



Endobronchial Treatment of Bronchial Carcinoid in the Elderly

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Published online: 19 August 2020
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Abstract

Purpose of the Review Although surgical resection is considered the gold standard of curative treatment for bronchial carcinoid, endobronchial treatment (EBT) can serve as a less invasive curative or palliative treatment in a selection of patients. It is unclear whether elderly patients with bronchial carcinoid should be treated in the same way as younger patients. In order to study the characteristics and treatment of elderly patients with bronchial carcinoid, we analyzed data from a cohort of patients that have been treated for bronchial carcinoid with EBT, surgical resection, or a combination of both. We used our existing database of patients referred for EBT and defined two groups of patients: ≥ 65 and < 65 years. We compared the characteristics, treatment, and causes of death between these groups. Successful EBT was defined as definitive treatment without signs of recurrence during follow-up with CT and bronchoscopy.

Recent Findings Thirty-five patients (19%) were ≥ 65 years. The incidence of atypical carcinoid was the same in both age groups (31%). Thirty-six of 184 patients (20%) were directly referred for surgical resection and 148 (80%) underwent EBT. There was no significant difference in success of EBT between patients < 65 years (58/122, 48%) and patients ≥ 65 years (15/26, 58%) ($p = 0.347$). Complication rates were similar in both groups. After unsuccessful EBT, only 70% (14/20) of the elderly patients was operated, whereas 93% (85/91) of the patients < 65 years was operated ($p = 0.001$). Disease specific mortality was 6% (2/35) in the group ≥ 65 years and 2% (3/149) in the group < 65 years.

Summary The incidence of atypical carcinoid is similar between the elderly and younger patients. Success rate and complication rate of EBT do not differ significantly between the age groups. After unsuccessful EBT, elderly patients were less likely to undergo surgical resection, which does not seem associated with excess disease specific mortality, although the number of events in this study is low.

Keywords Carcinoid · Neuro-endocrine tumor · Interventional bronchoscopy · Thoracic surgery · Elderly · Lung cancer

Introduction

Carcinoid tumors derive from pulmonary neuroendocrine cells and are part of the spectrum of neuro-endocrine tumors (NETs) [1, 2]. Pulmonary NETs represent around 20% of all lung tumors and consist of small cell carcinoma (SCLC), large cell neuroendocrine carcinoma (LC-NEC), and typical (TC) and atypical

carcinoid (AC) tumors. Carcinoid tumors have a more benign morphology, are less aggressive, and have a lower tendency to metastasize than SCLC and LC-NEC [3]. The incidence of bronchial carcinoid has increased in recent decades, probably due to a more prominent role of computed tomography in thoracic imaging and improved histopathology techniques [4]. The implementation of low-dose CT screening for lung cancer is likely to further increase the detection of subclinical carcinoid tumors [5]. Although surgical resection is considered the gold standard of curative treatment for both TC and AC, endobronchial treatment (EBT) can serve as a less invasive curative or palliative treatment in a selection of patients. With this technique, several studies have shown excellent long-term outcome [6–11]. A recent systematic review by Reuling et al. evaluated all studies utilizing either surgical resection and/or EBT [12]. The authors concluded that centrally located, small intraluminal pulmonary carcinoids, without signs of metastasis, can be treated with minimally invasive alternatives such as endobronchial treatment or

This article is part of the Topical Collection on *Pulmonology and Respiratory Care*

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parenchyma sparing surgical resection. They also emphasized the low quality of the available evidence and advised that future clinical research should preferably consist of prospective trials. The best candidates for EBT are purely intraluminal carcinoid tumors with a diameter < 20 mm on CT scan [13••].

It is unclear whether elderly patients with bronchial carcinoid should be treated in the same way as younger patients. In an analysis of the European Association of Thoracic Surgeons (ESTS) Neuroendocrine Tumours Working Group, 1109 patients with typical bronchial carcinoid were studied [14]. Mortality was associated with increased age, male gender, the presence of previous malignancies, peripheral tumors, higher TNM stage, and higher ECOG performance score. Because age is apparently an important prognostic factor and because most bronchial carcinoids do not behave aggressively, it is important to question the therapeutic benefit of treatments with curative intent in elderly and frail patients. In an analysis of 4111 patients with biopsy specimen-proven lymph node-negative typical carcinoid tumor of the lung, it was shown that non-operative management was associated with an increased risk for disease-specific mortality when compared with lobectomy [15]. Importantly, in T1 tumors, 5-year disease specific survival was still high (92%) without any treatment, suggesting that observation of asymptomatic peripheral typical carcinoid tumors or endoscopic management of symptomatic central carcinoid tumors may be considered in high-risk patients.

