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Review

Endobronchial and surgical treatment of pulmonary carcinoid tumors: A systematic literature review

E.M.B.P. Reuling[a,d,*], C. Dickhoff[a,b], P.W. Plaisier[d], H.J. Bonjer[a], J.M.A. Daniels[c]

[a] Department of Surgery, Cancer Center Amsterdam, Amsterdam University Medical Center, De Boelelaan, 1117, 1081 HV, Amsterdam, the Netherlands
[b] Department of Cardiothoracic Surgery, Cancer Center Amsterdam, Amsterdam University Medical Center, De Boelelaan, 1117, 1081 HV, Amsterdam, the Netherlands
[c] Department of Pulmonary Diseases, Cancer Center Amsterdam, Amsterdam University Medical Center, De Boelelaan, 1117, 1081 HV, Amsterdam, the Netherlands
[d] Department of Surgery, Albert Schweitzer Hospital, Albert Schweitzerplaats 25, 3318 AT Dordrecht, the Netherlands

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ABSTRACT

The treatment of pulmonary carcinoid has changed over the last decades. Although surgical resection is still the gold standard, minimally invasive endobronchial procedures have emerged as a parenchyma sparing alternative for tumors located in the central airways. This review was performed to identify the optimal treatment strategy for pulmonary carcinoid, with a particular focus on the feasibility and outcome of parenchyma sparing techniques versus surgical resection. A systematic review of the literature was carried out using MEDLINE, Embase and the Cochrane databases, based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement. Two separate searches of publications in endobronchial and surgical treatment in patients with pulmonary carcinoid, were performed. Outcomes were overall survival, disease free survival, recurrence rate, complications, quality of life, and healthcare costs. Combining the two main searches for endobronchial therapy and surgical therapy yielded 3111 records. Finally, 43 studies concerning surgical treatment and 9 studies related to endobronchial treatment for pulmonary carcinoid were included. Assessment of included studies showed that lymph node involvement, histological grade, tumor location and tumor diameter were identified as poor prognostic factors and seem to be important for patients with pulmonary carcinoid. For patients with a more favorable prognosis, tumor location and tumor diameter are important factors that can help decide on the optimal treatment strategy. Centrally located small intraluminal pulmonary carcinoids, without signs of metastasis can be treated with minimally invasive alternatives such as endobronchial treatment or parenchyma sparing surgical resection. Patients with parenchyma sparing resections should be followed with long term follow up to exclude recurrence of disease. In a multidisciplinary setting, it should be determined whether individual patients are eligible for parenchyma sparing procedures or anatomical resection. Overall evidence is of low quality and future studies should focus on prospective trials in the treatment of pulmonary carcinoid.

1. Introduction

Pulmonary carcinoid tumors are family of the neuro-endocrine tumors (NET), originating from the neuro-endocrine Kulchitsky cells, and comprise around 2% of all pulmonary cancers [1]. By morphological analysis, carcinoid tumors can be classified as typical carcinoid (TC) and atypical carcinoid (AC), depending on mitotic cell count (TC 0–2 and AC 2–10 per 2-mm^2) and on the presence of necrosis (AC) [2]. AC's exhibit a slightly more aggressive behaviour with a higher rate of recurrences and tendency to metastasize when compared to TC [1]. Carcinoids are often centrally located, predominantly intraluminal tumors without invasion of adjacent tissues [3]. These characteristics make them particularly suitable for parenchyma sparing surgical treatment options such as sleeve lobectomy or bronchoplastic procedures. Although surgery still is the standard treatment to date, endobronchial treatment modalities (e.g. laser treatment, cryotherapy) are gaining popularity. For selected patients with TC and AC, good results have been reported after endobronchial treatment (EBT) [4–14] and the low-grade nature of carcinoids, makes that incomplete endobronchial resection can still be completed by radical surgical resection, with good results 6,12. To justify its use, the outcomes of (initial) endobronchial treatment should not be inferior to surgical resection. Against this background this review of available literature was performed to identify the optimal curative treatment strategy for patients with pulmonary carcinoid, with a particular focus on the feasibility and outcome of endobronchial treatment and surgical techniques.

* Corresponding author at: Department of Surgery, Amsterdam University Medical Center, De Boelelaan, 1117 1081HV Amsterdam, the Netherlands.
E-mail address: e.reuling@vumc.nl (E.M.B.P. Reuling).

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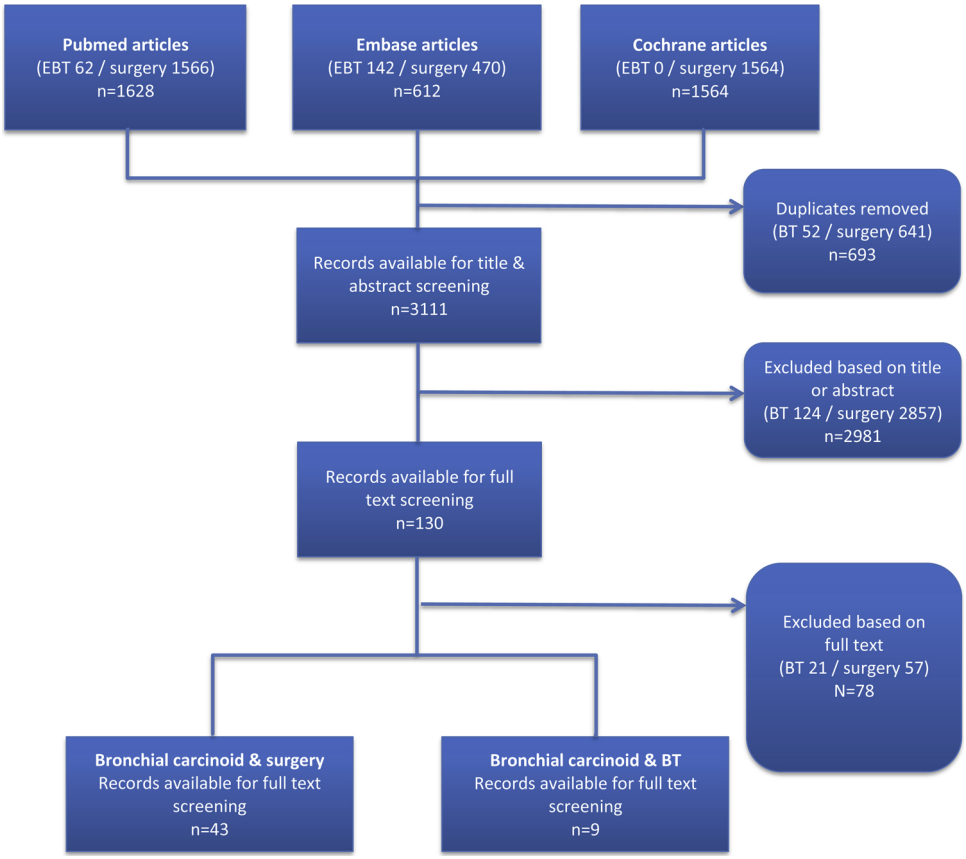

Fig. 1. Study selection process for records in endobronchial treatment (EBT) and surgery in pulmonary carcinoid.

