Silicone Stent Versus Fully Covered Metallic Stent in Malignant Central Airway Stenosis

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Background. **Airway stenting to restore airway patency in cases of malignant central airway obstruction is an effective palliation treatment. Our goal was to compare the efficacy after deployment and complications of a fully covered self-expandable metal stent (SEMS) (Aerstent) and a silicone stent (Dumon).**

Methods. **This was a retrospective cohort of 2 similar groups of patients with malignant central airway obstruction treated with stents between August 2012 and July 2017. Complications were assessed bronchoscopically. A competing risk for death analysis was performed to adjust the probability of developing a complication.**

Results. **Seventy patients (29 with silicone stents and 41 with SEMS) were included. Stent insertion was successful in all cases. Mucus retention was the most frequent complication (75.9% with silicone stents and 84.8% with SEMS; $P = .51$), followed by granulation tissue (51.7% with silicone stents and 41.3% with SEMS; $P = .52$) and migration (6.9% with silicone stents and 13.0% with SEMS; $P = .47$). In the first month, the cumulative incidence of a complication was 36.7% for silicone stents and 41.3% for SEMS and increased to 90.0% and 97.8% after 6 months, respectively (hazard ratio = 1.66; $P = .04$). A competing risk for death analysis showed an adjusted hazard ratio of 1.41 ($P = .49$) indicating no differences in overall complications between stents.**

Conclusions. **Both stents were equally successful and safe. The incidence of complications increased over time to 90% at 6 months for both stents. The risk of overall complications was higher for SEMS; nevertheless, when mortality was measured in a competitive risk analysis, no differences were found between SEMS and silicone stents.**

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Airway stenting is an effective treatment for symptom palliation in patients with malignant central airway obstruction (CAO) who are not candidates for surgery.[1] The restoration of airway patency is associated with marked improvements in symptoms,[2,3] quality of life,[4,5] and survival.[6-8] However, these benefits are undermined by long-term complications described for all commercialized stents.[9] The Dumon silicone stent (Novatech, Bess, Inc, Berlin, Germany) was introduced 30 years ago and is considered the reference standard.[10,11] Since then, only 2 studies have been published comparing different types of stents in malignant CAO.[12,13] In 1 study, the authors compared 2 uncovered metal stents (Accuflex and Strecker, Boston Scientific Corp, Boston, MA).[12] In another study, Dumon stents were compared with 2 different types of metallic stents: partially covered and fully covered self-expandable metal stents (SEMS) (Ultraflex, Boston Scientific; and Aero, Merit Endotek, South Jordan, UT).[13] However, the compared groups were not clinically similar in any of these articles and the probability of complications was not adjusted by

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mortality; therefore, accurate conclusions could not be reached. The aim of the current study was to compare effectiveness after deployment and complications accounting for the mortality of Dumon stents and Aerstent (Leufen Medical GmbH, Bess Group Company, Berlin, Germany), a recently launched, fully covered SEMS, in patients with malignant CAO.

Material and Methods

Study Design

We performed a retrospective review limited to the 5 years after the introduction of Aerstent in our practice in 2012. Consecutive patients with malignant CAO treated with Dumon or Aerstent stents at the Interventional Pulmonology Unit of Bellvitge Universitary Hospital between August 2012 and July 2017 were included. All patients were symptomatic, and surgical treatment had already been decided against by a multidisciplinary lung cancer team. Both stents were used indistinguishably by an experienced team. However, Aerstent was generally preferred for these situations: conical stenoses, smaller airway lumen (diameters between 9 and 11 mm, assessed by the 10-mm outer diameter of Efer-Dumon bronchial rigid scopes), and stenoses involving only bronchus intermedius. Aerstent was preferred as well in sicker patients with longer stenoses (more than 3 cm) that required major resection, because these patients could not tolerate long procedures.

Patients with benign stenoses, benign tumors, or fistula were excluded. Medical records, radiological files, and endoscopy images were reviewed. Two groups were compared: patients with Dumon stents and those with Aerstent stents. Analysis of stent complications was restricted to patients with at least 1 follow-up bronchoscopy performed at our Institution. The study was approved by the institutional review board (Clinical Research Ethics Committee at Bellvitge Universitary Hospital, Act PR012/19).

