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Therapeutic bronchoscopy for malignant airway stenoses: Choice of modality and survival

ABSTRACT

Background: There are no data regarding the factors influencing the choice of therapeutic bronchoscopic modality in the management of malignant airway stenoses.

Objectives: To assess the choice of therapeutic bronchoscopy modality and analyze factors influencing survival in patients with malignant central airway obstruction.

Materials and Methods: We performed 167 procedures in 130 consecutive patients, for malignant central airway obstruction, over six years.

Results: Laser was used either alone or in combination with stent insertion in 76% procedures. Laser only was used in 53% procedures for lesions below the main bronchi. Stents alone were used for extrinsic compression or stump insufficiency. Combined laser and stent insertion was most frequently used for lesions involving the trachea plus both main bronchi or only the main bronchi. The Dumon stent was preferred in lesions of the trachea and the right bronchial tree, the Ultraflex stent for lesions on the left side and stenoses below the main bronchi. Survival was better in patients with lung cancer, lesions restricted to one lung and when laser alone was used compared to esophageal cancer, metastases and tracheal involvement.

Conclusion: The choice of different airway stents can be made based on the nature and site of the lesion. Dumon stents are suited for lesions in trachea and right main bronchus and the Ultraflex stents on the left side and stenoses beyond the main bronchi. Survival can be estimated based on the diagnosis, site of the lesion and treatment modality used.

KEY WORDS: Lung cancer, bronchoscopy, stent, laser, malignant airway stenosis

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INTRODUCTION

Endobronchial laser therapy is commonly used as a tumor de-bulking tool for malignant central airway obstruction with or without stent insertion.[1] Airway stents counteract the extrinsic pressure and reestablish airway patency immediately. Various stent types are available for palliation of both benign and malignant airway stenosis.[2-5] These modalities allow immediate relief of acute respiratory distress, successful extubation, improvement of quality of life and prolonged survival.[6,7] To our knowledge, there are no data regarding the factors influencing the choice of therapeutic bronchoscopic modality in the management of malignant airway stenoses. Advantages and disadvantages of various stent types and experience with particular stent types are often discussed in literature.[3,8-10] Selection of the stent type has often been influenced by availability of a particular stent type, the conduct of a particular study, evolution in stent technology and training in the technique of rigid bronchoscopy. Metallic stents can be inserted using flexible and rigid bronchoscopy. However, silicone stents can only be inserted using rigid bronchoscopy and, therefore, lack of training is an important factor not allowing physicians to consider the Dumon stent. According to a survey of the American Association for bronchology, only 27% of the respondents were trained in rigid bronchoscopy and less than 5% of respondents had on the job training.[11] The actual numbers might be lower as there was only a 30% response rate for this survey and a likely selection bias.[11]

Bronchoscopic laser, silicone and metallic stents are available at our institution. The choice of treatment modality was guided by patient factors and not influenced by training or availability of a stent type. Therefore, we undertook this retrospective study to analyze factors that have led us to choose the therapeutic bronchoscopic modality in our set up. The aims of this study were to assess the patient factors which have influenced the choice of interventional modality and to analyze the factors influencing survival in patients undergoing

therapeutic bronchoscopy for malignant central airway obstruction.

MATERIALS AND METHODS

All consecutive patients who underwent therapeutic bronchoscopy for the treatment of malignant central airway obstruction over last six years were included. Clinical data were retrospectively obtained from medical records. Follow-up information was obtained from the medical records or contact (letter and/or telephone) with the referring physicians or general practitioners. Patients with benign lesions were excluded from the analysis. The "nature of lesion" was classified either as extrinsic, intrinsic (endoluminal and/or sub mucosal) or combined extrinsic and intrinsic. This study was approved by the Ethikkommision Beider Basel.