2. Materials and methods

2.1. Search strategy

A literature search was performed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA)-statement [15]. Studies reporting on endobronchial treatment, surgical treatment, or both, for pulmonary carcinoid tumors, were identified using the online databases MEDLINE (PubMed), Embase (Ovid), and the Cochrane Database of Systematic Reviews and Central Register of Controlled Trials (Wiley). Studies were searched by a clinical librarian and investigator (ER) up to July 2018. Search terms included controlled terms (MeSH in PubMed and Emtree in Embase) as well as free text terms. Free text terms only were used in The Cochrane Library. Only English language papers were included in the review.

A first search was based on bronchoscopic treatment for pulmonary carcinoid. The following keywords and medical subject heading (MeSH) terms were used: "Carcinoid Tumor"[Mesh] OR carcinoid*[tiab] OR neuroendocrin*[tiab]) AND ("Lung"[Mesh] OR "Lung Diseases"[Mesh] OR lung[tiab] OR lungs[tiab] OR pulmonar*[tiab] OR bronchop*[tiab] OR bronchu*[tiab] OR bronchi*[tiab] OR trache*[tiab]. 'Carcinoid'/de OR 'neuroendocrine tumor'/de OR carcinoid*:ab,ti OR neuroendocrin*:ab,ti. The first combination, carcinoid* or neuroendocrin*) and (lung or lungs or pulmonar* or bronch* or trache*)):ti,ab,kw was combined with Bronchoscop* or endoscop* or endobronch*:ti,ab,kw, and ibt or laser* or (initial near/3 treatment*):ti,ab,kw.

A second search was based on surgery for pulmonary carcinoid. The following search terms were used: "Carcinoid Tumor"[Mesh] OR carcinoid*[tiab] OR neuroendocrin*[tiab]) AND ("Lung"[Mesh] OR "Lung Diseases"[Mesh] OR lung[tiab] OR lungs[tiab] OR pulmonar*[tiab] OR bronchop*[tiab] OR bronchu*[tiab] OR bronchi*[tiab] OR trache*[tiab])), (("Carcinoid Tumor"[Mesh] OR carcinoid*[ti] OR neuroendocrin*[ti]) AND ("Lung"[Mesh] OR "Lung Diseases"[Mesh] OR lung[ti] OR lungs[ti] OR pulmonar*[ti] OR bronchop*[ti] OR bronchu*[ti] OR bronchi*[ti] OR trache*[ti]. "Thoracic Surgery, Video-Assisted"[Mesh] OR "Thoracotomy"[Mesh] OR "Pneumonectomy"[Mesh] OR "surgery" [Subheading] OR "Surgical Procedures, Operative"[Mesh] OR "Perioperative Care"[Mesh] OR surger*[tiab] OR surgical*[tiab] OR operation*[tiab] OR operative*[tiab] OR perioperati*[tiab] OR bronchoplast*[tiab] OR sleeve resect*[tiab] OR lobectom*[tiab] OR pneumonectom*[tiab] OR thoracotom*[tiab] OR vats[tiab]. Word variations have been searched.

2.2. Study selection

Inclusion criteria were 1) human studies with patients of 18 years and older 2) endobronchial or 3) surgical treatment of 4) pulmonary carcinoid. Exclusion criteria were as follows: 1) case studies < 10 patients 2) non-English language studies, posters or meeting abstracts, 3) publication before 1990 and 4) population based studies. The records were first screened for title or abstract by two independent reviewers (ER and CD), and subsequently screened for full text. A standardized form was used for each study. Following the removal of duplicates, articles were initially screened by title and abstract to exclude non-relevant reports. The remaining articles were accessed in full text and further screened to identify those meeting the inclusion criteria. Finally, the reference lists of relevant articles were searched. Debate over article selection was resolved with consensus.

2.3. Outcome measures

The evaluated outcomes were overall survival, disease free survival, recurrence rate, complications, quality of life, and healthcare costs. This review defined major complications as re-admission, re-operation and

peri-or postoperative death. Others were registered as minor complications. Assessment of included studies showed that lymph node involvement, histological grade, tumor location and tumor diameter were identified as poor prognostic factors and were consequently further analyzed.

2.4. Data extraction and analysis

Meta-analysis was not feasible because the included studies were heterogeneous in terms of outcome measures. Overall and disease free survival and recurrence is influenced by different prognostic factors such as lymph node involvement, histology, tumor diameter and location. Prognostic factors with $p < 0.05$ in the multivariate analysis of the included studies, were further analyzed.

3. Results

The study selection flow-chart is presented in Fig. 1. Combining the two main searches for endobronchial therapy and surgical therapy yielded 3111 records. Subsequently, 693 duplicates were removed. After abstract and title screening, 2981 records were excluded, leaving 130 studies for full text screening. Finally, 9 studies for endobronchial treatment (Appendix A), and 43 studies for surgical treatment (Appendix B) meeting the inclusion criteria, were included and analyzed.

3.1. Description of studies

3.1.1. Endobronchial treatment

Patient and study characteristics of included reports on EBT are presented in Appendix A. All studies were non-randomized cohort studies (7 retrospective and 2 prospective), performed in Europe and published in the 21th century. Six studies included patients with TC only [4,5,7,9–11], whereas 3 included patients with both TC and AC [6,8,12]. For resection of the carcinoid tumor, 7 studies used laser therapy [4–7,9,11,12], of which 5 also used cryotherapy [4–6,8,12], 1 study described diode laser or argon plasma coagulation [8] and 1 study used a forceps [10]. Pre-treatment evaluation of intrabronchial and/or extrabronchial tumor localization was assessed with both CT scan and bronchoscopy in 7 studies [4–6,8–10,12], and not reported in 2 studies [7,11]. Completing surgery for residual or recurrence of disease was common practice in all selected studies.

