Background: Treatment of early superficial bronchogenic carcinoma (ESBC) is under debate, and no consensus has been achieved. Different therapeutic methods have been proposed, including surgical resection and endoscopic methods.

Study objective: To assess the efficacy of cryotherapy in patients with ESBC.

Patients and methods: Patients included in the study had histologically proven ESBC after fiberoptic bronchoscopy. Cryotherapy was performed through a rigid bronchoscope. Efficacy was assessed by endoscopy with multiple biopsies 1 month after treatment and during the follow-up period. Parameters studied were response to treatment, adverse effects, and survival.

Results: We included 35 patients (34 men and 1 woman). The mean age was 61 ± 9 years. Multiple locations of ESBC were observed in seven patients (20%). Complete response rate at both 1 month and 1 year was 91% (32 patients). No severe adverse effects were noted. Local recurrence was observed within 4 years in 10 patients (28%). A follow-up period of at least 4 years was available in 22 patients; of them, 11 patients (50%) were long-term survivors.

Conclusion: Our results suggest that cryotherapy is an effective method of treatment in patients with ESBC. Due to its relative tolerance compared to surgery, cryotherapy could be proposed as a first-line therapy in this population with high carcinogenic risk.

Lung cancer mortality has remained unchanged over the years.1,2 Most patients die from distant metastasis, despite aggressive therapy. In bronchogenic carcinoma in situ (CIS), the tumor is limited to the epithelium without rupture of the basement membrane.3 When the basement membrane is not intact, the lesion is still considered CIS if there is no invasion of the lamina propria.3,4 These lesions, called early superficial bronchogenic carcinoma (ESBC), are multifocal in about 15% of patients2,5 and are incapable of metastasis.3,4 However, their recurrence after surgical treatment is frequent, since subsequent primary tumors develop in about 5% of patients each year.5

Opinions concerning the management of ESBC are not unanimous, and few reports deal with these lesions.4 In the past, therapeutic options had been limited to surgical resection. As surgical resection failed to avoid development of another primitive lung cancer, endoscopic therapies such as photodynamic therapy (PDT) were tested.6–9 Cryotherapy is one of these conservative therapies, while it has never been tested as a primary treatment of these tumors. Its effects result from the selective cellular necrosis due to tissue freezing and the elimination of their vascularization. This is an inexpensive and safe method, but the results are somewhat delayed. Nitrous oxide-driven cryoprobes are most often used. Cooling is due to the Joule Thompson effect.10–13 The aim of this study was to evaluate the efficacy of such a cryotherapy used as the unique treatment in patients with ESBC.14 The parameters studied were tolerance, response to treatment at 1 year, disease-free interval, and overall survival.
Materials and Methods

Patient Selection Criteria

All patients with an exclusive diagnosis of ESBC detected by conventional white-light flexible bronchoscopy (FB) were eligible for the protocol. These lesions presented as irregular and well-limited zones of thickening. The ESBC features defined on criteria previously described3,4 were further proven on multiple biopsies, with negative radiographic and CT scans findings. After informed consent, these patients underwent cryotherapy alone (even when operable).

Population

Thirty-five patients (34 men and 1 woman) with 41 lesions (Fig 1) were enrolled in this study between March 1985 and April 1997. Inclusions were stopped after this date in order to obtain a sufficient follow-up duration. These patients were treated in 10 different French centers: Saint Etienne (16 patients), Strasbourg (5 patients), Rouen (4 patients), Grenoble (3 patients), Tours (2 patients), Bordeaux (1 patient), Chevilly-Larue (1 patient), Dieppe (1 patient), Nimes (1 patient), and Orleans (1 patient).

About one half of the lesions were discovered at systematic FB checkups, and the others were found after various complaints, including hemoptysis, cough, and sputum. Seven patients (20%) had two or more lesions. The locations of the different lesions are presented in Figure 1. These lesions were histologically defined as typical CIS in 27 patients, and were considered as CIS in a broad sense in the other 8 patients because the basement membrane was not intact, although without invasion of the lamina propria.3,4

The mean patient age was 61 ± 9 years (range, 33 to 80 years). All patients were smokers, and 14 of them had COPD. Most of the patients (42%) had a clinical history of bronchogenic (seven patients) or upper aerodigestive tract carcinomas (eight patients) treated previously by surgery or radiotherapy.