At our institution we have a cohort of patients that have been treated for bronchial carcinoid with EBT, surgical resection, or a combination of both [6, 11]. In order to study the characteristics and treatment of elderly patients we analyzed data from this cohort.

Methods

With Institutional review board approval (VU University Medical Center, IRB00002991), a cohort of patients with (suspected) bronchial carcinoids referred to our tertiary referral center for EBT was established between June 1991 and August 2015. Details of this patient cohort and the EBT technique have been described previously [8, 13••]. In short, prior to treatment, all patients underwent a computed tomography (CT) scan of the chest and bronchoscopy as part of the routine workup. After informed consent, EBT was performed by experienced interventional pulmonologists and procedural data were registered. The procedure was planned based on information obtained from the chest CT scan and the bronchoscopy. Patients were excluded from EBT in the case of extraluminal growth, lymph node involvement, or evidence of multifocal/disseminated disease on CT scan. EBT was performed under general anesthesia. At the discretion of the interventional pulmonologist, removal of the carcinoid tissue was established using different ablative

techniques, in the majority of patients, electro- or cryosurgery or mechanical debulking, or a combination of these techniques. After removal of the intraluminal lesion, the base was treated with cryotherapy in order to ablate any residual disease in the bronchial wall. The excised specimen was sent to the pathologist for histological diagnosis and classification. To detect residual disease, repeat bronchoscopy and CT scan were typically planned 6 weeks after EBT. In the absence of residual disease, patients were followed with CT scan and bronchoscopy annually. In patients with minimal residual disease EBT was repeated if deemed feasible. In patients with more extensive residual disease, surgical resection was performed. Patients who were medically inoperable or patients who refused operation were followed with CT scan and bronchoscopy and, in case of symptomatic bronchial obstruction (e.g. dyspnea, post obstruction pneumonia), bronchoscopic debulking was offered.

For the current analysis, we used our existing database and defined two groups of patients: ≥ 65 and < 65 years. We compared patient characteristics, treatment, and causes of death between these groups. Successful EBT was defined as definitive treatment without signs of recurrence during follow-up with CT and bronchoscopy.

Statistical Analysis

Data are presented as mean \pm standard deviation unless stated otherwise. Differences between groups were determined using the chi-square test or Fisher exact test for nominal variables.

Results

Table 1 shows the patient characteristics. Thirty-five patients (19%) were 65 years or older. The mean age of the group < 65 years was 42.9 (SD, 13.5), and the mean age of the group ≥ 65 years was 70.4 (SD, 5.5). There was a slight female predominance in both groups. American Association for Anesthesiologists (ASA) physical status was higher in the elderly patients, with an ASA score of III in 43% of elderly patients versus 9% in younger patients. Median overall follow-up time was 72 months. The incidence of atypical carcinoid was the same in both age groups (31%).

Figure 1 demonstrates the flow of patients through the treatment modalities. Thirty-six of 184 patients (20%) were directly referred for surgical resection, of whom 33 were operated. The remaining 148 patients underwent EBT, which was successful in 49% (73/148). EBT was unsuccessful in 75 patients (51%), 66 of whom underwent surgical resection (88%). There was no significant difference in success of EBT between patients < 65 years (58/122, 48%) and patients ≥ 65 years (15/26, 58%) ($p = 0.347$). Complication rates were similar in both groups, 10% in patients < 65 years and 11% in patients ≥ 65 years. The most common complications were

Table 1 Patient characteristics

	< 65 years (n = 149)	≥ 65 years (n = 35)
Mean age (SD) (years)	42,9 (13.5)	70,4 (5.5)
Gender		
Male	58 (39)	16 (46)
Female	91 (61)	19 (54)
Smoking history		
Current	20 (13)	7 (20)
Former	55 (37)	11 (31)
Never	68 (46)	1 (40)
Unknown	6 (4)	3 (9)
Presenting symptoms		
Pneumonia	55 (37)	10 (29)
Hemoptysis	25 (17)	3 (9)
Chronic cough	30 (20)	7 (20)
Dyspnea	22 (15)	11 (31)
Other	11 (7)	2 (6)
No symptoms	6 (3)	2 (6)
ASA physical status score		
I	80 (54)	7 (20)
II	56 (38)	13 (37)
III	13 (9)	15 (43)
IV	0 (0)	0 (0)
Histology		
Typical carcinoid	102 (69)	23 (66)
Atypical carcinoid	46 (31)	11 (31)
Unclassified	1 (1)	1 (3)

Values are n (%) unless otherwise specified

ASA American Society of Anesthesiologists

peri-procedural bleeding, desaturation, and bronchospasm. In two patients, a bronchial stricture was noted during follow-up after electrocautery treatment.

