative procedures [1]. As we have previously reported that TMA therapy is well-tolerated and effective in patients with MCAO [11], we do not believe that adoption of this procedure would have affected our results. Thirdly, we could not advise all the patients about the benefits of post-TBI anticancer therapy, because some patients were admitted to our hospital for the purpose of TBIs alone. If a greater number of patients in the MX group had received post-TBI anticancer therapy, a better prognosis might have been achieved in all the patients of the MX group.

In conclusion, it is beneficial for MCAO patients with endoluminal obstruction or mixed-type obstruction to receive post-TBI anticancer therapy following ablative procedures.

Declarations

Compliance with ethical standards

Funding

No funding was received from any source for this work.

Conflict of interests

The authors have no conflict of interests to declare.

Ethical approval

All procedures involving human participants were performed in accordance with the ethical standards laid down by the institutional and/or national research committees and were in compliance with the principle of the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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Tables

Table 1 Patient and disease characteristics

	TM group N = 19	MX group N = 23	EX group N = 19	*P*
Age, years	73 (45-88)	71 (47-92)	68 (41-85)	-
Gender, women	6 (32)	2 (9)	4 (21)	0.175
Charlson comorbidity index	1 (0-2)	1 (0-2)	0 (0-2)	-
PS before the TBI				
1-2	12 (63)	16 (70)	13 (68)	0.899
3-4	7 (37)	7 (30)	6 (32)	0.899
Symptoms before the TBI				
Dyspnea on exertion	12 (63)	15 (65)	13 (68)	0.942
Cough/Bloody sputum	6 (32)	5 (22)	2 (11)	0.284
Stridor	1 (5)	2 (9)	2 (11)	0.835
Others	0	1 (4)	2 (11)	0.320
Respiratory failure	6 (32)	6 (26)	6 (32)	0.901
Pathological type of lung cancers				
Any	14 (74)	16 (70)	14 (74)	0.941
Squamous cell carcinoma	9 (47)	11 (48)	7 (37)	0.735
Adenocarcinoma	1 (5)	4 (17)	5 (26)	0.212
Adenoid cystic carcinoma	2 (11)	0	0	0.102
Others	2 (11)	1 (4)	2 (11)	0.695
Origin of the metastatic lung tumors				
Any	5 (26)	7 (30)	5 (26)	0.941
Esophageal cancer	0	2 (9)	4 (21)	0.091
Thyroid cancer	2 (11)	2 (9)	0	0.369
Others	3 (16)	3 (13)	1 (5)	0.570
Previous anticancer therapy, yes	6 (32)	10 (43)	12 (63)	0.142

Data are expressed in numbers (%) or median values (range)

PS, performance status; TBI, transbronchial intervention

Table 2 Transbronchial interventions

	TM group	MX group	EX group	*P*
	N = 19	N = 23	N = 19	
Location of the malignant central airway obstruction				
Trachea/tracheal bifurcation	11 (58)	14 (61)	12 (63)	0.946
Right main bronchus	4 (21)	5 (22)	5 (26)	0.914
Left main bronchus	4 (21)	4 (17)	2 (11)	0.672
Efficacy of the TBI				
TMA	19 (100)	23 (100)	0	<0.001
Stent placement	1 (5)	7 (30)	19 (100)	<0.001
Airway patency restoration	18 (95)	17 (74)	17 (89)	0.138
Improvement of symptoms or PS	16 (84)	15 (65)	14 (74)	0.379
Number of sessions	2 (1-4)	2 (1-3)	1 (1-2)	-
Complication during the TBI				
Any	1 (5)	4 (17)	3 (16)	0.469
Endobronchial bleeding	1 (5)	3 (13)	0	0.227
Hypoxemia requiring intubation	0	2 (9)	1 (5)	0.430
Airway reocclusion*	0	2 (9)	0	0.181
Stent migration	0	0	2 (11)	0.102
Complication after the TBI (>24 hours)				
Any	0	3 (13)	7 (37)	0.008
Bacterial pneumonia	0	2 (9)	3 (16)	0.206
Hemoptysis	0	1 (4)	2 (11)	0.320
Stent migration	0	0	2 (11)	0.102
Additional procedures after the TBI				
Any	5 (26)	5 (28)	5 (26)	0.922
TMA	5 (26)	3 (13)	4 (21)	0.551
Stent placement	1 (5)	4 (17)	2 (11)	0.465

Data are expressed in numbers (%) or median values (range)

PS, performance status TBIs; transbronchial interventions; TMA, transbronchial microwave ablation

*airway reocclusion because of bronchial epithelial detachment, as a result of the normal bronchial mucosa having been accidentally coagulated during the TMA procedure.