Methods

DATE (LP 500; La Motte d’Aveillans, France) or ERBE (ERBOCRYO CA; Tubingen, Germany) equipment was used. In case of a central location of the tumor, rigid cryoprobes were employed, while flexible probes were used for peripheral locations. Both nitrous oxide-driven cryoprobes were introduced through a rigid bronchoscope under general anesthesia. Rigid cryoprobes were utilized for 19 patients (54%), flexible cryoprobes for 7 patients (20%), and both rigid and flexible cryoprobes for the last 9 patients (26%). Treatment of lesions was performed according to the method described earlier.13 Briefly, three cycles of freezing and thawing are performed in each point. Each freezing period lasts about 20 s. All the tumor surface and a marginal area of 5 mm of normal mucosa around the tumor were treated. The distance between two adjacent applications of the cryoprobe is about 5 mm. In these infiltrative lesions, often located on a carina, the probe is applied laterally on each side of that carina, and then the tip of the probe is applied along the carina crest itself. Ten to 15 days after the first cryotherapy session, an endoscopic control was performed to evaluate macroscopically residual lesions in order to perform a second session if necessary (in 12 patients) as well as to extract the necrotic slough.

Evaluation of Response and Follow-up

Follow-up was performed using radiography and FB with multiple biopsies at the site treated with cryotherapy at 1, 3, 6, and 12 months, and then every year. Biopsies were performed of all other lesions detected during endoscopic controls.

Statistical Analysis

Student's t test was used to compare the mean values of the variables of the groups studied. Survival was studied from the date of diagnosis to the last date of contact, using the Kaplan-Meier product limit estimation with log-rank test. A p value of ≤ 0.05 was considered significant for all tests. Statistical analysis was performed with StatView 4.5 software (SPSS; Chicago, IL).

Results

Tolerance

Tolerance to cryotherapy was judged excellent. There was neither hemoptysis nor bronchial wall perforation. There were no severe adverse effects due to general anesthesia. We did observe transient fever following cryotherapy in the first patients; this was prevented later by preventive corticosteroid administration. Necrotic slough never caused significant cough or dyspnea as is sometimes observed when cryotherapy is used as a debulking method.13

Local Tumor Control

Results were available for all patients at 1 month and at 1 year. A complete histologic response was obtained in 32 of 35 patients at 1 month (91%) and lasted a full year. One of three patients with a residual lesion at 1 month died in the sixth month of a metastatic disease. This patient had a clinical...
history of lobectomy and underwent radiotherapy for carcinoma 15 months earlier. The two other patients were administered a second treatment with cryotherapy on lesions that were still in situ, with a survival of 36 months and 50 months, respectively.

Seven other patients presented with a local recurrence after the 12-month evaluation; a total of 10 patients (28%) had recurrence. The disease-free interval of these seven patients ranged from 13 to 45 months. The median overall survival of these patients was 37 months, ranging from 19 to 50 months. These recurrences presented as an invasive carcinoma in six patients and as a CIS in one patient. This last patient was treated again using cryotherapy, with an overall survival of 50 months. The invasive carcinomas were treated with surgery in three patients and with radiotherapy in two patients; the last patient had respiratory insufficiency and could not undergo any salvage treatment. Method failures are shown in Figure 2.

Second Carcinoma

A second carcinoma was diagnosed in eight patients (23%), 5 to 46 months after cryotherapy, although the effectiveness of the treatment was proved. Of these patients, three were treated with cryotherapy again, obtaining a complete response and a survival ranging from 15 to 89 months. The remaining five patients presented with an invasive bronchogenic carcinoma 5 to 27 months after cryotherapy. Of these five patients, two patients had a clinical history of pulmonary resection for carcinoma and one patient had been treated a few months earlier for a larynx carcinoma.

Longer Follow-up

A 2-year follow-up was available in 32 patients. Twenty of these 32 patients (62.5%) were still alive at this time. For 22 patients, a follow-up period of at least 4 years (48 to 89 months) was available. Of these 22 patients, 11 patients (50%) were still alive and were considered as long-term survivors.

At the time of assessment, 19 of 35 patients were dead; 13 patients died of carcinoma (all of them squamous cell invasive carcinoma), and the remaining 6 patients died of an unrelated cause. Of the 13 patients who died of bronchogenic invasive carcinoma, only 6 patients died of a recurrence of the cancer on the site initially treated with cryotherapy. The seven other patients developed a second cancer at another site.

Overall median survival and overall median disease-free survival are shown in Figures 3, 4. The eight patients with CIS in a broad sense exhibited

![Figure 2. Graphic representation of complete responses and cryotherapy failures in study patients.](http://publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21964/)
the same course as the whole group, with a disease-free interval ranging from 21 to 53 months (not significant).