3.1.2. Surgical treatment

Studies related to surgical treatment were predominantly retrospective cohort studies [3,13,16–41] and performed in Europe [3,13,17–19,21–29,31,36,38,40–50]. Both anatomical pulmonary resections (lobectomy, bilobectomy and pneumonectomy) and parenchyma sparing surgical techniques (segmentectomy, sleeve lobectomy, bronchial sleeve, wedge or enucleation of the tumor) were described. Three studies only performed parenchyma sparing resections [27,42,46], 1 study described a bronchotomy procedure in polypoid growing TC [3], 1 study presenting a bronchoplastic resection without lung resection [36], 2 studies also combined EBT with surgery [13,14]. Studies who performed a parenchyma sparing resection did not show more recurrences compared to studies with only anatomical resections. None of the studies reported on surgical or parenchyma sparing resection via VATS procedure. Studies were heterogeneous in defining parenchymal sparing, limited or bronchoplastic resection.

3.2. Outcome measures

3.2.1. Overall survival & disease free survival

Several studies reported on disease free survival (DFS), but the majority reported overall survival (OS) (Tables 1 & 2). Five and ten year OS for TC ranged from 82 to 100% and 60–100%, and for AC 50–95% and 38–75% respectively [13,17,18,20,22–31,34,35,38,39,41–44,46–49,51–53]. Five-and ten year DFS for TC ranged from 83 to 100% and 73–95% for TC, and 44–87% and 24–71% in AC, respectively [3,16,18,20,30,49–51,53]. No studies reported DFS in endobronchial treated pulmonary carcinoid.

3.2.2. Recurrence rate

Recurrence of disease was defined as loco-regional (bronchial or hilar/mediastinal lymph nodes) or distant recurrence (distant metastasis) (Table 3). Recurrence in surgery ranged loco-regionally from 0 to 8% [3,14,27,32,36,42,46,52] [41,54] and distantly from 0 to 23% [14,27,36,42,46,49] respectively. The loco-regional and distant recurrence rate was lower in EBT treated patients, ranging from 0 to 5% [5,7–9,11] to 0–4% [4,5,7–9,11] respectively. Atypical carcinoid had a higher incidence of recurrence, especially in higher N + stage [20,22,24,31,45,51]. From studies included in this review, there was a lower recurrence rate in parenchyma sparing surgery (loco-regional 0% and distant 0%) [3,14,27,36,42,46] and EBT (loco-regional 0–11% and 0–4%) [4,8,9,11], compared to studies with also anatomical resection.

3.2.3. Complications

Complications were commonly reported, with an overall complication rate for surgery and EBT ranging from 1 to 63% and 0–30%, respectively (Table 4). However, no clear definition for complications was defined, and the number of patients included varied from 11 to > 250 patients [3–14,18,20,21,23–25,27–33,35–39,41,42,44,46,48–50]. Table 4 presents all documented complications. Frequently reported complications after surgery were prolonged air leak, respiratory tract infections, cardiac arrhythmias and empyema. Three studies described stenosis after lung preserving surgery, treated with revision surgery or bronchoscopic dilatation [14,35,42]. The most important complication resulting from EBT was bleeding which was usually stopped using endobronchial interventions such as cryotherapy, adrenaline injection, Xylomethazolin or compression. Only one study reported a massive bleeding during EBT, which needed emergency surgery [6]. Three studies reported 2 stenosis after EBT, which were treated non surgically [5,7,11].

3.2.4. Quality of life

For pulmonary carcinoid, there were no studies identified reporting on quality of life.

3.2.5. Healthcare costs

There are no studies assessing healthcare costs in patients with pulmonary carcinoid.

3.3. Prognostic factors

3.3.1. Lymph node involvement

Lymph node involvement impacts on survival. Overall survival in N1 and N2 disease was 60–93% [20,22,28,34,35,38] and 50–55% [20,22,34,35] after 5 and 10 years respectively, compared to 90–100% [22,28,34,35,38] and 74–93% [22,28,31,34,35] in stage 1 disease. Lymph node involvement in AC showed a much poorer overall survival (5 year: stage I 85–100%, stage II 62–100% and stage III 0–28%, 10 year: stage I 72–100%, stage II 66% and stage III 0%) compared to TC (5 year: stage I 99–100%, stage II 75–100% and stage III 33–50%, 10 year: stage I 92–100%, stage II 75%, stage III 0%) [24,25,31,45]. Survival assessed in AC consisted small groups of patients compared to TC.

3.3.2. Histology

AC was found in 10–35% of all included patients [22,31] and is known to be poor a prognostic factor due to a more aggressive character than TC [16,20,22,24,28–32,34,35,38,44,45,47–51,53–55]. AC is associated with higher N status and recurrence rate when compared with TC. Some studies suppose that AC originates in older patients, which

Table 1
Overall survival (OS), -: no results in article, TC: typical carcinoid, AC: atypical carcinoid, EBT: endobronchial therapy.

	Endobronchial therapy(%)				Surgical resection(%)				Remark
	TC		AC		TC		AC		
	5 yrs	10 yrs	5 yrs	10yrs	5 yrs	10 yrs	5 yrs	10 yrs	
Shah et al. [17]	–	–	–	–	100	–	78	–	
Ducroq et al. [18]	–	–	–	–	92	88	–	–	
Ferguson et al. [20]	–	–	–	–	90	–	70	–	
Ruggieri et al. [21]	–	–	–	–	–	77	–	40	
Filosso '02 et al. [22]	–	–	–	–	97	93	77	52	
Fiala et al. [23]	–	–	–	–	99	87	95	74	
Kaplan et al. [51]	–	–	–	–	82	60	65	40	
Mezetti et al. [24]	–	–	–	–	92	90	71	60	
Cardillo et al. [25]	–	–	–	–	99	–	70	–	
Daddi et al. [26]	–	–	–	–	96	–	88	–	
Terzi et al. [27]	–	–	–	–	98	96	68	50	Only 3 AC included
Divisi et al. [43]	–	–	–	–	96	–	68	–	
Kyriss et al. [44]	–	–	–	–	94	82	92	62	
Rea et al. [28]	–	–	–	–	98	92	78	65	
Bini et al. [29]	–	–	–	–	91	91	88	44	
Rizzardi et al. [46]	–	–	–	–	100	100			
Ferolla et al. [47]	–	–	–	–	97	90	76	67	
Machuca et al. [30]	–	–	–	–	91	89	56	47	
Aydin et al. [31]	–	–	–	–	92	83	73	46	
Wei et al. [34]	–	–	–	–	100	92	90	75	
Zhong et al. [35]	–	–	–	–	90	74	74	58	
Filosso '13 et al. [48]	–	–	–	–	91	86	69	43	
Ichiki et al. [52]	–	–	–	–	91	–	91	–	Only 11 patients included
Filosso '14 et al. [49]	–	–	–	–	89	83	58	38	
Maurizi et al. [38]	–	–	–	–	100	–	88	–	
Herde et al. [53]	–	–	–	–	86	86	83	47	
Neuberger et al. [13]	–	–	–	–		89	–	68	
Yang et al. [39]	–	–	–	–	88	–	50	–	
Kasprzyk et al. [41]	–	–	–	–	96	–	83	–	
Lukrasz et al. [10]	89	84	–	–	–	–	–	–	
Neyman et al. [11]	94	–	–	–	–	–	–	–	Maximum 3 years follow up

