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Morbidity and extent of surgical resection of carcinoid tumors after endobronchial treatment

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ABSTRACT

Objectives: This study assessed whether endobronchial therapy (EBT) for bronchial carcinoid, if not curative, reduces the extent of the surgical resection and whether EBT is associated with increased surgical morbidity.
Material and methods: Analysis was performed in a cohort of patients with bronchial carcinoid who have undergone surgical resection. A group that underwent EBT before the surgery (S + EBT) was compared with a group where no EBT was performed (S-EBT). Postoperative complications were also compared between both groups.
Results: A total of 254 patients treated for a bronchial carcinoid tumor between 2003 and 2019 were screened for inclusion. A total of 65 surgically treated patients were included, of whom 41 (63%) underwent EBT prior to surgery. In 5 out of 41 patients (12%) from the S + EBT group, less parenchyma was resected versus 2 out of 24 (8%) from the S-EBT group (OR 1.528, 95% CI 0.273–8.562, $p = 1.000$). Two patients from the S + EBT group (5%) underwent lobectomy instead of sleeve lobectomy versus 0 from the S-EBT group (OR 1.051, 95% CI 0.981–1.127, $p = 0.527$). Comparing complications between the S + EBT and S-EBT group did not result in increased postoperative surgical morbidity (15% S + EBT, 24% S-EBT).
Conclusion: EBT, if not curative, does not reduce the extent of the subsequent surgical resection. Therefore, if curative EBT is not anticipated, patients should directly be referred for surgery. If curative EBT seems feasible, it should be attempted not only because surgical resection can be prevented, but also because failure of EBT is not associated with excess surgical morbidity.

Introduction

Carcinoid tumors in the lung are pulmonary neoplasms that are characterized by neuroendocrine differentiation and comprise approximately 2% of all pulmonary malignancies [1]. Carcinoid tumors are frequently located in the central airways, and are predominantly located intraluminally without invading adjacent tissues [2]. Morphological analysis allows these tumors to 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) [1]. Although the treatment of pulmonary carcinoids has evolved, surgery is considered the cornerstone of treatment for early stage disease ever since. Nevertheless, minimally invasive endobronchial treatment (EBT) has emerged as a potential alternative for intraluminal located bronchial carcinoid tumors. Recent studies report at least comparable survival, recurrence and complication rates for EBT when compared to surgery in selected patients with small (<2 cm), intraluminal carcinoid tumors [3–11].

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Abbreviation list

AC	atypical carcinoid
CT-scan	computed tomography
EBT	endobronchial treatment
S + EBT	patients pre-operatively treated with EBT
S-EBT	patients not preoperatively treated with EBT
TC	typical carcinoid

Where EBT can be curative for patients with small intraluminal carcinoid tumors, tumor debulking prior to surgery may potentially result in less lung parenchyma that has to be removed during surgery to achieve complete resection of the tumor [12]. In addition, EBT may reduce the need for sleeve resection in order to achieve radical margins when bulky tumors are removed and facilitates pre-operative bronchial imaging to assess tumor margin in the bronchial wall. However, pre-operative EBT might impair subsequent surgery by inducing inflammation and airway scarring [13].

Against this background, we aimed to identify whether EBT prior to surgery reduces the volume of resected lung parenchyma and diminishes the need for sleeve lobectomies in patients with bronchial carcinoid tumors. Also, the impact on surgical morbidity of this strategy was evaluated.

Material and Methods

A cohort of patients from 2 University Medical Centers (Amsterdam University Medical Center and Radboud University Medical Center, IRB IRB00002991) was screened for eligibility after approval of the institutional Medical Ethical Committees. Detailed information regarding patient characteristics of the cohort and EBT technique were previously described [11]. For this study, patients diagnosed with bronchial carcinoid, who had surgical resection between 2003 and 2019, were screened for inclusion. Two groups of patients were defined: patients who had prior EBT before surgery (S + EBT group), and those not preoperatively treated with EBT (S-EBT group). Baseline patient and tumor characteristics, peri- and postoperative complications, and follow-up data were collected from an existing database.