When looking at patients in whom there was an indication for surgical resection (either directly or after non-curative EBT), we found that only 70% (14/20) of the elderly patients was operated, whereas in the group < 65 years 93% (85/91) of the patients was

operated ($p = 0.001$). Table 2 shows the reasons that surgery was not performed and the outcome of those patients. In the group < 65 years patient refusal was the most common reason for not performing surgery. One patient of 64 years was not operated because of comorbidity/frailty, but has been well for a long time. One patient was not operated because of synchronous non-Hodgkin lymphoma, which was also the cause of death. In the group ≥ 65 years, the most common reason not to operate was comorbidity/frailty and one patient of 65 years was deemed operable, but refused surgery. Four out of six patients died of another cause, one patient died after 159 months of an unknown cause and one patient is still alive and well with disease. Disease-specific mortality was 6% (2/35) in the group ≥ 65 years and 2% (3/149) in the group < 65 years.

Discussion

This study shows that in our cohort of patients referred for endobronchial treatment of carcinoid, 19% of patients is ≥ 65 years. When comparing patients who are ≥ 65 years with those who are < 65 years, the incidence of atypical carcinoid is similar (31%), and success rate of EBT did not differ significantly (48% for patients < 65 years versus 58% for patients ≥ 65 years, $p = 0.347$). After unsuccessful EBT, elderly patients were less likely to undergo surgery (70% versus 93%, $p < 0.001$). In the elderly patients, the most common reason not to operate was comorbidity/frailty, while in the patients < 65 years the most common reason was patient refusal. Disease-specific mortality was 6% (2/35) in the group ≥ 65 years and 2% (3/149) in the group < 65 years.

Although surgical resection is the most effective treatment, with excellent local control rate and lymph node staging, it makes sense that fewer elderly patients undergo surgery when compared with younger patients, because carcinoid tumors are usually less aggressive compared with other lung malignancies. Specifically, in elderly and frail patients, factors such as age, comorbidity, life expectancy, estimated therapeutic benefit, and patient preference should all be considered in clinical decision making. Even when it comes to non-small cell lung cancer (NSCLC), a much more

Fig. 1 Flow of patients through different treatment modalities

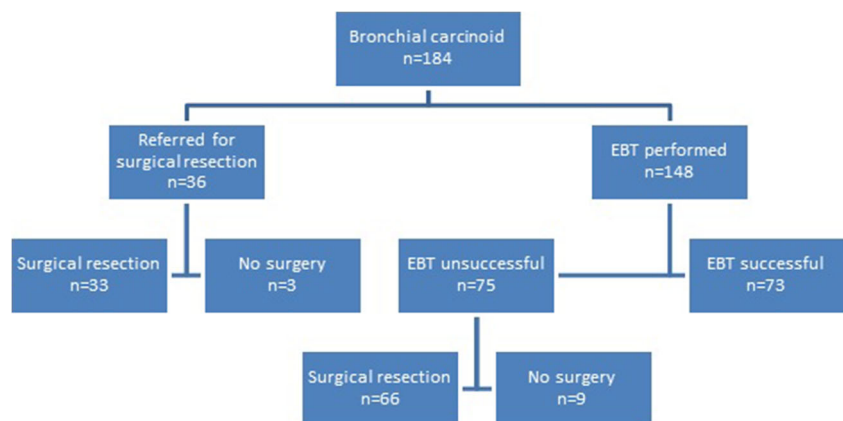


Table 2 Reasons for not performing surgery when indicated and outcome

Age (years)	Reason for not performing surgery	Follow-up time (months)	Status
< 65 years			
43	Refused surgery, pneumonectomy 20 yrs. Later	237	Alive no disease
51	Refused surgery	98	Alive with disease
51	Refused surgery	122	Alive with disease
55	Diagnosed with non-Hodgkin lymphoma	140	Dead other cause
61	Refused surgery	191	Alive with disease
64	Comorbidity/frailty	100	Alive with disease
≥ 65 years			
65	Refused surgery	3	Dead other cause
74	Comorbidity/frailty	30	Dead other cause
76	Comorbidity/frailty	90	Dead other cause
77	Comorbidity/frailty	159	Dead of unknown cause
79	Comorbidity/frailty	19	Dead other cause
81	Comorbidity/frailty	52	Alive with disease