negatively affects survival in these patients. [19,31,35,45]. Survival is also negatively influenced by AC. Five year overall survival ranged from 50 to 95% and declined to 38–75% after 10 years [13,17,20–31,34,35,38,39,41,43,44,47,48,51,53]. Five and ten year disease free survival was 44–81% and 24–71% respectively [16,20,30,38,49,48–51].

3.3.3. Tumor diameter & location

Tumor location [28,45] and diameter [12,39,45,54] are important factors to predict successful treatment. Seventy percent of all carcinoids are centrally located [29,31]. Although central localization is not precisely defined, it usually means that the tumor can be visualized during bronchoscopy before the level of the subsegmental bronchi. Central tumors seem to have a better prognosis than peripheral tumors [16], which might be explained by the fact that peripheral tumors are often larger, and are associated with a higher incidence of AC [31,45]. Central tumors usually present with symptoms related to bronchial obstruction (pneumonia, cough, wheezing) and therefore it is assumed that they are diagnosed earlier than peripheral tumors, which are more asymptomatic. One study described that purely intraluminal growing carcinoid tumors of ≤ 2 cm are candidates for successful EBT [12]. Two studies described a diameter of > 3 cm is related to a worse outcome and higher N stage [31,39]. A median tumor diameter of 22.5 mm was seen in the N0 group compared to a tumor diameter of 33.5 mm and 38 mm in the N1 and N2 group. The 10-year survival rate was 93% for the N0 group and declined to $< 30\%$ for the N1 group and N2 group [31]. Another study showed that 50% of the AC tumors had a tumor diameter of > 3 cm [39].

Table 2
Disease free survival (DFS), -: no results in article, TC: typical carcinoid, AC: atypical carcinoid.

	Endobronchial therapy(%)				Surgical resection(%)			
	TC		AC		TC		AC	
	5 yrs	10 yrs	5 yrs	10yrs	5 yrs	10 yrs	5 yrs	10 yrs
Chugtai et al. [16]					97	95	44	44
Ducroq et al. [18]	–	–	–	–	100	91	–	–
Tastepe et al. [3]	–	–	–	–	100	–	–	–
Ferguson et al. [20]	–	–	–	–	95	–	73	–
Kaplan et al. [51]	–	–	–	–	87	82	67	45
Machuca et al. [30]	–	–	–	–	94	–	74	–
Filosso '14 et al. [49]	–	–	–	–	83	73	49	24
Maurizi et al. [38]	–	–	–	–	93	–	44	–
Cusamano et al. [50]	–	–	–	–	99	90	87	71

Table 3
Recurrence rate; loco-regional[1]: recurrence local or hilar/mediastinal, distant[2]: distant metastasis, ND: not definable; - : no results in article, EBT: endobronchial therapy, TC: typical carcinoid.

	Endobronchial therapy			Surgical resection			Remarks
	Total n/total population (%)	Loco-regional[1] n (%)	distant[2] n (%)	Total n/total population (%)	Loco-regional[1] n (%)	distant[2] n(%)	
Chugtai et al. [16]	–	–	–	9/84 (11)	4 (5)	5(6)	
Shah et al. [17]	–	–	–	2/29 (6)	1 (3)	1 (3)	
Ducroq et al. [18]	–	–	–	4/139 (3)	1 (1)	3 (2)	Only TC; discrepancy in text, study described 2 local recurrences and 3 distant metastasis, but stated only 4 recurrences
Tastepe et al. [3]	–	–	–	0/16 (0)	0	ND	Only bronchotomy procedures.
El Jamal et al. [19]	–	–	–	7/95 (7)	4 (4)	3 (3)	
Ferguson et al. [20]	–	–	–	8/139 (6)	ND	ND	
Fadel et al. [42]	–	–	–	0/30 (0)	0	0	Only 16 patients included, performed only sleeve lobectomy.
Filosso '02 et al. [22]	–	–	–	12/126 (10)	4 (3)	8 (7)	
Fiala et al. [23]	–	–	–	2/96 (21)	ND	ND	
Kaplan et al. [51]	–	–	–	4/206 (2)	2 (1)	2 (1)	
Terzi et al. [27]	–	–	–	0/25 (0)	0	0	Only bronchosplastic procedures
Kyriss et al. [44]	–	–	–	11/111 (10)	1 (1)	8 (9)	2 recurrences unknown
Garcia-Yuste et al. [45]	–	–	–	32/661 (5)	8 (1)	24 (4)	
Rea et al. [28]	–	–	–	20/252 (8)	2 (1)	18 7)	
Bini et al. [29]	–	–	–	ND	ND	ND	Recurrence not clearly defined
Rizzardi et al. [46]	–	–	–	0/70 (0)	0	0	Sleeve & bronchoplastic procedures in TC
Ferolla et al. [47]	–	–	–	ND	ND	12	
Machuca et al. [30]	–	–	–	8/126 (6)	5 (4)	3 (2)	
Aydin et al. [31]	–	–	–	15/104 (14)	ND	ND	
Bagheri et al. [32]	–	–	–	1/40 (3)	0	1 (3)	
Dewan et al. [33]	–	–	–	1/31 (3)	ND	ND	
Wei et al. [34]	–	–	–	9/82 (11)	ND	ND	
Zhong et al. [35]	–	–	–	9/131 (7)	3 (2)	6 (5)	
Filosso '13 et al. [48]	–	–	–	36/126 (28)	8 (6)	28 (22)	
Ichiki et al. [52]	–	–	–	2/11 (18)	0	2 (18)	
Nowak et al. [36]	–	–	–	0/13 (0)	0	0	Bronchoplastic procedure without lung resection
Filosso '14 et al. [49]	–	–	–	30/106 (28)	5 (5)	25 (23)	
Jethava et al. [37]	–	–	–	3/30 (10)	2 (7)	1 (3)	
Maurizi et al. [38]	–	–	–	8/65 (12)	2 (3)	6 (9)	
Herde et al. [53]	–	–	–	4/59 (7)	1 (2)	3 (5)	
Cusumano et al. [50]	–	–	–	13/195 (7)	5 (3)	8 (4)	
Kasprzyk et al. [41]	–	–	–	15/90 (17)	7 (8)	8 (9)	
Pikin et al. [14]	–	–	–	0/25 (0)	0	0	Combined EBT & parenchyma sparing surgery
Cattoni' 18 et al [54]	–	–	–	83/409 (20)	33 (8)	50 (12)	
Cavaliere et al. [7]	0/35 (0)	0	0	–	–	–	3 operated after surgical resection and no signs of recurrence
Bertoletti et al. [4]	2/18 (11)	2 (11)	0	–	–	–	Only TC inlcuded
Lukrasz et al. [10]	1/28 (4)	ND	ND				Only TC included, 1 recurrence which was successful operated.
Fruchter et al. [9]	0/10 (0)	0	0	–	–	–	
Neyman et al. [11]	0/25 (0)	0	0	0/48 (0)	0	0	Patients received EBT or (complementary) surgery
Brokx et al. [6]	10/112 (9)	6 (5)	4 (4)	–	–	–	Patients not suitable for EBT were referred for surgery
Dalar et al. [8]	0/29 (0)	0	0	–	–	–	8 patients were operated after EBT
Boyaci et al. [5]	0/14 (0)	0	0	–	–	–	Only TC included
Reuling et al. [12]	10/125 (8)	ND	ND	3/125 (2)	ND	ND	Patients not suitable for EBT were referred for surgery