Three surgeons with at least 10 years of experience in thoracic surgery, from 3 different centers, were asked to analyze the study cohort (KH, AV, CD). Blinded for previous treatment with EBT and actual performed surgical procedure, they reviewed anonymized baseline ≤5 mm sliced Computed Tomography (CT) images together with CT- and bronchoscopy reports of patients with pathology proven pulmonary carcinoid tumors. Based on these reports and imaging, the experts were asked to make a surgical resection plan with curative intent of the carcinoid tumor. A structured form was used to capture the proposed surgical approach (open/video assisted thoracoscopic surgery (VATS)), the type of resection (wedge, segmentectomy, bilobectomy, lobectomy, sleeve lobectomy, bronchial sleeve resection, bronchotomy, pneumonectomy), nodal resection (node sampling or radical lymphadenectomy), and which lymph node station according the IASLC node map [14].

For the analysis of the impact of EBT on surgical extent, we compared the type of resection that was performed with the proposed procedure by the surgical panel. We defined parenchyma saving as 1) the resected amount of parenchyma was less than proposed by the panel, e.g. segmentectomy instead of a proposed lobectomy, lobectomy instead of a proposed bilobectomy, lobectomy instead of a proposed pneumonectomy, or bronchotomy instead of a proposed parenchyma resection, or as 2) a less extended resection than proposed, e.g. lobectomy instead of a proposed sleeve lobectomy. For a numeric expression of the preserved amount of parenchyma, the number of resected lung segments was compared with the number of segments proposed by the panel. For interobserver agreement in proposed type of surgery, 3 categories were defined: 1) full consensus; all 3 surgeons proposed the same surgical procedure, 2) near consensus; 2 out of the 3 surgeons proposed the same surgical procedure, and 3) no consensus; none of the surgeons proposed the same surgical procedure. Full and near consensus were determined as consensus and included for analysis.

Analyses

The statistical analyses and calculations were performed with SPSS 26.0 (SPSS Inc., Chicago, Illinois, USA). Data are presented as frequency and percentage for categorical variables and as mean and range for continuous variables. The $\chi 2$ and Fisher exact tests were used to compare categorical variables. To assess normal distribution, the Two-Sample Kolmogorov-Smirnov Test was used. Differences in mean values of continuous variables were analysed by the independent samples T-test. A p value less than 0.050 indicated statistical significance.

Results

Demographics

A total of 254 patients diagnosed with bronchial carcinoid tumor between 2003 and 2019 were screened for inclusion. Excluded were patients who were not operated (successfully performed EBT ($n = 71$)), unfit for surgical resection ($n = 5$), lost to follow-up ($n = 1$), suffering metastatic disease ($n = 1$), refusing surgery ($n = 2$) or whose CT imaging, radiological or bronchoscopy reports were missing ($n = 109$) (Fig. 1). A total of 65 patients operated for carcinoid tumors located in the central airway or proximal segmental bronchi were selected. Forty-one patients received preoperative EBT (S + EBT, 63%), and 24 patients were directly referred for surgery (S-EBT, 37%). Demographics and tumor characteristics are presented in Table 1. Patient and tumor characteristics were equally distributed in both groups, except for tumor histology based on pre-operative tumor sampling, with typical carcinoid accounting for 76% of patients in S + EBT compared with 38% in S-EBT group ($p = 0.002$). The surgical procedures performed in the S + EBT group included 16 (39%) lobectomies, 10 (25%) bilobectomies, 11 (27%) sleeve lobectomies, 2 (5%) bronchial sleeve and 1 (2%) segmental resections, and 1 (2%) sleeve with segmental resection. In the S-EBT group there were 10 (43%) lobectomies, 3 (13%) bilobectomies, 6 (25%) sleeve lobectomies, 1 (4%) bronchial sleeve and 4 (17%) segmental resections. In both S + EBT and S-EBT group, resection was predominantly performed via thoracotomy (85% and 71% respectively). After surgery, pathological examination revealed TC in 22 (54%) and AC in 17 (41%) patients in the S + EBT group, and 14 (58%) TC and 10 (42%) in the S-EBT group. In 2 patients (5%) with S + EBT, no residual tumor was found in the resected specimen; 1 patient (2%) was resected for atypical carcinoid, another patient was successfully treated with EBT but developed an airway stenosis on the site of EBT, for which surgical treatment was indicated. Radical resection was achieved in all but 1 patient ($n = 40$, 98%) treated with S + EBT and 22 (92%) patients who were not preoperatively treated with EBT. However, pathology results were unavailable for 2 (8%) S-EBT patients.