Rigid bronchoscopy (Efer-Dumon, Karl Storz Optics; Germany) was performed under general anesthesia in the operating room. Laser ablation (Deka Medical Electronic Associates, Italy) was performed either through the rigid bronchoscope or via the flexible bronchoscope inserted in the rigid bronchoscope. Argon plasma was used in five patients when laser was not available. As laser and argon plasma are both de-bulking tools, they were grouped together under laser for the purposes of analysis. The Dumon (Novatach, France), Polyflex (Ruesch AG, Kernen-Rommelshausen, Germany) and the Dynamic Y stents (Ruesch, Germany) were inserted using dedicated equipment as described elsewhere.[2,12,13] Ultraflex stent (Boston Scientific, Galway, Ireland) insertion was done by passing the catheter delivery system via the rigid bronchoscope past the lesion. The Ultraflex stent was then deployed under vision or fluoroscopy guidance (two patients).[10,14] Laser therapy was used in case of intrinsic lesions. Coring of the tumor with the tip of the rigid bronchoscope was typically employed to de-bulk the tumor after laser application. Stents were placed in the presence of extrinsic compression and combined extrinsic compression and intrinsic lesions. Stent insertion was also undertaken in patients with intrinsic lesions when there was significant airway obstruction (more than 50% of the lumen) after laser therapy or significant involvement of the airway wall. These principles were uniformly used by both bronchoscopists in the unit.

Statistical analysis was done with SPSS (SPSS Inc, Version 12). Lung function data are presented as median and interquartile range. Other data are presented as median (95% confidence interval). The Chi-square test was used to assess significance for factors affecting the choice of treatment modality. Kaplan Meier log rank analysis was performed to examine the following factors for survival: gender, underlying disease, nature of lesion, site of lesion, bronchoscopic treatment modality, chemotherapy and radiotherapy. Factors which were significant in using this analysis and age were then analyzed using the Cox regression model applying backward stepwise logistic regression. A *P*-value of less than 0.05 was considered statistically significant.

RESULTS

Overall, 182 therapeutic bronchoscopy procedures were performed in 140 patients. Eleven procedures (10 patients) were performed for benign lesions and four stent extraction procedures were excluded from analysis. Therefore, 167 procedures were analyzed in 130 patients with malignant central airway obstruction (male : female 88:42; median age was 63 years). Overall, laser therapy was used in 127 procedures in 98 patients and stents were placed during 105 procedures in 93 patients. Laser therapy as the only therapeutic modality was used during 62 out of 167 (37%) procedures; only stent insertion was undertaken in 40 out of 167 (24%) procedures and combined laser followed by stent insertion were performed in 65 out of 167 (39%) procedures. In total, 15 Y-stents and 93 tube stents (Dumon 34, Polyflex 13, Ultraflex 46) were placed. In three patients, two stents were inserted in one procedure and, therefore, a total of 108 stents were inserted. For the purpose of analysis of site, nature of lesion and underlying disease, these additional stents were considered as a "procedure" and, therefore, for selected analysis there are 170 procedures.

The diagnoses were lung cancer in 103 out of 167 (62%) procedures, esophageal cancer in nine out of 167 (5%) and pulmonary metastases in 55 out of 167 (33%). In 26 (16%) procedures the lesions were limited only to the trachea; in 20 (12%) to the trachea plus either or both the main bronchi; in 52 (31%) to the left bronchial system; in 68 (41%) to the right bronchial system and in one procedure the left as well as the right bronchial system were involved. One hundred one procedures (61%) were performed for intrinsic lesions, 10 (6%) for extrinsic lesions and 49 (29%) for combined intrinsic and extrinsic lesions. Two procedures were performed for treatment of stump insufficiency after pneumonectomy and five for treatment of an esophageal tracheobronchial fistula (grouped together as airway insufficiency).

