Artigo original

Early detection and treatment of squamous cell lung cancer

Diagnóstico precoce e tratamento do carcinoma escamoso de pulmão

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ABSTRACT

In this review, we discuss the detection, staging, and treatment of early-stage squamous cell lung cancer, with a focus on bronchoscopic techniques, including electrocauterization, argon plasma coagulation, cryotherapy, neodymium:yttrium-aluminum-garnet laser therapy, photodynamic therapy, and intraluminal brachytherapy.

The cure rate achieved with bronchoscopic techniques is 43-97%. Most bronchoscopic strategies are less morbid and less toxic than is non-bronchoscopic radiation therapy. Success depends on the application of stringent selection criteria for appropriate tumors, smaller tumors responding better. In some cases, electrocauterization, argon plasma coagulation, and cryotherapy can be conducted safely in an outpatient setting.

There is sufficient technology available for the detection and treatment of early-stage squamous cell lung cancer. The greatest challenge is to determine whether early detection and treatment improves survival in high-risk populations and is cost-effective.

Keywords: Carcinoma, non-small-cell lung/diagnosis; Carcinoma, squamous cell/therapy; Bronchoscopy/trends.

RESUMO

Neste artigo de revisão, discutimos os métodos para detecção, estadiamento e tratamento do carcinoma epidermoide precoce com foco em técnicas broncoscópicas, como eletrocautério, coagulação com plasma de argônio, crioterapia, laser neodímio:ítrio-alumínio-granada, terapia fotodinâmica e braquiterapia intraluminal.

A taxa de cura com as técnicas broncoscópicas é 43-97%. A maioria das estratégias broncoscópicas apresenta menor morbidade e toxicidade que a radioterapia. O sucesso depende da aplicação rigorosa de critérios de seleção de acordo com o tumor, sendo que aqueles menores apresentam melhor resposta. Em alguns casos, o eletrocautério, a coagulação com plasma de argônio e a crioterapia podem ser utilizados ambulatorialmente com segurança.

Há suficiente tecnologia disponível para a detecção e tratamento precoce do câncer de pulmão epidermoide. O maior desafio é determinar se a detecção e o tratamento precoces melhoram a sobrevida em coortes de alto risco e se tal abordagem é custo-efetiva.

Descritores: Carcinoma pulmonar de células não pequenas/diagnóstico; Carcinoma escamoso/terapia; Broncoscopia/tendências.

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INTRODUCTION

Non-small cell lung cancer is the leading cause of cancer death worldwide (1,2). The disappointing fact that the overall five-year survival rate is only approximately 15% is mainly attributable to the fact that the disease is often at an advanced stage at the time of diagnosis and to the limited effectiveness of treatments for metastatic disease. Even for stage I or II lung cancer, which is usually treated with curative intent, five-year survival is only 50-60% (3), because of the potential for subsequent primary lung tumors and metastases. In contrast, the prognosis of early-stage, centrally located in situ squamous cell lung cancer (stage 0) is excellent, the five-year survival rate being 90% (4-8). As can be seen in Table 1, the World Health Organization has devised a classification system that divides premalignant squamous cell tumors into nine categories (grades A through I), ranging from normal to invasive carcinoma (9). The invasive potential of these tumors and the need for curative treatment are both controversial (10,11). The natural history of premalignant tumors is difficult to study because these tumors are often asymptomatic and are discovered by chance. In addition, most facilities treat the tumors at the time of detection rather than awaiting the development of invasion (5-8,11). The reported rates of progression from carcinoma in situ (CIS) to invasive cancer range from 20% to 67%, even when bronchoscopic procedures are used (12-15). This underscores the need for effective detection and treatment strategies, especially in patients with a reasonable life expectancy.

Table 1 - World Health Organization system for the classification of premalignant bronchial tumors (9).

Grade	Histologic characteristic
A	Normal
B	Inflammation/bronchitis
C	Hyperplasia
D	Squamous metaplasia
E	Mild dysplasia
F	Moderate dysplasia
G	Severe dysplasia
H	Carcinoma in situ
I	Invasive carcinoma

Screening trials for the early detection of lung cancer in high-risk populations are ongoing and are likely to identify large numbers of patients. Subjecting these patients to the classical treatment for early-stage lung cancer (radical surgical resection) might not be in their best interest, for several reasons. First, early-stage squamous cell lung cancer is often centrally located, which necessitates either bronchotomy, lobectomy (typically sleeve lobectomy), or pneumonectomy. Second, patients often present with synchronous or metachronous tumors that would require multiple resections. Third, the patients with the highest risk of lung cancer often have significant comorbidities, such as chronic obstructive pulmonary disease (COPD) and cardiovascular disease. The cumulative morbidity and mortality of such an aggressive approach might therefore be too high a burden. One alternative, potentially curative, approach to these patients is the use of minimally invasive tissue-sparing bronchoscopic treatment modalities such as electrocauterization, argon plasma coagulation (APC), cryotherapy, and photodynamic therapy (PDT). In this review, we discuss the methods for the detection, staging, and treatment of early-stage squamous cell lung cancer, with a focus on bronchoscopic techniques.