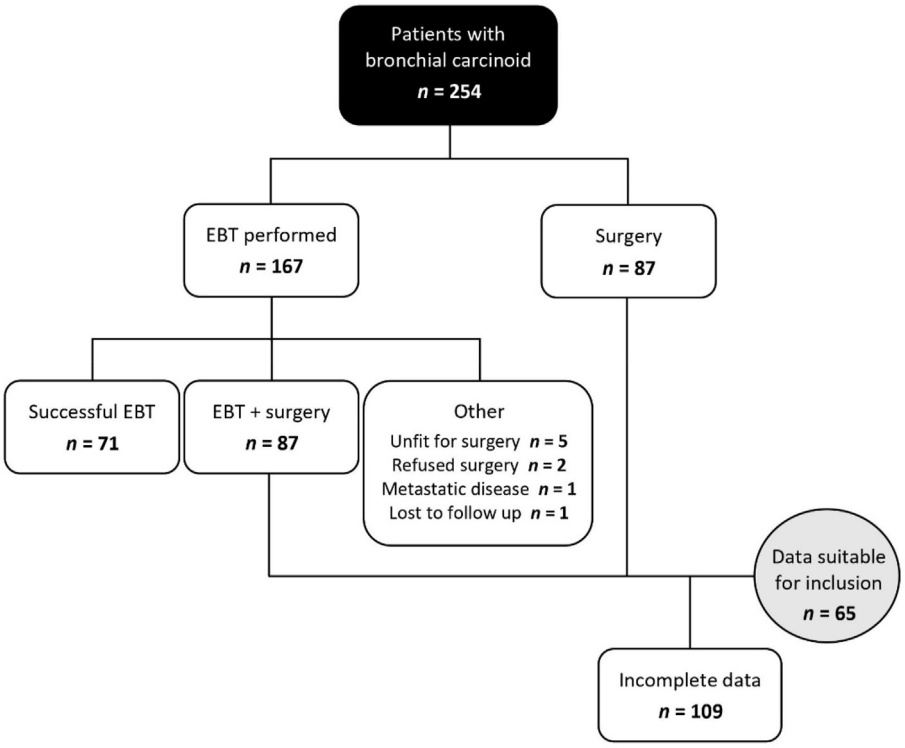

Fig. 1. Flowchart for patients surgically and non-surgically (EBT) treated for bronchial carcinoid.

Morbidity

Reported complications from the EBT procedure were bleeding (controlled during the same procedure) ($n = 5$, 12%) and bronchial stricture ($n = 2$, 5%) due to scar tissue formation on the site of EBT. Bronchial strictures were all resolved with a surgical intervention. Furthermore, mild bronchospasm ($n = 1$, 2%), bradycardia ($n = 1$, 2%) and temporary vocal cord paralysis ($n = 1$, 2%) (Table 2) were documented. The perioperative course in the S + EBT group remained uneventful in 85% ($n = 34$) of the patients, compared with 76% ($n = 18$) in the S-EBT group. After surgery, complications were mainly self-limiting, except for a lingular torsion after trisegmentectomy of the left upper lobe, urging a completion upper lobe resection and a surgical plication of the diaphragm due to phrenic nerve damage in the S-EBT group. Pre-operative EBT was not associated with a higher peri-and postoperative complication rate on univariate analysis (odds ratio [OR], 0.618; 95% confidence interval [CI], 0.180 to 2.115; $p = 0.526$).

Extent of surgery

Overall, based on pretreatment CT images and reports obtained from CT-scan and bronchoscopy, the panelists nearly or fully agreed on type of resection needed to achieve radical margins in 60 patients (92%). No consensus was found in 5 patients (8%). The panelists reached predominantly full consensus in proposed lobectomies (24/35, 71%) and sleeve lobectomies (9/11, 82%) (Fig. 2). We found 7 patients (11%) in whom less parenchyma was resected than proposed by the panel: 5 out of 41 patients (12%) from the S + EBT group and 2 out of 24 (8%) from the S-EBT group (OR 1.528, 95% CI 0.273–8.562, $p = 1.000$) (Table 3). Two patients from the S + EBT group (5%) underwent lobectomy instead of a proposed sleeve lobectomy (OR 1.051, 95% CI 0.981–1.127, $p = 0.527$). The actual procedure was in 16 cases (25%) more extensive than the procedure proposed by the panelists, with equal percentages in the S + EBT ($n = 10$, 24%) and S-EBT group ($n = 6$, 25%).