There was no significant year effect for the treatment modality (laser, stent or both) and the underlying disease as well as the nature of the lesion. There was a significant association with the use of stent alone for esophageal cancer involving the trachea or bronchi ($P = 0.001$) [Figure 1]. There was no significant difference between the use of a specific stent type and underlying disease ($P = 0.19$). Laser was used either alone or in combination with stent insertion whenever there was an intrinsic component of airway obstruction [Figure 2a]. There was also a significant association with the use of stent alone for extrinsic compression and airway insufficiency ($P < 0.0001$) [Figure 2a]. For intrinsic lesions, the Dumon and Ultraflex stents were similarly used, whereas the Ultraflex stent was most commonly used for combined intrinsic and extrinsic lesions and only extrinsic lesions [Figure 2b]. There was a significant association between the treatment modality and the site of the lesion [Figure 3a] ($P < 0.0001$). Stent insertion alone was most commonly used for lesions involving the

trachea plus either of the main bronchi and only the trachea. The use of laser alone was significantly influenced by the presence of lesions below the main bronchi. Combined laser and stent insertion were most frequently used for lesions involving the trachea plus both main bronchi or only the main bronchi. There was a significant association between the stent type used (irrespective of laser use) and the site of lesion [Figure 3b] ($P = 0.0003$). The Dumon stent was most commonly used in the trachea and the right bronchial tree, whereas the Ultraflex stent was most often used for lesions on the left side. For lesions involving the trachea and both the main bronchi, Y stents were used (Dumon 9, Polyflex 3, Dynamic 3).

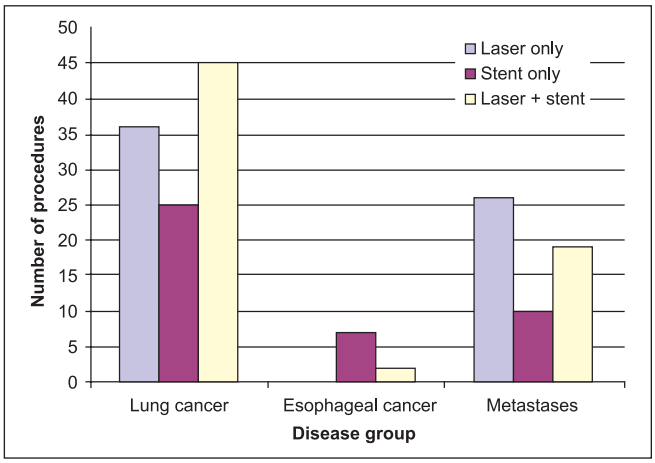

Figure 1: Treatment modality based on the underlying disease

Overall, complications were observed in 33% (43 out of 130) patients. Complications following stent insertion were observed in more than 50% of patients with the Polyflex stent [Table 1]. Malignant stent restenosis due to tumor progression was the most common complication noted with Polyflex stent (31%) followed by the Ultraflex stent (20%). In addition, one patient with esophageal cancer, who was treated with laser and insertion of Dumon stent in the trachea, developed an esophago-tracheal fistula at the distal end of the stent. Ventricular arrhythmias during stent insertion (non-fatal), severe cough after a Polyflex stent insertion in the trachea (stent removed) and acute laryngospasm were noted in one