Table 4
Complications; minor[1]: non-major, major[2]: re-admission, re-operation, peri-or postoperative death. ND; not definable, - ; no results in article, ARF: acute renal failure, BPF: bronchopulmonary fistula, ChT: chylothorax, CV: cardiovascular, CVA: cerebral vascular accident, EBT: endobronchial treatment, HF: heart failure, HTX: hematothorax, LCNEC: large cell neuro endocrine tumor, LRTI: lower respiratory tract infection, PAL: prolonged air leak, PTX: pneumothorax, Pulm: pulmonic, RI: respiratory insufficiency, SCLC: small cell lung carcinoma WI: wound infection.

	Total n/total population (%)	EBT		Total n/total population (%)	Surgery		Remarks
		Minor[1] n (%)	Major[2] n (%)		Minor[1] n (%)	Major[2] n (%)	
Ducroq et al. [18]	–	–	–	19/139 (14)	19 (14)	0	9x PAL, 1x ChT, 1x cardiac arrhythmia, 6x pleural space disease & 1x empyema for which thoracostomy, 1x unknown fever,
Tastepe et al. [3]	–	–	–	6/16 (38)	6 (38)	0	Only 16 patients included, 3x sputum retention, 1x BPF, 2x granulation tissue for which bronchoscopic removal
Ferguson et al. [20]	–	–	–	ND	ND	ND	7% CV, 15% pulm, 12% other, 1 perioperative death
Ruggieri et al. [21]	–	–	–	3/18 (17)	3 (17)	0	2x PAL, 1x atelectasis
Fadel et al. [42]	–	–	–	3/30 (10)	2 (7)	1 (3)	1x bronchial stenosis for which re-operation, 1x empyema, 1x HTX
Fiala et al. [23]	–	–	–	11/96 (11)	10 (10)	1 (1)	5x atelectasis, 5x PAL, 1x BPF for which surgical intervention.
Mezzetti et al. [24]	–	–	–	9/98 (9)	9 (9)	0	4x cardiac arrhythmia & 5x LRTI
Cardillo et al. [25]				24/163 (15)	ND	ND	7x pulm, 5x CV, 8x other, 4x mixed
Terzi et al. [27]	–	–	–	0 (0)	0	0	Only bronchoplastic procedures
Kyriss et al. [44]	–	–	–	18/111 (16)	ND	ND	4x bleeding, 3x PTX, 3x HF, 1x bronchial stomp insufficiency, 7x unknown
Rea et al. [28]	–	–	–	17/252 (7)	15 (6)	2 (1)	4 PTX after chest tube removal, 4 A F, 3 PA L, 2 HTX for which blood transfusion, 2x empyema, 2x re-operations for stenosis
Bini et al. [29]	–	–	–	ND	ND	ND	
Rizzardi et al. [46]	–	–	–	1/70 (1)	ND	ND	Only bronchoplastic procedures; 1x empyema
Machuca et al. [30]	–	–	–	34/126 (27)	28 (22)	6 (5)	12x LRTI, 4 PA L, 4x WI, 4 pleural effusion (conservative treatment), 4x other minor clinical complications, 3x HTX & 1x empyema for which re-operation, 2x per-operative deaths
Aydin et al. [31]	–	–	–	17/104 (16)	ND	ND	5x LRTI, 4x PAL, 2x PTX, 2x empyema, 2x ChT, 1 arrhythmia, 1 postoperative bleeding
Bagheri et al. [32]	–	–	–	6/38 (16)	6 (16)	0	4x PAL, 2x WI; 2 patients not operated
Dewan et al. [33]	–	–	–	4/31 (13)	4 (13)	0	4x atelectasis with prolonged air leak
Zhong et al. [35]	–	–	–	13/131 (10)	10 (8)	3 (2)	4x AF, 3x PAL, 2x WI, 1 vocal cord paralysis, reoperation for 1x HTX, 1x BPF and 1x bronchial stenosis
Filosso '13 et al. [48]	–	–	–	9/126 (7)	ND	ND	1x cardiac arrhythmia, 2x LRTI, 4x RI, 1x CVA, 1x pleural effusion
Nowak et al. [36]	–	–	–	0 (0)	0	0	Only bronchoplastic procedures without lung resection
Filosso '14 et al. [49]	–	–	–	ND	ND	ND	Also included LCNEC & SCLC
Jethava et al. [37]	–	–	–	19/30 (63)	18 (60)	1 (3)	9x PAL, 4x cardiac arrhythmia, 3x PTX, 1x HF, 1x ARF, 1x bleeding for which re-operation.
Maurizi et al. [38]	–	–	–	10/65 (15)	9 (14)	1 (1)	4x PAL, 3x cardiac arrhythmia, 1x atelectasis, 1x pneumonitis, 1x bleeding for which re-operation.
Yang et al. [39]	–	–	–	6/44 (14)	6 (14)	0	2x PAL, 2x LRTI, 1x arrhythmia, 1x WI
Kasprzyk et al. [41]	–	–	–	ND	ND	ND	5x AF, 3x PAL, 3x PTX, 2x atelectasis, 2x LRTI, 1x pleural hematoma, 1x WI, 1x psychosis, 1x bleeding for which re-operation (discrepancy among complications in Table (n = 20) and text (n = 13)
Pikin et al. [14]	–	–	–	7/25 (28)	6 (24)	1 (4)	Combined approach of EBT and complementary surgery; 4x LRTI, 1x cardiac arrhythmia, 1x WI, 1x bleeding after EBT for which operation.
Cavaliere et al. [7]	7/35 (20)	ND	ND	–	–	–	7x hemorrhage which treated conservatively, 2x stenosis
Bertoletti et al. [4]	0/18 (0)	0	0				
Lukrasz et al. [10]	1/28 (4)	1 (4)	0	–	–	–	1x bleeding
Fruchter et al. [9]	ND	ND	ND	–	–	–	Only 10 patients included; only mentioned that no major complications occurred.
Neyman et al. [11]	3/25 (12)	2 (8)	1 (4)	0/48 (0)	0	0	1x not fatal fire in bronchoscope, 2x bronchial stenosis for which dilatation in EBT group.
Dalar et al. [8]	6/29 (21)	6 (21)	0	–	–	–	6x bleeding which was treated conservatively
Boyaci et al. [5]	6/14 (43)	ND	ND	–	–	–	2 arrhythmias, 1x bleeding for which local application, 1x hypoxia, 2 stenosis for which cryo-and balloon dilatation, 1x granulation tissue for which cryotherapy (discrepancy among complications in Table (n = 6) and text (n = 7)
Reuling et al. [12]	17/125 (14)	16 (13)	1 (1)				Patients not suitable for EBT were referred for surgery, 11x bleeding for which conservative treatment, 1x bronchospasm, 1x broken tooth, 1x vocal cord paralysis, 2x stricture, 1x major bleeding for which emergency operation and stricture for which balloon dilatation.