Discussion

To the best of our knowledge, this is the first study that evaluated the effect of EBT on the extent of subsequent surgery and on surgical outcome in patients with bronchial carcinoid tumors. No significant impact on the amount of resected lung parenchyma was found when S + EBT was compared with S-EBT, although it reduced the amount of resected lung segments and sleeve lobectomies needed to achieve radical resection in some patients. In addition, we found surgical morbidity equally distributed in both the S + EBT and S-EBT group, and complications were mostly self-limiting.

After adding the current findings to the existing literature, it can be postulated that the parenchyma sparing effects of EBT are mainly achieved by preventing surgical resection. Apparently, if EBT is not curative, its effects on ensuing surgical resection with regard to the volume of resected lung parenchyma are modest, considering that in only a few patients less parenchyma was resected than predicted prior to EBT by the panel of surgeons. Although not supported by the data from this study, a possible explanation for this observation is the relation between de base and shape of the carcinoid and its position in the bronchial tree. Especially a carcinoid tumor with a polypoid shape and long stalk, that extends significantly beyond an important bifurcation proximal from its base, can be a good candidate for debulking. Reduction of the tumor back into the originating bronchus can help to facilitate lobectomy instead of pneumonectomy or sleeve lobectomy. Detailed anatomical information based on CT-scan and bronchoscopy images helps to select optimal treatment. Bronchoscopy offers a clear impression of the intraluminal extension of the tumor and where it is attached to the bronchial wall, guiding the extent of resection needed to achieve radical bronchial margins [15].

Table 1
Demographics - ASA: American Society of Anesthesiologists; EBT: endobronchial treatment; VATS: video-assisted thoracoscopic surgery; S + EBT: patients pre-operatively treated with EBT; S-EBT: patients not pre-operatively treated with EBT; * clinically high suspicious for carcinoid due to positive Octreotide scan, ^3 patients: extraluminal disease and operated within 3 weeks after EBT, 1 patient: residual tumor at 4 months follow up, 1 patient: recurrence of disease 5 years after initial EBT.

Demographics	S + EBT ($n = 41$)	Percentage (%)	S-EBT ($n = 24$)	Percentage (%)	*p*-value
Patients					
- Female	28	68	17	71	**0.830**
- Male	13	32	7	29	**0.830**
Age at surgery, median in years [IQR]	48 [31-59]		56 [42-64]		**0.317**
Comorbidity					
- ASA1	23	56	8	33	**0.076**
- ASA2	13	32	12	50	**0.143**
- ASA3	5	12	4	17	**0.715**
Pre-operative tumor sampling					
- Typical	31	76	9	38	**0.002**
- Atypical	6	15	1	4	**0.246**
- No tumor	0	0	1*	4	**0.369**
- Undifferentiated	1	2	5	21	**0.023**
- Not performed	3	8	8	33	**0.014**
Number of EBT, median [IQR]	1 (1-1.5)		NA		–
Time between EBT and Surgery, median in months [IQR]	2 (0.50-4.5)		NA		–
Surgical approach					
- Open	35	85	17	71	**0.204**
- VATS	6	15	7	29	**0.204**
Surgical procedure					
- Lobectomy	16	39	10	43	**0.834**
- Bilobectomy	10	25	3	13	**0.342**
- Sleeve lobectomy	11	27	6	25	**0.871**
- Bronchial sleeve resection	2	5	1	4	**1.000**
- Sleeve with segmental resection	1	2	0	0	**1.000**
- Segmental resection	1	2	4	17	**0.058**
Pathology result after surgery					
- Typical	22	54	14	58	**0.714**
- Atypical	17	41	10	42	**0.987**
- No tumor	2	5	0	0	**0.527**
Tumor diameter					
- ≤0.5 cm	6	15	0	0	**0.077**
- >0.5-≤1 cm	7	17	3	13	**0.733**
- >1-≤2 cm	11	27	10	42	**0.217**
- >2 cm	17	41	11	45	**0.731**
Lymph node status					
- N0	36	88	22	92	**1.000**
- N1	5^	12	0	0	**0.149**
- N2	0	0	1	4	**0.369**
- Unknown	0	0	1	4	**0.369**
Resection margin					
- R0	40	98	22	92	**0.549**
- R1	1	2	0	0	**1.000**
- Unknown	0	0	2	8	**0.133**