aggressive disease than carcinoid, the elderly are less likely to undergo surgery. In 2001 in the Netherlands, 32% of elderly patients (≥ 75 years) with early-stage NSCLC did not receive treatment with curative intent [16]. After the introduction of stereotactic body radiotherapy (SBRT) as a potential curative treatment of NSCLC in 2003, the proportion of Dutch elderly patients not receiving treatment with curative intent decreased to 19% by 2013 [17••]. In the Netherlands, SBRT is currently the prevailing treatment in octogenarians with stage I NSCLC [18••]. For bronchopulmonary carcinoid however, experience with SBRT as an alternative for surgical resection is limited. An analysis from the US National Cancer Database showed that 154 patients with cT1-2N0M0 typical bronchopulmonary carcinoid were treated with radiotherapy [19]. About 47% of the patients was 75 years or older, and 84 (55%) were treated with SBRT, while the remainder were treated with conventionally fractionated radiotherapy. Propensity-matched Kaplan–Meier analysis revealed improved survival with lung SBRT (median: 66 vs 58 months; $p = 0.034$) [19]. The patients in our cohort typically exhibit very central bronchial lesions, which might not be good candidates for stereotactic radiation due to their location in a large central airway and risk of lumen perforation [20]. In our institution, we do not currently use any form of radiotherapy for centrally located carcinoid tumors.

Endobronchial therapy might be the preferred modality for inoperable patients and patients with small intraluminal tumors. It also has the advantage that it can be repeated if required. Broxk et al. have reported on the long-term outcome after first-line bronchoscopic therapy in patients with bronchial carcinoid [8]. One hundred twelve patients were treated, with a median age of 47 years (range 16–77 years). Eighty-three patients (74%) had typical carcinoid, and 29 (26%) atypical carcinoid. EBT only was ultimately curative in 42% of the cases (47/112). Reuling et al. looked for predictors of successful EBT in a cohort of one hundred and twenty-five patients [13••]. Multivariate analysis

showed that a tumor diameter < 15 mm and purely intraluminal growth on computer tomography (CT scan) were predictive of successful radical endobronchial treatment. The success rate for intraluminal tumors with a diameter < 20 mm was 72%.

To further improve the treatment of bronchial carcinoid, especially in frail patients in whom the balance between overtreatment and under treatment is tight, biomarkers could be particularly useful. Recently, CD44 and orthopedia homeobox (OTP) protein expression have shown promise as prognostic biomarkers in pulmonary carcinoid. OTP is a homeodomain-containing transcription factor that mainly plays a role in the development of neuroendocrine cell lineages in the hypothalamus and in the differentiation of neuroblasts [21, 22]. CD44 seems to exhibit tumor suppressive effects by promoting apoptosis, but on the other hand seems to be involved in epithelial-to-mesenchymal transition and in promoting cell survival, and not surprisingly has been associated with both favorable as well as poor prognosis in different tumor types [23–25]. Swarts et al. studied mRNA expression levels of CD44 and OTP in 56 frozen pulmonary carcinoid specimens and CD44 and OTP protein expression in 292 pulmonary carcinoids [26]. They found that low transcriptional as well as low protein expression levels are strongly associated with a poor long-term survival rate of pulmonary carcinoid patients. If additional studies confirm that these markers can indeed reliably separate carcinoid with a favorable prognosis from carcinoids with a poor prognosis, they could be used to determine the most suitable treatment and follow-up strategy.

In conclusion, our cohort shows that the incidence of atypical carcinoid is similar between the elderly and younger patients. Furthermore, success rate and complication rate of EBT do not differ significantly between the age groups. After unsuccessful EBT, elderly patients are less likely to undergo surgery, which does not seem associated with excess disease specific mortality, although the number of events in this study

is low. Treatment and follow-up of elderly patients with bronchopulmonary carcinoid may be improved by further study and implementation of some promising biomarkers.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights This article does not contain any studies with human or animal subjects performed by any of the authors.

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