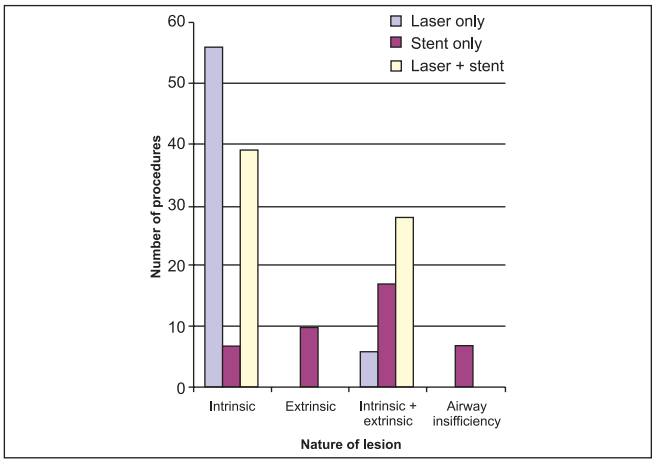

Figure 2a: Treatment modality based on nature of lesion

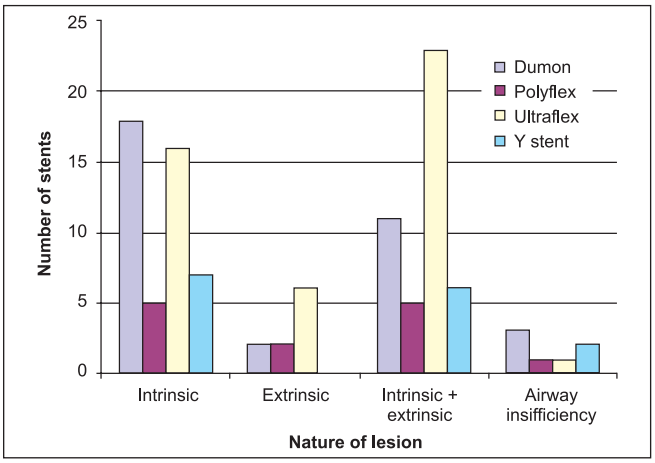

Figure 2b: Stent type based on nature of lesion

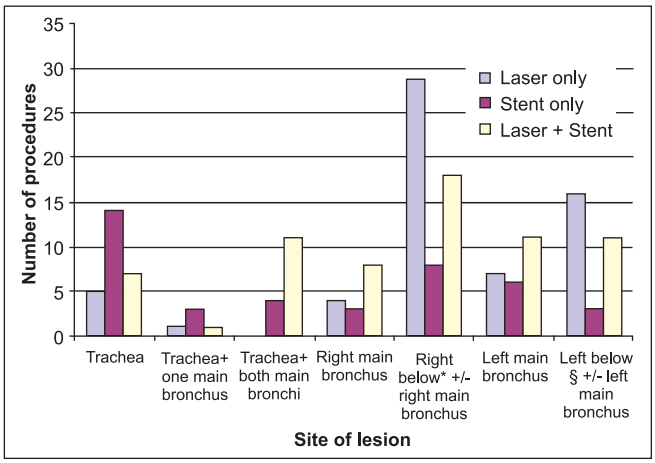

Figure 3a: Treatment modality based on the site of lesion, *Below right main bronchus, §Below left main bronchus

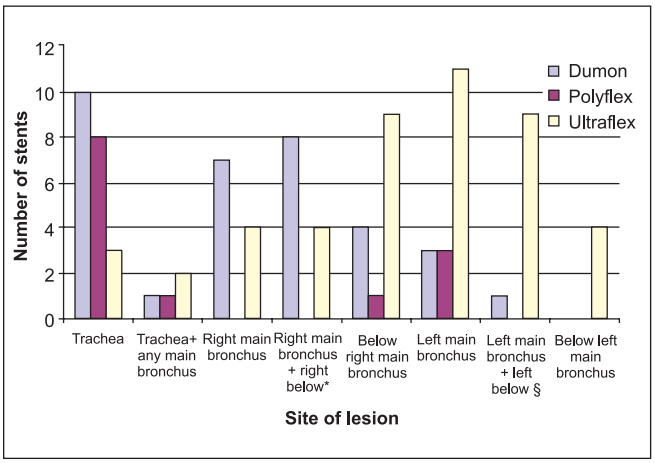

Figure 3b: Stent type based on the site of lesion, *Below right main bronchus, §Below left main bronchus

patient each. Death within 24 hours of intervention occurred in three patients (2%) due to infection, pericardial effusion and respiratory failure (one patient each).