Additionally, a diagnostic CT can support these findings, visualizes extra-luminal involvement, and is a reliable tool for excluding lymph node involvement [16,17]. Finally, although there is no clear evidence to support this, bronchoscopic debulking may improve patients' pre-operative physical condition by resolving post-obstruction pneumonia, resulting in less perioperative morbidity. Therefore, a multidisciplinary setting with surgeons, radiologists and interventional pulmonary physicians is strongly advised for accurate treatment planning in patients with carcinoid tumors.

The incidence of complications from EBT can be reduced in well trained hands of experienced interventional pulmonologists who are familiar with endobronchial treatment. Nevertheless, EBT might lead to potentially serious complications such as airway wall perforation or vascular injury [13,18,19]. We found 5 (12%) minor bleedings which could all be treated bronchoscopically with suction, topical adrenaline, xylomethazolin or a bronchial blocker. Furthermore, no airway wall perforation was seen. Clinicians might argue that EBT potentially induces strictures or stenosis of the involved bronchus and impairs subsequent surgical resection or has its impact on perioperative course. In this study, strictures ($n = 2$) did not negatively influence the extent or outcome of the subsequent surgical resection and the extra step of EBT in the S + EBT group compared with the S-EBT group did not result in increased perioperative surgical morbidity (17% S + EBT, 25% S-EBT).

The use of minimally invasive surgical techniques has increased in the last decade [20–22]. The patients in our study predominantly underwent resection via thoracotomy. This could be explained by the fact that a significant proportion of the patients were treated more than a decade ago. All VATS procedures in our study group were performed after 2008. Another explanation for the high incidence of open surgical approach is the fact that bronchial carcinoids are often located in the central airways, which makes the surgery more complex and probably less suitable for a video-assisted approach. Finally, the location of the tumor, which is sometimes situated directly after the airway junction between two

Table 2
Complications after EBT and surgery in the S + EBT and S-EBT group - * All conservatively treated, ~ conservatively treated with drainage, ∞ re-operation with lingula resection.

Complications after EBT	EBT (n = 41)	No EBT (n = 24)	OR [95% CI], p-value
No complications	31 (76%)	NA	
Any complication	10 (24%)	NA	
Bleeding*	5 (12%)	NA	
Stricture	2 (5%)	NA	
Bronchospasm	1 (2%)	NA	
Bradycardia	1 (2%)	NA	
Vocal cord paralysis	1 (2%)	NA	
Complications after surgery			
No complications	34 (83%)	18 (75%)	1.619 [0.473, 5.545], 0.526
Any complication	7 (17%)	6 (25%)	0.618 [0.180, 2.115], 0.526
Atrial fibrillation	2 (5%)	1 (4%)	
Atelectasis	1 (2%)	1 (4%)	
Pneumonia	1 (2%)	1 (4%)	
Persistent wheezing	1 (2%)	0 (0%)	
Empyemā	0 (0%)	1 (4%)	
Parapneumonic effusion	1 (2%)	0 (0%)	
Extended air leak	1 (2%)	0 (0%)	
Phrenic nerve damage	0 (0%)	1 (4%)	
Torsion of the lingula∞	0 (0%)	1 (4%)	

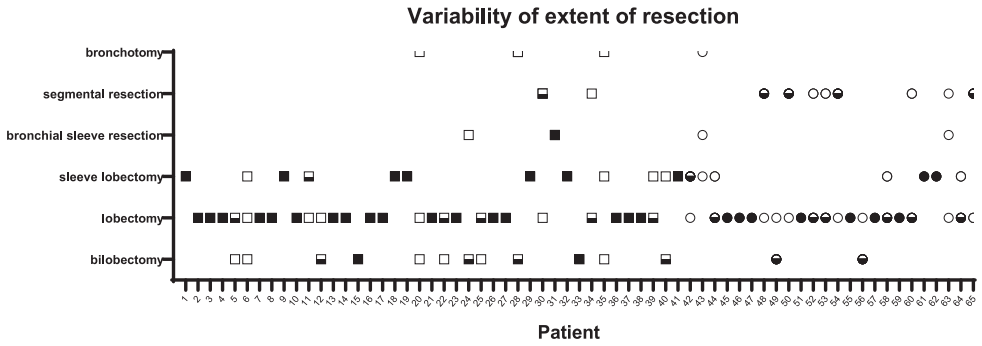

Fig. 2. Graphic representation of consensus among all experts in the S + EBT (squares) and S-EBT group (circles). One black symbol per patient corresponds to full consensus (all surgeons agreed) and three white symbols per patient indicate no consensus among surgeons. The combination of one lower half black and one white symbol per patient represents near consensus (2 out of 3 surgeons agreed).