Methods

Both types of stents were placed with a rigid bronchoscope (Dumon-Efer, La Ciotat, France) under general anesthesia, using mechanical ventilation. Aerstent stents were deployed under direct fluoroscopic guidance. All patients received prophylactic antibiotics and steroids. A chest x-ray (CXR) was performed after the procedure. Twice-daily saline nebulizations were prescribed as home treatment and a follow-up flexible bronchoscopy was scheduled a month after stent deployment. Further bronchoscopy follow-up was planned at 3 and 6 months unless a medical complication was suspected in the interim. In the event of stent-related complications that could not be treated, or for patients with disease regression, the Dumon and Aerstent stents were removed under rigid bronchoscopy. The preestablished time frame for Dumon stent exchange was 2 years.

Definitions

The stent deployment was considered efficient if at least 80% of the lumen of the airway was restored. Complications were determined bronchoscopically in stable or symptomatic patients, in line with our internal protocol, given the lack of international standardized criteria. Complications included mucus retention, granulation tissue formation, migration and deterioration of stent integrity.

Mucus retention was considered to be any kind and volume of secretions attached to the stent. To classify the degree of mucus retention, we estimated first the degree of obstruction and then the maneuvers required for its removal. Mucus retention was classified as: (1) mild: wet secretions causing no obstruction and easily cleaned with saline and suction; (2) moderate: predominantly dry secretions causing partial obstruction, requiring a mucolytic agent or warm saline, as well as mechanical removal using other devices in addition to suction (for instance, the tip of the bronchoscope or biopsy forceps); or (3) severe: nearly complete or complete obstruction with thick, solid secretions requiring mechanical removal with the tip of the rigid bronchoscope and rigid suction catheters.

Granuloma tissue formation consisted of any inflammatory tissue obstructing the proximal or distal stent lumen. Migration was considered to exist whenever there was a stent displacement of at least 5 mm in relation to the previous location, assessed by pictures or video recording. Stent disruption was defined as any change in the structure of a metal stent affecting the silicone coating or metal mesh. We did not encounter stent perforation.

Statistical Analysis

Baseline characteristics of included patients are described using mean and SD for continuous variables and frequencies for categorical variables. Differences between groups were assessed by chi-square test and t test, attending to type and variable distribution. Main outcomes were incident complications after stent insertion or death. Time to event was measured from the date of stent insertion until the first complication, death, loss to follow-up, or stent removal, whichever came first. Study groups were compared raw and adjusted, using a Cox proportional hazard regression model and expressed with hazard ratios (HR). Clinically relevant covariates such as age, sex, smoking status, histology, and disease stage were used as adjustment factors. Finally, a Fine and Gray[14] regression model was used to analyze the time to event, counting death as a competing risk and expressed with sub-HR. The proportional hazard assumption of Cox models was tested graphically and analytically. The statistical significance level was set at P less than .05. Statistical analyses were carried out using the R software package (version 3.4.0 for Windows, R Foundation, Vienna, Austria).

Table 1. Clinical Characteristics of Patients at Stent Insertion and Those With Follow-up, Grouped by Type of Stent (Dumon and Aerstent)