For tumor progression, six Dumon stents were replaced either by a Y-stent (n = 4) or a larger Dumon stent (n = 2), and one Polyflex by another larger Polyflex stent. A Dumon stent which insufficiently covered the tracheo-esophageal fistula was replaced by a larger Ultraflex stent. Of the three Dumon stents which migrated, one was replaced by a larger diameter stent and two were extracted and not replaced due to adequate lumen following tumor shrinkage as result of chemotherapy and radiotherapy. An Ultraflex stent as well as a Polyflex stent, which migrated, were not extracted as their position was not causing airway obstruction and patients were pre-terminal due to tumor progression. Mucus plugging was treated with flexible bronchoscopy and nebulized saline or a bronchodilator. Significant granulation tissue obstructing the airways or leading to retention of secretions was treated either with excision forceps biopsy or laser via flexible bronchoscopy. Hemoptysis occurred in eight patients during the clinical course.

Both pre and post-intervention spirometry were available in 87 patients. The median pre-treatment FEV1% predicted was 62% (49 to 72%) and post-treatment FEV1% predicted was 62% (50 to 76%). The median pre-treatment FVC% was 68% (55 to 78%) and post-treatment FVC% was 69% (57 to 81%).

Out of the 130 patients included in the study, 17 were still alive at the time of analysis. Factors significantly influencing survival using Kaplan Meier log rank analysis were underlying disease, site of lesion, nature of lesion and treatment modality [Table 2]. Multivariate analysis using a Cox regression model revealed underlying disease, site of lesion and treatment modality as being independent predictors of survival. The Kaplan Meier estimates for survival for these factors are plotted in Figures 4a-c.

Table 1: Complications associated with stent insertion

Complication	Dumon (%) n=34	Polyflex (%) n=13	Ultraflex (%) n=46	Y stent (%) n=15	Total (%) n=108
Malignant stent restenosis	6 (18)	4 (31)	9 (20)	2 (13)	21 (19)
Mucus plugging	1 (3)	2 (15)	3 (7)	2 (13)	8 (7)
Stent migration	3 (9)	1 (8)	1 (2)	0	5 (5)
Granulation tissue	2 (6)	0	0	1 (7)	3 (3)
Total	12 (35)	7 (54)	13 (28)	5 (33)	37 (34)

DISCUSSION

The primary indication for bronchoscopic laser resection is relief of central airway obstruction.[15,16] The common indications for airway stent insertion in malignant disease are intrinsic lesions, extrinsic compression, complex strictures and central airway fistulae.[15,16] There are no clear data about factors such as disease type or site of lesion which may influence the use of a single or combined modality in the treatment of intrinsic lesions. A prospective trial comparing various interventional modalities is desirable but is likely to be very difficult because of the differences in the handling and training of the silicone stents compared to self expanding metallic stents. The findings of our study show that laser only is sufficient in almost half of the patients who have pulmonary metastasis (excluding esophageal cancer). Laser only was also used on more than half of the occasions in case of malignant airway involvement below both the main bronchi either alone or with multiple segment involvement including the main bronchi. Stent insertion alone was used in all patients with

Table 2: Factors influencing survival following therapeutic bronchoscopy for malignant central airway obstruction

Factor	Survival			*P* value	
	Median months (95% C.I.)*	3 month %	6 month %	Univariate analysis	Multivariate analysis
Underlying disease				0.02	0.003
Lung cancer	5.5 (3.3 – 7.8)	61	45		
Metastases	3.0 (2 – 3.9)	49	33		
Esophageal cancer	2.5 (0 – 6.8)	29	14		
Site of lesion				0.0009	0.028
Trachea	1.8 (0.5 – 3.1)	36	27		
Trachea + left main bronchus + right main bronchus	1.6 (0.3 – 2.9)	27	20		
Left side	4.8 (0.5 – 9.2)	60	46		
Right side	4.7 (2.7 – 6.8)	67	45		
Nature of lesion				0.009	0.217
Intrinsic	5.7 (3.6 – 7.9)	67	48		
Extrinsic	2.4 (.18 – 4.62)	40	27		
Combined intrinsic and extrinsic	2.3 (1.4 – 3.1)	41	27		
Treatment modality				0.0004	0.001
Laser only	10.4 (4.9 – 16)	73	58		
Stent only	2.7 (1.4 – 4)	46	31		
Laser and Stent	3.0 (2 – 4)	48	31		