4. Discussion

This is the first systematic review evaluating both surgical -and endobronchial treatment for patients with pulmonary carcinoid tumors. Studies describing new techniques such as EBT and parenchyma sparing resection, are limited. However for selected patients, at least comparable survival, recurrence rate and complication rate can be achieved. Because of the low-grade nature of carcinoids, even incomplete endobronchial resection followed by radical surgical resection can result in good outcome 6,12. In patients with non-small cell lung carcinoma (NSCLC), parenchyma sparing resections are associated with better QOL compared to pneumonectomy [56]. Although pulmonary carcinoid tumors have a different morphology compared to other NSCLC, it is likely that parenchyma sparing resection or EBT for patients with pulmonary carcinoid also result in better QOL when compared with anatomical resections, although we could not conclude this from the included studies.

Not all patients with carcinoid located in the central airways are candidates for endobronchial treatment. Pulmonary carcinoids with extraluminal growth, larger tumor diameter, or with suspected locoregional or distant metastasis, are generally considered not suitable for EBT [12]. If curation cannot be achieved, other advantages of EBT arise, including desobstruction of the involved bronchus with ensuing resolution of post-obstructive pneumonia and limiting the extension of the subsequent surgical resection [13].

Survival is negatively affected by several prognostic factors such as tumor diameter, atypical carcinoid histology, and lymph node involvement. These prognostic factors have to be taken into account when selecting the appropriate treatment. Regarding tumor diameter, Aydin et al. described a median tumor diameter of 22.5 mm to be associated with N0 and a median tumor diameter of 33.5 mm and of 38 mm with N1 and N2, respectively [31]. Yang et al. showed that a tumor size of ≥ 3 cm outcome was significantly worse than for patients with a tumor size < 3 cm [39]. So, when EBT is selected, it is likely that patients with small tumors will benefit the most. A recent study, assessing prognostic factors for EBT in pulmonary carcinoid, showed that small intraluminal tumors of ≤ 2 cm are suitable for endobronchial resection. All other tumors should be referred for surgery [12]. Histological classification and tumor localization have shown prognostic significance in many studies. AC is associated with other poor prognostic factors such as larger diameter, peripheral location and increased incidence of lymph node involvement. Tumor localization is also important for selecting treatment, as only central carcinoids will be suitable for EBT. Although AC behaves more aggressively than TC, patients with small intraluminal AC and TC tumors and no signs of lymph node involvement might be appropriate candidates for lung parenchyma sparing procedures [6,8,12,13,27,42]. Lymph node status is also an important prognostic factor. Presence of lymph node involvement does not exclude surgical treatment because long-term survival is still possible for TC and AC treated with resection. About 90% of lymph node negative pulmonary carcinoid patients are still alive after 10 years, compared to around 50% in patients with lymph node involvement. Although lymph node involvement is rare in pulmonary carcinoid, compared to NSCLC, lymph node dissection is recommended. De Leyn et al. published the revised ESTS guidelines for preoperative mediastinal lymph node staging for non-small-cell lung cancer [57]. Whether these guidelines for pulmonary carcinoid should be applied in the diagnostic work-up for carcinoid tumors is unclear. Hilar (N1) or mediastinal (N2) lymph node involvement in pulmonary carcinoid will in most patients not change treatment, because neo-adjuvant treatment in pulmonary carcinoid has never been shown effective in increasing resectability or survival [58,59]. In addition, lymph node metastasis is rare, like it is in patients with T1 NSCLC. A growing number of T1N0 NSCLC patients are nowadays treated with stereotactic body radiation (SBRT) [60,61]. In these patients surgical lymph node staging, like in EBT for carcinoid, is lacking. The results of SBRT however, seem comparable. Therefore, small intraluminal typical and atypical tumors, without signs of extraluminal growth are good candidates for EBT, which is a less invasive treatment.