Table 3
Differences between the S+EBT (n=41) and S-EBT (n=24) groups with regard to parenchyma sparing surgery.

	S+EBT (*n*)	Lung segments saved	S-EBT (*n*)	Lung segments saved	OR (95% CI)	*p*-value~
Less lung parenchyma resected than proposed					1.528 (0.273-8.562)	1.000
- Segmentectomy instead of lobectomy	1	4	2	2		
				1		
-Lobectomy instead of bilobectomy	2	2	0	0		
		2				
-Lobectomy instead of pneumonectomy	0	0	0	0		
-Bronchotomy instead of parenchyma resection	0	0	0	0		
-Sleeve lobectomy instead of bilobectomy						
-Bronchial sleeve instead of sleeve lobectomy	1	5	0	0		
	1	3	0	0		
Reduced extent of surgery					1.051 (0.981-1.127)	0.527
-Lobectomy instead of sleeve lobectomy	2	0	0	0		
Total	7	16	2	3	2.265 (0.430-11.916)	0.466

lobes, complicates the use of stapling devices in this area because of the width of the stapling rows. In these patients, an open approach facilitates intraluminal inspection of the airway, reassuring radical resection, e.g. through bronchoplasty or sleeve lobectomy.

The findings of the present study must be interpreted in the context of several potential limitations. First, the surgical panel was not exposed to bronchoscopy images (only bronchoscopy reports and CT images and reports). Second, complications where retrospectively assessed, which might induce recall bias as complications might be under-documented in medical files. Third, we found 24% (10/41) discrepancy between preoperative biopsy diagnosis and definitive postoperative histology. This is in line with the results of a recent study which reported that classification of carcinoids based on pre-operative biopsies is imprecise [23].

Hypothetically, atypical carcinoid is unfavorable for EBT, as they have a poorer prognosis and a higher tendency to disseminate, and should be referred for surgery without prior EBT. However, good results have been reported for patients with small, intraluminal previous atypical carcinoid treated with EBT [11]. Finally, the lung sparing effect of EBT was not significant, however the sample size of the current study is limited. The incidence of bronchial carcinoid tumors is low, and EBT is currently limited to a small number of medical centers with sufficient expertise in interventional pulmonology. A large study, within an international collaborative, would allow analysis of the impact of EBT with more power.

Conclusion

EBT, if not curative, does not reduce the extent of the subsequent surgical resection. Therefore, if curative EBT is not anticipated, patients should directly be referred for surgery. If curative EBT seems feasible (small intraluminal lesions) it should be attempted not only because surgical resection can be prevented, but also because failure of EBT is not associated with excess surgical morbidity.

CRediT authorship contribution statement

E.M.B.P. Reuling: Conceptualization, Methodology, Software, Investigation, Resources, Data curation, Writing- original data, Visualization, Project administration. **D.D. Naves:** Software, Validation, Formal analysis, Investigation, Data curation. **K.J. Hartemink:** Investigation, Writing – review & editing. **E.H.F.M. van der Heijden:** Writing – review & editing. **P.W. Plaisier:** Writing – review & editing, Funding acquisition. **A.F.T.M. Verhagen:** Investigation, Writing – review & editing. **J.M.A. Daniels:** Conceptualization, Methodology, Writing – review & editing, Supervision. **C. Dickhoff:** Conceptualization, Methodology, Investigation, Writing – review & editing, Supervision.

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ER, CD and JD were responsible for the conception and design of the study and acquisition of data. CD, KH, AV participated as surgical panel. ER and DN performed analysis and interpretation of the data. The article has been written by ER and critically revised by the authors who all gave approval for submission. Each author has participated sufficiently in the contributions of this article and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was supported by a grant of ORAS (Oncological Research Albert Schweitzer Hospital).

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