**DISCUSSION**

The outcome of bronchogenic CIS is now clearly demonstrated as unfavorable, with progression to invasive carcinoma.15 This is confirmed by our results, since six of our seven recurrences were invasive lesions; therefore, ESBC must be treated aggressively.

The choice of therapy for ESBC is under debate.4 Surgical resection remains frequently recommended, while reports published are limited, present contradictory data, and include few patients.16-18 When the surgery concerns more than one lobe, the associated parenchymal amputation limits the therapeutic options in case of recurrence.4,16-18 However, limited resections, such as segmentectomy or sleeve resection, have never been evaluated in these lesions. The 5-year overall survival for surgery has ranged from 50 to 91%,17,18 and was only about 10% at 10 years in one of these reports.17

Moreover, several characteristics of this population with early stage lung cancers limit surgical efficacy: (1) at the time of diagnosis, these lesions are often multifocal (19% in our population); (2) later, the appearance of a second location in the follow-up is very frequent17 and reached 23% in our population; (3) functional impairment with severe COPD, common in such heavy smokers, as well as a history of bronchogenic or upper aerodigestive tract carcinoma (42% in our population) either contraindicate surgery or increase mortality. For example, in one surgical report,18 operative mortality rate was 5 to 6%, which is quite high.

Endoscopic methods such as PDT,19-25 laser therapy,26 and electrocautery27 would now appear to be more appropriate in patients with ESBC. A comparison to surgery and between endoscopic methods is difficult, however, due to the lack of randomized studies. And, to our knowledge, no prior report in the literature has studied ESBC patients treated with cryotherapy.14 Efficacy, tolerance, and cost analysis are needed to compare these endoscopic methods. In terms of efficacy and tolerance, cryotherapy provided a complete response at 1 month in 91% of our patients, and lasted for 1 year without any side effects. We obtained overall survival rates of 62.5% at 2 years and 50% at 4 years. The excellent tolerance to cryotherapy is underlined in all reports due to the selective cytotoxic action of cold, as it avoids collagen damage.11-13 The depth of the cytotoxic action of cryotherapy in the bronchial wall is > 3 mm,13 which is sufficient to cure early stage lung cancers.3-5 PDT results are similar, with complete response rates reaching 50 to 90%,20,21,24 and local recurrence rates from 10 to 31%,20,24,25 With PDT, long-term survivors have also been reported.20-25 However, side effects are more frequent and include severe or prolonged cutaneous photosensitization.19-25 Cavaliere et al26 successfully used Nd-YAG laser therapy in this indication in only 19 bronchogenic CIS selected from 1,585 malignant lesions. Due to the unselective action on the bronchial wall and the deep action of Nd-YAG laser, this method can also lead to severe complications, such as hemorrhage or perforation, especially in untrained hands.

Bronchoscopic electrocautery using soft coagulation has been evaluated27 in 13 patients with T1N0M0 lesions with a complete response rate of 80%, but with a median follow-up limited to 22 months. Side effects of electrocautery are limited for this indication. However, electrocautery is not as safe as cryotherapy for the bronchial wall: of the 13 patients treated, bronchial stenosis scars were described in 2 patients. Also, necrosis of the cartilage arches has been reported in humans after a 3- to 5-s...
application in soft coagulation mode; in animals, a severe stenosis is always obtained in case of circumferential application.

High-dose rate brachytherapy has been evaluated for limited lesions, but not specifically in bronchogenic CIS. This method produces severe adverse events, such as severe hemoptysis, fistula formation, and bronchial stenosis, and seems to be more appropriate for tumors infiltrating the entire bronchial wall and the peribronchial tissues.

The cost of each method must be taken into account, including devices and consumables. A cryotherapy unit with rigid cryoprobes is a very inexpensive device, about $8,000, which is less than electrocautery devices. Moreover, electrocautery requires a special insulated fiberoptic bronchoscope. These low costs contrast with the Nd-YAG laser unit (> $100,000) or with the very expensive devices for high-dose rate brachytherapy or PDT, which need two simultaneous lasers plus the cost of photosensitizers.

CONCLUSION

For ESBC, we think that conservative therapy could be proposed as first-line treatment, sparing the pulmonary parenchyma and allowing surgical salvage when necessary. A frequent endoscopic control is recommended to detect recurrence or other locations. Based first on the efficacy-tolerance ratio and then on the favorable cost of each method, we suggest that cryotherapy should be the best first choice. Randomized trials with long-term follow-up are needed to compare results of cryotherapy to those of surgery as well as other endoscopic methods in ESBC, even if patients are candidates for resection.

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REFERENCES


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