Variable	Total Patients (n = 92)			Patients With Follow-up (n = 70)		
	Dumon (n = 38)	Aerstent (n = 54)	P[a]	Dumon (n = 29)	Aerstent (n = 41)	P[a]
Age, y (mean [SD])	64.1 (11.7)	60.2 (10.5)	.11	64.6 (11.9)	60.0 (10.4)	.10
Sex, n (%)						
Male	36 (94.7)	38 (70.4)	.01	27 (93.1)	29 (70.7)	.05
Smoking status, n (%)			.42			.34
Smoker and exsmoker	34 (89.5)	45 (83.3)		26 (89.7)	33 (80.4)	
Never smoker	4 (10.5)	9 (16.7)		3 (10.3)	8 (19.5)	
Lung cancer, n (%)	27 (71.1)	43 (79.6)	.48	22 (75.9)	30 (73.2)	.99
Histology, n (%)			.64			.39
Squamous cell	15 (55.5)	21 (48.8)		13 (61.9)	14 (46.7)	
Adenocarcinoma	5 (18.5)	10 (23.3)		4 (19.0)	6 (20.0)	
Small-cell lung cancer	1 (3.7)	5 (11.6)		0	4 (13.3)	
Non-small cell lung cancer	5 (18.5)	5 (11.6)		3 (14.3)	5 (16.7)	
Adenoid cystic carcinoma	0	1 (2.33)		0	1 (3.33)	
Atypical carcinoid	0	1 (2.33)		0	0	
Neuroendocrine cancer	1 (3.7)	0		1 (4.76)	0	
Stage, n (%)[b]			.50			.61
IIIA-IIIB	14 (58.3)	18 (46.2)		12 (60.0)	14 (48.3)	
IV	10 (41.7)	21 (53.8)		8 (40.0)	15 (51.7)	
Non-lung cancer malignancies, n (%)	11 (28.9)	11 (30.4)	.48	7 (24.1)	11 (26.84)	.99
Stent deployed at time of initial diagnosis of cancer, n (%)	24 (64.9)	25 (46.3)	.13	18 (62.1)	18 (43.9)	.21
Chemotherapy and/or radiotherapy treatment received after stent placement, n (%)	29 (78.4)	39 (72.2)	.68	25 (86.2)	32 (78.0)	.58

[a]All tests were chi-square except for age, for which a *t* test was performed; [b]7th TNM Classification of Malignant Tumors.

Results

Between August 2012 and July 2017, 157 stents were deployed in 140 patients. We placed 54 stents in 48 patients to treat fistulas or benign CAO and excluded them from the study. A total of 92 patients with malignant CAO were included; 22 patients did not undergo at least 1 follow-up bronchoscopy, and therefore only survival data could be recorded for them. The remaining 70 patients, accounting for 75 stents, were included in the complications analysis. This group was similar to the initial study group (Table 1).

Stent insertion achieved at least 80% of free lumen of the airways in all patients, as confirmed endoscopically and by postprocedure chest x-ray. There were no major procedure-related complications during deployment or in the following 24 hours. Two patients in the Dumon group and 9 in the Aerstent group were treated with more than 1 stent. Table 1 lists the clinical characteristics of patients in both groups; Table 2 describes the stent shape and location. Patients' clinical profiles were comparable between study groups except for sex distribution (there was a predominance of Aerstent in women). With regard to location, more Dumon stents were placed in the trachea and more Aerstent in bronchus intermedius. The percentage of type of stent favored Dumon for bifurcated stent (45% vs 27% for Aerstent); however, this difference was not statistically significant.

Stent Removal

A total of 7 of 29 Dumon stents (24.1%) and 11 of 46 Aerstent stents (23.9%) were removed during follow-up, equivalent to removal rates of 4.4 (95% confidence interval [CI], 1.8-9.1) and 6.5 (95% CI, 3.2-11.6) per 100 person-month, respectively ($P = .54$). Four of 7 patients in the Dumon group and 6 of 11 patients in the Aerstent group had the stent removed because of disease regression after other treatments. The other 8 patients had the stent removed because of recurrent severe mucus retention and infection or migration. None of the long-time surviving patients reached the preestablished time frame for Dumon stent exchange.

Complications Analysis

Overall, a median of 2 flexible bronchoscopies (interquartile range, 1:4) were performed during follow-up. Table 3 presents cumulative incidence complications and median time to complications by stent type. Cumulative incidence curves over time, per stent and complication, are shown in Figure 1. One month after stent insertion, the probability of any first complication was

Table 2. Location and Number of Stents Deployed

Variable	Total Number of Stents (n = 103)			Stents With Follow-up (n = 75)		
	Dumon (n = 40)	Aerstent (n = 63)	P^a	Dumon (n = 29)	Aerstent (n = 46)	P^a
Type of stent, n (%)			.095			.06
Straight	22 (55.0)	46 (73.0)		16 (55.2)	36 (78.3)	
Y (tracheobronchial)	18 (45.0)	17 (27.0)		13 (44.8)	10 (21.7)	
Location of straight stents, n (%)			<.001			.014
Bronchus intermedius	5 (22.7)	7 (15.2)		5 (31.2)	6 (16.7)	
Left main bronchus	4 (18.2)	5 (10.9)		4 (25.0)	5 (13.9)	
Right main bronchus and bronchus intermedius	1 (4.55)	26 (56.5)		1 (6.25)	18 (50.0)	
Trachea	12 (54.5)	8 (17.4)		6 (37.5)	7 (19.4)	

[a]All tests were chi-square. Data are shown as n (%).