There's no consensus in duration of follow up after parenchyma saving procedures. However a recent study showed only a recurrence of 8% after a 10 year follow up in patients with pulmonary carcinoid treated with EBT [12]. Concurrent surgical salvage was uncompromised. This might suggest that annual close surveillance after 10 years might be omitted, or at least decreased in frequency. Because determination of pTNM is not possible for those patients with carcinoid tumors treated with EBT and the predominantly slow growing nature of this tumor, a close long term follow up of at least 10 years with bronchoscopy for intraluminal and CT scan with coronal and sagittal reconstruction, is advised. This to exclude recurrence and/or metastatic disease [6,12].

TC and AC have a more indolent tumor characteristic when compared with NSCLC, inclusion of pulmonary carcinoids in the TNM for NSCLC is under debate [40,54,62]. This issue was discussed by Cattoni et al [54]. They regrouped tumor stage creating a unique neuroendocrine prognostic system which might better predict survival. To date, however, pulmonary carcinoids are staged according the TNM-system for non-small cell lung cancer (NSCLC) [63]. The staging of pulmonary carcinoids may benefit from separating carcinoid tumors from other NSCLC cases because their pathologic and clinical outcomes are highly variable among different subtypes when compared with NSCLC [62].

To evaluate location, extent of the tumor and local or distant metastasis, both CT and bronchoscopy were used in included studies. Imaging techniques with FDG-PET/CT for TC are unreliable for diagnosis of carcinoid, due to low uptake of FDG [64–66]. Newer techniques using 68Gallium (68Ga) Dotatate, which is a somatostatin analogue and used as a tracer in PET-CT scanning, show promising results in diagnosing pulmonary carcinoid, with a reported diagnostic accuracy of $> 90\%$ [67–73]. However, differentiation between TC and AC is not possible with these imaging techniques, and therefore histologic biopsy remains mandatory. For central tumors, bronchoscopic biopsy results in the diagnosis in the majority of patients. In patients with a more peripheral localization, not reachable during bronchoscopy, transthoracic puncture of the lesion might help for definite diagnosis. Optimal histopathological analysis is based on morphology (mitotic index) and additional parameters such as Ki-67 labeling index, and can be challenging. Pathologists can sometimes only hint towards the diagnosis of a neuroendocrine tumor or typical and atypical carcinoid. It is important not to compromise outcome, by ruling out regional and distant microscopic spread, especially for patients who are possible candidates for EBT. With a reported negative predictive value and sensitivity of $> 80\%$ for the assessment of nodal involvement in patients with pulmonary carcinoids, a preoperative CT scan seems to be a reliable tool for excluding lymph node involvement, and is therefore mandatory in the workup for patients with pulmonary carcinoid tumors [16,43]. Endobronchial ultrasound (EBUS) is standard in the work up for centrally located NSCLC, or NSCLC with clinical suspected lymph node involvement. However, the role of EBUS in pulmonary carcinoid is unclear. Even large series examining the efficacy of EBUS in pulmonary carcinoid report no or only very rare diagnosis of carcinoid tumor [74,75].

The most important limitation of this systematic review is that no randomized trials have been performed at present, and most studies were retrospective. Therefore, results have to be interpreted with caution. For example, this review showed a lower loco-regional (0–5%) and distant recurrence (0–4%) rate in the EBT and parenchyma sparing surgery group compared to anatomical resections (0–8% and 0–23% respectively). Patients that are selected for parenchyma sparing procedures are probably "better" patients, with small carcinoid tumors and thus a lower probability of lymph node involvement. This systematic review performed a search from studies published from 1990 onward. Studies performed in the nineties were often of poor quality with a low

patient number inclusion. All included studies are classified among low or very low evidence, regarding the Grades of Recommendation, Assessment, Development and Evaluation Working Group (GRADE criteria) [76]. The low incidence of pulmonary carcinoid presents a great challenge for performing randomized controlled trials. International multicenter collaboration is necessary in order to acquire more robust data about the available treatment options and their effects on important endpoints such as overall survival, disease free survival, quality of life and cost-effectiveness. Unfortunately, EBT is currently limited to a low number of centers with sufficient expertise in interventional pulmonology. Nonetheless, it should be feasible to perform such studies within an international collaborative.

It is important to underscore that patient selection for parenchyma sparing procedures and anatomical resection should be done during multidisciplinary discussion in centralized referral centers with experienced radiologists for accurate and systematic CT scan evaluation, interventional pulmonologists familiar with endobronchial treatment, and pulmonary surgeons with experience in bronchoplastic procedures.

5. Conclusion

Tumor histology, tumor diameter and nodal status seem to be important prognostic factors for survival in patients with pulmonary carcinoid. For patients with a more favorable prognosis, tumor location and tumor diameter are important factors that can help decide on the optimal treatment strategy. The factors can help physicians to determine the optimal curative treatment strategy for their patients, while also keeping the treatment burden in mind. Centrally located small intraluminal pulmonary carcinoids, without signs of metastasis can be treated with minimally invasive alternatives such as endobronchial treatment or parenchyma sparing surgical resection. Patients with parenchyma sparing resections should be followed with a long term close clinical and radiological follow up to exclude recurrence of disease. Multidisciplinary tumor board discussion is essential in patient selection and should precede all treatments. Unfortunately, the quality of the available evidence is low and future studies should focus on prospective trials in the treatment of pulmonary carcinoid.

Disclosure

The authors declare no conflict of interest.