* C.I. = 95% Confidence Intervals

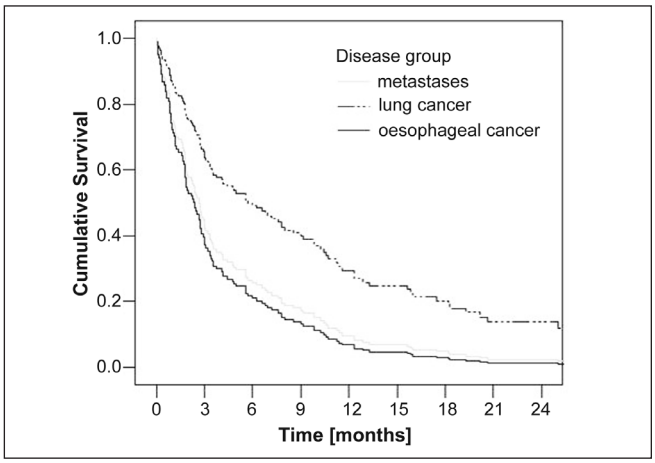

Figure 4a: Kaplan Meier estimates of survival based on the disease group

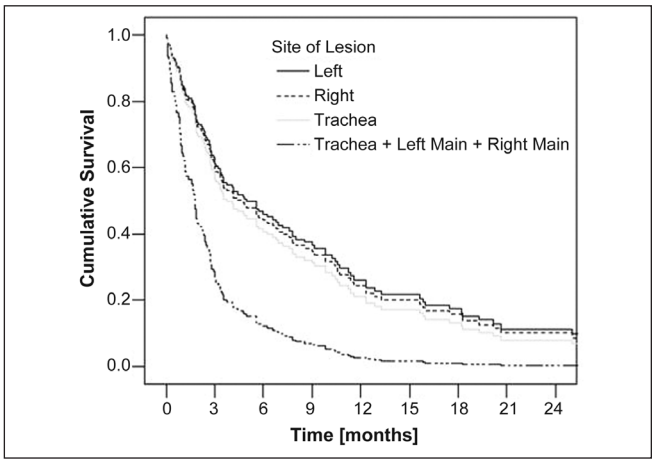

Figure 4b: Kaplan Meier estimates of survival based on site of lesion

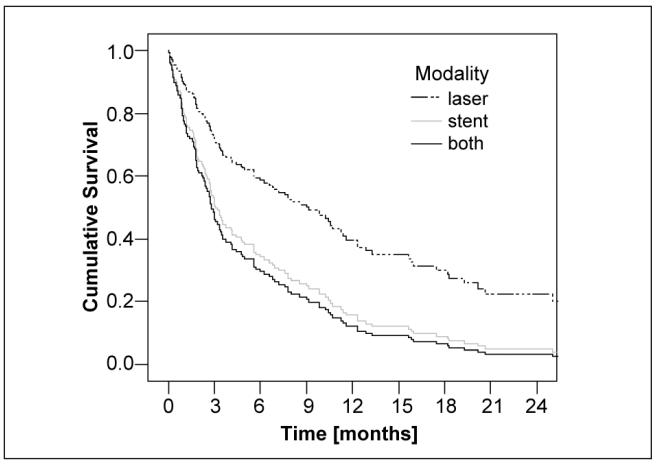

Figure 4c: Kaplan Meier estimates of survival curve based on the treatment modality

extrinsic compression, more than three quarters of cases who had airway problems associated with esophageal cancer and in more than half cases with tracheal disease or tracheal disease involving a main bronchus. Combined laser and stent insertion was used in more than 75% cases when there was tracheal disease, which involved both the main bronchi and in half the patients with lesions restricted to the main bronchi. The findings of our study show that the use of a single or combined interventional modality in the treatment of malignant central airway obstruction is influenced by the underlying disease, nature of the lesion and the site of the lesion.