37.9% for the Dumon stent and 41.3% for the Aerstent stent. The cumulative incidence of silicone detachment or perforation for the Aerstent stent was 0% in the first month, 13.2% at 3 months, and 44.8% at 6 months. No stent fracture occurred in this study, and only 1 patient presented with tumor ingrowth after silicone coat detachment or perforation.

When all complications were considered, a Cox model showed a higher risk for complication for Aerstent (HR = 1.66; 95% CI, 1.01-2.7; $P = .04$). Accounting for death as a competing event, the raw association still suggested a higher risk of complication for Aerstent, at the limit of statistical significance (HR = 1.67; 95% CI, 1.00-2.78; $P = .047$). Adjustment for age, sex, smoking status, histology, and stage modified these estimates to a nonstatistically significant result (adjusted HR = 1.41; 95% CI, 0.54-3.76; $P = .49$). By type of complication, Aerstent showed a statistically significant higher risk for mucus retention (HR = 1.77; 95% CI, 1.03-3.03; $P = .04$).

Comment

The results of this study show that the recently launched SEMS Aerstent is equivalent to the reference standard Dumon silicone stent in terms of restoring airway patency, the feasibility of removing the stent, and its overall complications rate. This study compared two stents based on a cohort of well-balanced groups of patients with malignant CAO.

We found that mucus retention was the most frequent complication (75.9% for Dumon and 84.8% for Aerstent), followed by granulation tissue (51.7% for Dumon and 41.3% for Aerstent) and migration (6.9% for Dumon and 13.0% for Aerstent). Unlike previous studies,[9,12] we decided to express the results by calculating the cumulative incidence (the cumulate probability of experiencing an event during follow-up) and the median time to appearance, because, as stated by Ost and colleagues,[13] incidence proportions (the number of complications divided by the total of patients) do not account for time at risk and do not inform the reader of the trend.

The current study also shows that the probability of presenting complications of any kind increases continuously over time (Figure 1). In the first month, the probability was 36.7% for the Dumon stent and 41.3% for the Aerstent stent, increasing until the third month to 82.9% for the Dumon stent and 93.5% for the Aerstent stent, respectively, before practically leveling off (90% for the Dumon stent and 97.8% for the Aerstent stent). These data cannot be compared with other studies because there are no previously published results expressed in this way with similar stents.

Overall, the Aerstent group showed a higher probability of developing a complication than the Dumon group (HR = 1.66; 95% CI, 1.01-2.7; $P = .04$). However, because death precludes the occurrence of the first stent complication,[15,16] the probability of complications was adjusted according to the cohort's mortality. The raw association still suggests a higher risk for complication for Aerstent, although the result was at the limit of statistical significance (HR = 1.67; 95% CI, 1.00-2.78; $P = .047$). Finally, adjustment for age, sex, smoking status, histology, and stage modified these estimates to a nonstatistically significant result (adjusted HR = 1.41; 95% CI, 0.54-3.76; $P = .49$).

When each complication was analyzed separately, a similar trend was observed for both stents. On average, mucus retention appeared 1.1 month after stenting, and granulation tissue after 1.4 months, whereas migration occurred later. Ost and colleagues[13] presented their results globally for 3 types of stents and found that median time to mucus plugging was 1.3 months, to granulation tissue 1.4 months, and to stent migration 1.43 months. Although the order of appearance was the same, interval times were longer in the current study. These differences might be explained by the different kinds of metal stents used and by a different approach to follow-up.