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Appendix A

Author	Study design	Year	Patients number	Histology TC/AC	Therapy	Follow up	Remarks
Cavaliere et al. [7]	Retrospective cohort	2002	35	35/0	YAG laser	Max 198 mths	
Bertolleti et al. [4]	Prospective cohort	2006	18	18/0	Yag laser/Cryotherapy	44.5 mths*	
Luckraz et al. [10]	Retrospective cohort	2006	28	28/0	Biopsy forceps	8.8 yrs˜	
Fruchter et al. [9]	Retrospective cohort	2009	10	10/0	Laser therapy	29 mths*	
Neyman et al. [11]	Retrospective cohort	2012	25	25/0	YAG laser	3 years *	Total population; 25 EBT & 48 surgical resection
Brokx et al. [6]	Prospective cohort	2015	112	83/29	YAG laser/cryotherapy	112 mths*	
Dalar et al. [8]	Retrospective cohort	2016	29	24/5	Diode laser/APC/cryotherapy	49 mths*	
Boyaci et al. [5]	Retrospective cohort	2017	14	14/0	APC©/YAG laser/electrosurgery/mechanical excision/cryotherapy	32 mths*	
Reuling et al. [12]	Retrospective cohort	2017	125	106/19	YAG laser, cryo- or electrosurgery, mechanical debulking	82 mths*	

Patient and study characteristics of included selected research for bronchoscopic treatment for pulmonary carcinoid; APC: Argon plasma-coagulation, AC: atypical carcinoid, EBT: endobronchial therapy. *: mean, ˜: median, TC: typical carcinoid.

Appendix B

Author	Study design	Publication year	Patients number	Histology TC/AC	Surgery conservative/ radical resection	Follow up	Remarks
Chugtai et al. [16]	Retrospective cohort	1997	84	72/12	15/69	6.8 yrs*	
Shah et al. [-17]	Retrospective cohort	1997	29	24/5	5/22	Max. 5 yrs	
Ducrocq et al. [18]	Retrospective cohort	1998	139	139/0	33/106	87 mths˜	
Tastepe et al. [3]	Retrospective cohort	1998	16	–	16/0	Max 23 yrs	Only bronchotomy procedures
El Jamal et al. [19]	Retrospective cohort	2000	95	81/14	28/43	3.9 yrs*	
Ferguson et-al. [20]	Retrospective cohort	2000	139	109/26	32/107	53.1 mths*	4 histology results were unknown
Ruggieri et al. [20]	Retrospective cohort	2000	18	13/5	3/15	Max. 10 yrs	

Fadel et al. [42]	Retrospective cohort	2002	30	25/5	30/0	64 mths*	Only sleeve resections
Filosso et al. [22]	Retrospective cohort	2002	126	82/44	26/96	99 mths*	4 surgical procedures were unknown
Fiala et al. [23]	Retrospective cohort	2003	96	77/19	40/55 (A-B)	77.8 mths*	1 patient had tracheal carcinoid for which operation could not be performed.
Kaplan et al. [51]	Retrospective Cohort	2003	206	144/62	?	75.2 mths*	
Mezzetti et al. [24]	Retrospective cohort	2003	98	88/10	23/65	–	
Cardillo et al. [25]	Retrospective cohort	2004	163	121/42	10/153	58 mths*	
Daddi et al. [26]	Retrospective cohort	2004	87	79/8	19/68	–	
Terzi et al. [27]	Retrospective cohort	2004	25	22/3	25/0	137 mths*	Only bronchopastic procedures
Divisi et al. [43]	Prospective cohort	2005	42	26/16	6/36	Max 5 yrs	
Kyriss et al. [44]	Retrospective cohort	2006	111	97/14	7/103	73.4 mths*	1 exploratory thoracotomy
Garcia et al. [45]	Retrospective & prospective cohort	2007	661	569/92	141/494	Max 5 years	Operations less than inclusion, unclear.
Rea et al. [28]	Retrospective cohort	2007	252	174/78	103/149	121 mths*	
Bini et al. [29]	Retrospective cohort	2008	54	45/9	12/42	67 mths*	
Rizzardi et al. [46]	Retrospective cohort	2008	70	70/0	70/0	14 yrs˜	Sleeve & bronchoplastic procedures in TC
Ferolla et al. [47]	Retrospective cohort	2009	123	100/23	24/99	73.8 mths (TC) 69.3 mths* (AC)	
Machuca et al. [30]	Retrospective cohort	2010	126	110/16	30/98	Max 10 years	1 patient had 3 wedge resections in 1 operation
Aydin et al. [31]	Retrospective cohort	2011	104	84/20	56/72	72 mths*	
Bagheri et al. [32]	Retrospective cohort	2011	40	36/4	8/30	9.5 yrs*	
Cao et al. [55]	Retrospective cohort	2011	186	164/22	25/173	8.0 yrs*	12 patients underwent 2 separate surgical resections
Dewan et al. [33]	Retrospective cohort	2012	31	28/3	5/26	Max 3 yrs	
Wei et al. [34]	Retrospective cohort	2011	82	60/22	33/9	135 mths*	
Zhong et al. [35]	Retrospective cohort	2012	131	106/25	42/89	87 mths*	
Filosso et al. [48]	Retrospective cohort	2013	126	83/43	18/108	60 mths˜	
Ichiki et al. [52]	Retrospective cohort	2013	11	6/5	0/11	–	
Nowak et al. [36]	Retrospective cohort	2013	13	12/1	13/0	6.3 yrs˜	Bronchoplastic procedure without lung resection
Filosso et al. [49]	Retrospective cohort	2014	106	71/35	7/99	6.5 yrs˜	
Jethava et al. [37]	Retrospective cohort	2014	30	28/2	5/25	–	
Maurizi et al. [38]	Retrospective cohort	2014	65	55/10	22/43	58 mths˜	
Herde et al. [53]	Retrospective cohort	2015	59	47/12	19/36	4.4 yrs˜	4 not operated
Neuberger et al. [13]	Retrospective cohort	2016	208	119/13	61/49	70 mths˜	Compared EBT & surgery with only surgery
Yang et al. [39]	Retrospective cohort	2017	44	32/12	11/33	59 mths*	
Cattoni et al. [40]	Retrospective cohort	2017	240	240/0	73/167	42 mths˜	
Cusumano et al. [50]	Retrospective cohort	2017	195	159/36	36 /159	75 mths˜	
Kasprzyk et al. [41]	Retrospective cohort	2017	90	69/21	9 /81	Max. 10 yrs	
Pikin et al. [14]	Retrospective cohort	2018	25	23/2	25/0	84 mths˜	Combined EBT & parenchyma sparing surgery
Cattoni et al. [54]	Retrospective cohort	2018	409	341/68	ND	51 mths	Total included patients was 510 (409 TC/AC & 101 LCNEC)

Patient and study characteristics of included selected research for surgical treatment for pulmonary carcinoid. AC: atypical carcinoid, LCNEC: large cell neuro endocrine carcinoma.*: mean, ˜: median, mths: months, -: no results in article, TC: typical carcinoid, yrs: years.

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