In our study, the Dumon stent was chosen for more than half of the interventions in the trachea and the right main bronchus with or without involvement of the lower bronchi. The Ultraflex stent was used for left sided stent placement in 80% of occasions and for lesions restricted below the right main bronchus for more than 60% occasions. We attribute this to the favorable anatomy of the trachea and the right bronchial tree, which permits easier placement of the Dumon stent, compared to the left side, whereas, the Ultraflex stent delivery system can be easily guided in the left bronchial tree. If there is no angulation or diameter change then either stent can be used. However, if there is angulation or change in diameter metallic stents are preferred. The airway lumen is more tapering and often more irregular for lesions located below the main bronchi. Hence the Ultraflex stent is better suited in such situations as it is relatively thin walled compared to the Dumon stent. The Ultraflex stent is able to adapt more easily to the changing caliber of the airway. On the other hand, the Dumon silicone stent is not best suited for such lesions as it is more rigid and does not have a favorable wall to lumen ratio. One might argue that the Ultraflex stent can be placed in all areas where the Dumon stent was placed. However, Dumon stents are much cheaper than the Ultraflex stents. Hence, in a clinical set-up where both the stent types are available for use, the Dumon stent seems to be the choice for lesions in the trachea, right main bronchus and the Ultraflex stent for lesions on the left side and those located below the right main bronchus. Furthermore, the radial expansile force of the Ultraflex stents makes it the preferred choice for extrinsic lesions or combined intrinsic and extrinsic lesions.

The complications associated with stent placement include re-obstruction by tumor, granuloma formation at stent extremity, mucous plugging and stent migration and with laser include perforation of airway wall and fire.[15,16] There were no specific complications associated with the use of laser. Stent associated complications were observed in one third of patients [Table 1]. Complications were seen in more than 50% patients with the Polyflex stent and hence have led to caution in its use. The Dumon stent or covered stents have been preferred over uncovered stents as they might offer a barrier for tumor progression in to the airway-stent lumen. However, as also observed in our study tumor progression might occur proximal or distal to the stent and might need to be treated with laser de-bulking, insertion of an additional stent or stent replacement with a larger stent. Stent migration often occurs

due to stent under-sizing or shrinkage of tumor following chemotherapy and/or radiotherapy. In such situations, stents may be replaced, extracted or considered to be left *in situ* alone in selected pre-terminal patients if they do not obstruct a functional airway.

The Cox regression analysis shows that the underlying disease, site of lesion and the treatment modality are independent predictors of survival. Patients with esophageal cancer with airway involvement had the worst prognosis, probably due to the extensive degree of disease compared to patients with lung cancer or pulmonary metastases. Patients with tracheal disease with involvement of the main bronchi had the worst prognosis with 75% of patients in this group being treated with Y stents. The worse prognosis of patients with tracheal disease with or without involvement of the main bronchi is perhaps as a result of more severe disease compared to having disease restricted to one lung. Overall, patients in whom laser therapy was used as the only treatment modality had a better survival compared to those in whom stent was placed with or without the concomitant use of laser. In our set up, stent insertion was undertaken mostly in patients with extrinsic compression with or without intrinsic lesions, whereas only laser therapy was used in patients with intrinsic lesions in whom adequate re-canalization (more than 50% of the lumen) could be obtained without the need for stent insertion to support the airway wall. Thus, patients who needed only laser therapy probably had less severe airway obstruction or lesions suited for treatment with only laser therapy (e.g. polypoid lesions).

To summarize, the choice of different airway stents can be made based on the nature and site of the lesion. Dumon stents are suited for lesions in trachea and right main bronchus and the Ultraflex stents on the left side and stenoses beyond the main bronchi. Based on our model, we estimate that patients with lung cancer, in whom malignant airway obstruction is restricted to only one lung and in whom only laser therapy suffices, have a better prognosis compared to other patients with malignant airway obstruction who are treated with stent insertion, have tracheal involvement or esophageal cancer or pulmonary metastases.

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