While the trend in terms of the appearance of complications was similar for both stents, the risk for mucus retention was significantly higher for the Aerstent stent than for the Dumon stent (HR = 1.77; 95% CI, 1.03-3.03; $P = .04$). In contrast, Ost and colleagues[13] found that the

Table 3. Complications of Dumon and Aerstent Stents Expressed as Cumulative Incidence and Median Time to Complication

Complications	Dumon (n = 29)	Aerstent (n = 46)	P[a]
Mucus retention, n (%)	22 (75.9)	39 (84.8)	.51
Mild (%)	77.3	87.5	
Moderate (%)	13.6	10.0	
Severe (%)	9.1	2.5	
Median time, mo	1.18 (0.99-2.50)	1.02 (0.80-1.15)	
Granulation tissue, n (%)	15 (51.7)	19 (41.3)	.52
Median time, mo	1.41 (0.99-3.78)	1.31 (1.02-2.78)	
Migration, n (%)	2 (6.90)	6 (13.0)	.47
Median time, mo	3.78 (1.61-5.52)	1.91 (1.02-4.36)	
Silicone detachment/perforation, n (%)	N/A	10 (21.3)	N/A
Median time, mo	N/A	2.20 (1.02-4.00)	

[a]All tests were chi-square. Data are shown as n (%) or median time (confidence interval).

N/A, not applicable.

Dumon stent presented a higher risk for developing mucus retention compared with Ultraflex, a metal partially covered stent. Differences between Aerstent and Ultraflex require a comparative clinical study for this issue to be clarified. Mucus retention is the first step toward biofilm formation and bacterial colonization, which in turn are the main cause of clinical infection. In a systematic review by Agrafiotis and coworkers,[17] 19% of patients with stents experienced a pulmonary infection. There is also a possible link between the presence of colonization and granuloma tissue formation; all initiatives aimed at controlling microorganism colonization are therefore warranted.[18] One possible solution could be to provide inner coatings with higher hydrophobicity, which could reduce biofilm formation.[19]

In the current cohort, stent metal mesh fracture was not observed. Mesh fracture is more common in uncovered stents but has also been described with covered stents.[20,21] More importantly, the mesh did not break down when we removed the stent with rigid forceps. This