Table 3 Post-TBI anticancer therapy and prognosis

	TM group N = 19	MX group N = 23	EX group N = 19	*P*
Post-TBI anticancer therapy				
Any	14 (74)	7 (30)	11 (58)	0.017
Chemoradiation	4 (21)	2 (9)	2 (11)	0.459
Cytotoxic chemotherapy	8 (42)	4 (17)	8 (42)	0.137
Thoracic radiotherapy alone	4 (21)	1 (4)	1 (21)	0.145
EGFR-TKIs	1 (5)	0	2 (11)	0.291
Immune checkpoint inhibitors	1 (5)	0	2 (11)	0.291
No. of anticancer therapy regimens	2 (1-5)	1 (1-2)	1 (1-4)	-
Reasons for not administering post-TBI anticancer therapy				
Any	5 (26)	16 (70)	8 (42)	0.017
Patient refusal	4 (21)	8 (35)	2 (11)	0.172
Poor performance status	1 (5)	5 (22)	5 (26)	0.203
TBI failure	0	3 (13)	1 (5)	0.195
Outcome, death				
Any	12 (63)	19 (83)	17 (89)	0.119
Cancer-related death	10 (53)	18 (78)	17 (89)	0.030
Death from other cause	2 (11)	1 (4)	0	0.320

Data are expressed in numbers (%) or median values (range)

EGFR-TKI, epidermal growth factor receptor-tyrosine kinase inhibitor; PS, performance status TBI; transbronchial intervention

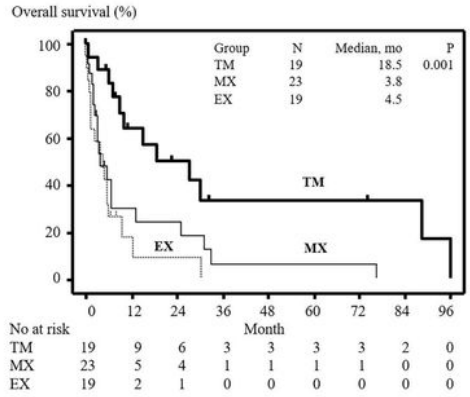
Table 4 Multivariate analysis to identify factors influencing the overall survival time

	Univariate analysis (Log rank test)	Multivariate analysis (Cox's proportional hazard model)		
	P-value	HR	95% CI	*P*-value
Age, years (≥70 / <70)	0.273			
Gender (Women/men)	0.185			
Performance status (3-4/1-2)	0.252			
Previous anticancer therapy, yes	0.001	1.332	0.560-3.160	0.517
Tracheal tumor obstruction, yes	0.280			
Respiratory failure, yes	0.314			
Endoluminal obstruction, yes	0.001	0.609	0.231-1.602	0.314
TMA, yes	0.006	0.294	0.113-0.770	0.013
Stent placement, yes	0.001	0.819	0.262-2.565	0.732
Airway patency restoration, yes	<0.001	0.239	0.106-0.538	0.005
Complications of TBIs, yes	0.131			
Post-TBI anticancer therapy, yes	<0.001	0.194	0.087-0.431	<0.001

CI, confidence interval; HR, hazard ratio; TBIs, transbronchial interventions; TMA, transbronchial microwave ablation

Figures

(a)



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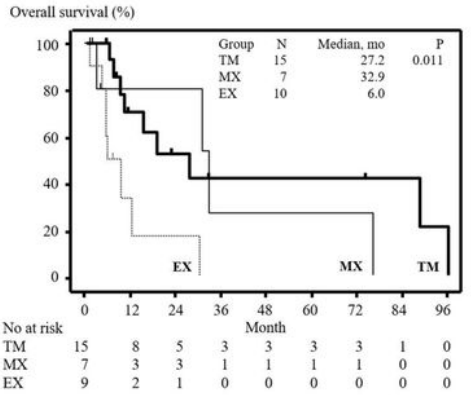

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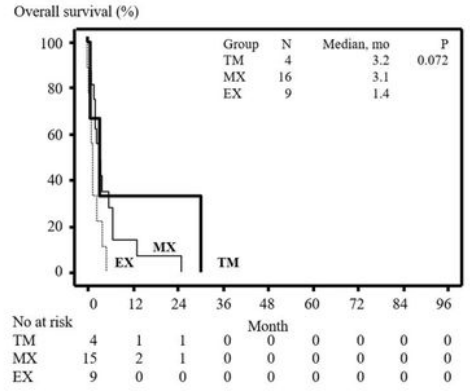

Figure 1

Study flowchart

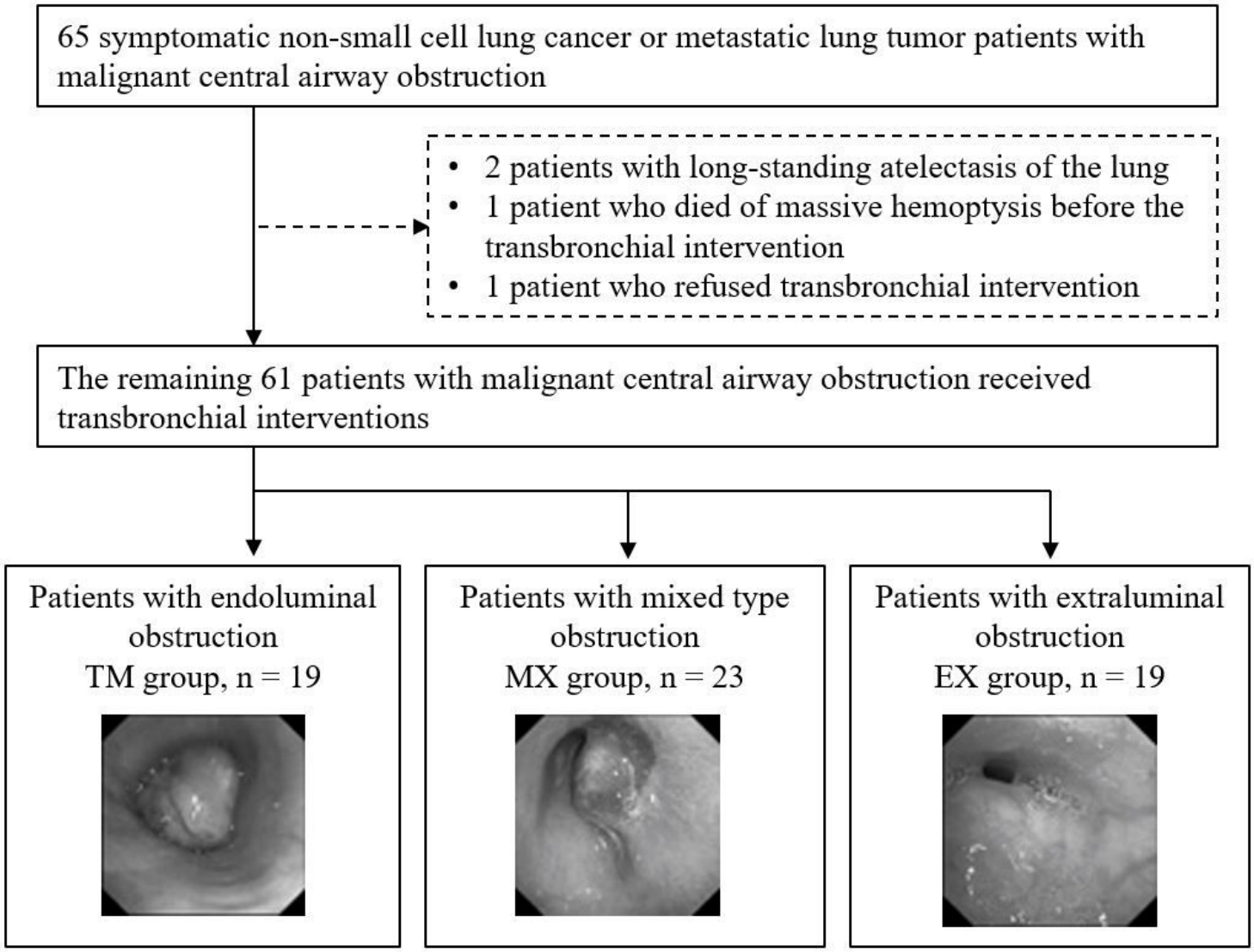

Figure 2

Overall survival after TBI in MCAO patients with endoluminal obstruction (TM group), extraluminal obstruction (EX group) and mixed-type obstruction (MX group); (a) all the patients, (b) patients who received best supportive care alone, and (c) patients who received post-TBI anticancer therapy MCAO, malignant central airway obstruction; TBI, transbronchial intervention,