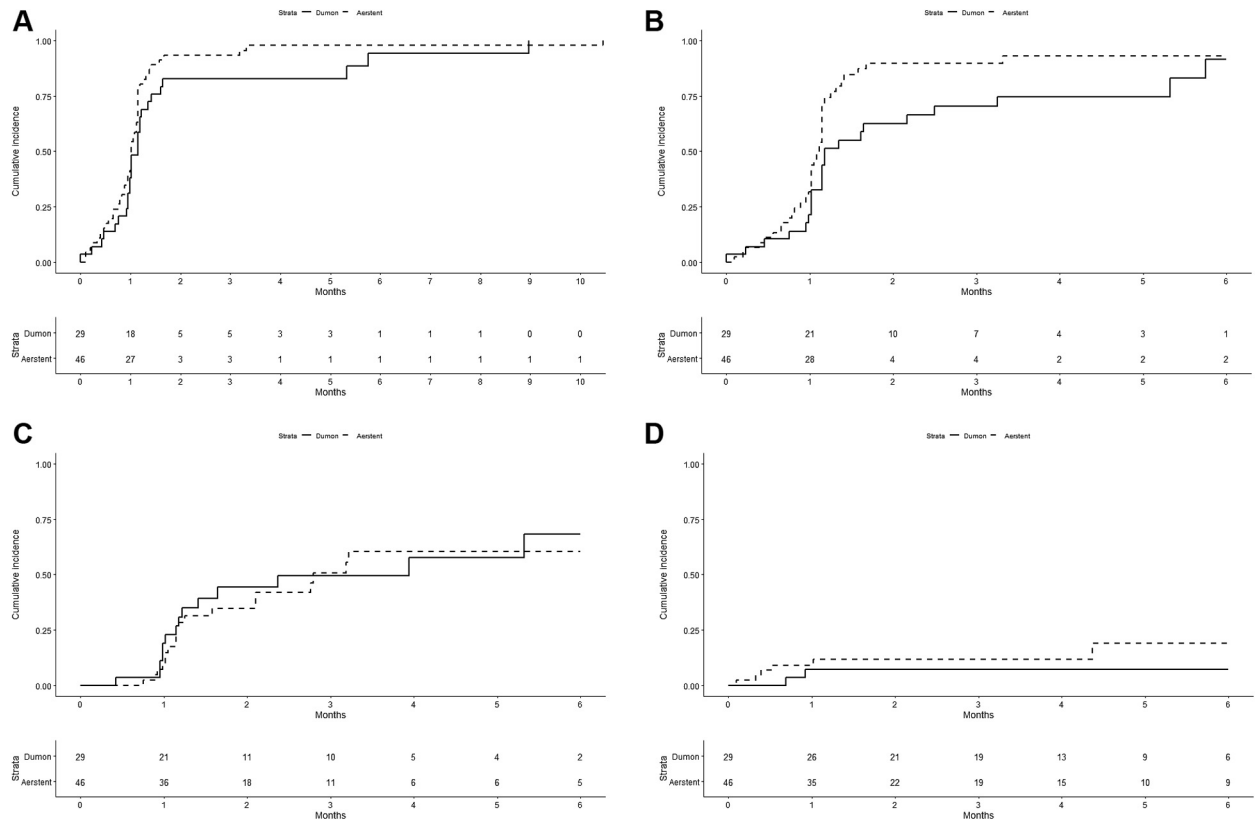

Figure 1. Complications of Dumon and Aerstent stents expressed by cumulative incidence curves per stent and complication: (A) overall complications; (B) mucus retention; (C) granulation tissue; (D) migration.

particularly resistant and highly elastic recoil could be explained by the mechanical properties of the monofilament mesh and the type of internal silicone film cover.[22] Nevertheless, silicone coat detachment was observed in 21.3% of cases at a median of 2.2 months. This complication was associated with granuloma formation and with tumor growth that required specific bronchoscopic treatments, such as laser photocoagulation and mechanical resection.

The current study had a number of flaws. Although the compared groups were similar at stent implantation, some interventions during follow-up were not registered and could have had a role in the survival and type of complication, including the type and duration of chemotherapy, complications resulting from chemotherapy or radiotherapy, and organ dysfunctions. Also, as stated in a similar study,[13] a selection bias might have occurred affecting overall survival in the expandable metal stent group, because these stents are easier to place and thus tend to be implanted in sicker patients who do not tolerate longer procedures. Other selection biases affect gender and location. In the current study, there was a larger proportion of female subjects in the Aerstent group than in the Dumon group (29.3% versus 6.9%), because women generally have smaller airway diameters and metal stents have a more convenient stent wall thickness to outer diameter ratio (1.5 mm wall thickness in Dumon stents versus 0.25 mm for Aerstent stents). The Aerstent was implanted more often than the Dumon stent in conical stenosis (50% versus 6.25%), which might be explained by its physical proprieties. This monofilament SEMS permits different diameters to be adapted by expanding its length without kinking or collapsing. Another limitation is that we may have overestimated the occurrence of complications, because our clinical protocol includes an active bronchoscopic follow-up. Although 1 study suggested that bronchoscopic follow-up is not necessary,[23] we consider the quality of life of oncology patients to be better if a smaller number of urgent complications appears at the cost of performing a procedure under stable clinical conditions. Finally, objective information concerning clinical outcomes after stent deployment (ie, the dyspnea score) was not reported, and there is a lack of information about the clinical impact of complications regarding symptoms, procedures needed, and their impact on patients' quality of life. As with the previous selection and observation biases, these limitations can be corrected only in a prospective randomized study.

Both stents were equally effective in restoring patency for malignant CAO, but the risk for complications was higher for Aerstent. Nevertheless, no statistically significant differences were found when mortality was accounted for in the competitive risk analysis. Mucus retention was the most frequent complication overall and affected the Aerstent stents more than the Dumon stents. In any case, the number of patients with any complication increased dramatically over time, reaching 90% at 6 months. New developments in stent materials and designs are required to reduce the risk for complications.

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