DETECTION OF EARLY-STAGE SQUAMOUS CELL LUNG CANCER

The classic screening method for centrally located early-stage lung cancer is sputum cytology. However, this method is limited by its low sensitivity, which is due to sampling error and technical difficulties in the preparation of samples, as well as to significant variations in intra- and inter-observer agreement. The advent of white-light bronchoscopy (WLB), performed with a flexible (fiberoptic) bronchoscope, has enabled visual inspection of the central airways. However, despite recent technological advances in fiberoptic videoendoscopic techniques, the sensitivity of WLB for detecting early-stage lung cancer remains low. This inspired investigators to enhance the performance of bronchoscopy by employing additional optical techniques, such as autofluorescence and optical coherence tomography.

Autofluorescence Bronchoscopy

The rate at which preneoplastic lesions and CIS are detected has increased significantly since autofluorescence imaging has come into use. Autofluorescence bronchoscopy (AFB), which combines autofluorescence imaging with WLB, utilizes spectral differences in fluorescence and absorption to distinguish between normal and dysplastic bronchial epithelium. These differences have been the basis for the design of various autofluorescence imaging devices. Recent advances include the use of a combination of reflectance and fluorescence (16-19). Whereas early systems were developed for fiberoptic bronchoscopy, the latest generation of devices are integrated into videoendoscopic systems.

Figure 1 shows the SAFE-3000® system (Pentax Corp., Tokyo, Japan), which uses illumination from a semiconductor laser diode emitting light at a wavelength of 408 nm and detects autofluorescence, with a single high-sensitivity color charge-coupled device sensor, in the 430-700 nm fluorescence spectrum. Reflected blue light is used to generate a fluorescence-reflectance image. The white-light and fluorescence im-

ages can also be made to display simultaneously (Figure 2). The Lucera® autofluorescence imaging system (Olympus Corp., Tokyo, Japan) uses blue light (395-445 nm) for illumination. An autofluorescence image (490-700 nm)—as well as two reflectance images, one green (550 nm) and one red (610 nm)—are captured sequentially and integrated by a video processor to produce a composite image.

Figure 1 - The Pentax SAFE 3000® autofluorescence system.

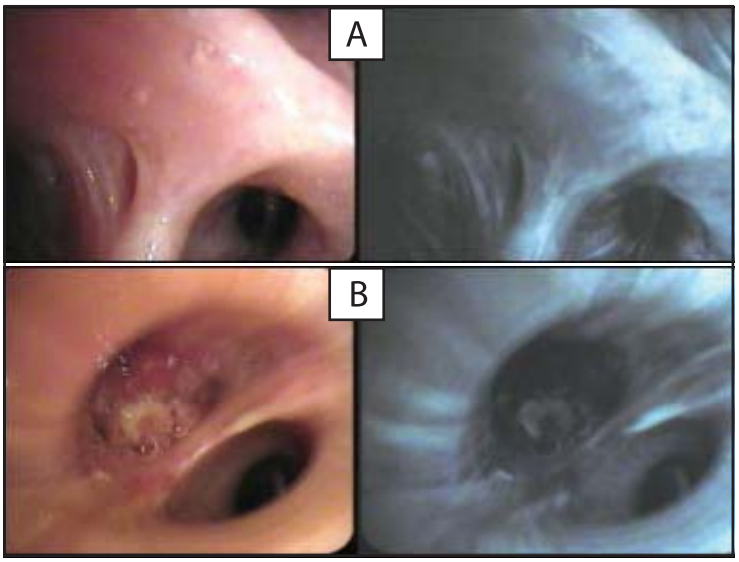

Figure 2 - Normal bronchial epithelium (A) and squamous cell lung cancer (B), seen using the Pentax SAFE 3000® system. Note the reduced tissue autofluorescence at the site of the tumor. The image on the left is white-light imaging, and the image on the right is autofluorescence imaging.

The reported sensitivity of WLB is 9-58%, whereas AFB performs better, with a sensitivity of 44-82%. The drawback of that increased sensitivity is that the specificity of AFB is only 46-75%, compared with 62-95% for WLB. False-positive findings increase the number of unnecessary biopsies, which reduces the cost-effectiveness of this technique. However, according to recent data, in areas that, despite benign histopathology, exhibit abnormal autofluorescence, there are more chromosomal aberrations, and the presence of multiple areas of abnormal autofluorescence might be an indicator of increased lung cancer risk (20,21). The use of a quantitative score during autofluorescence imaging has been shown to improve specificity (22).

High-Magnification Videoendoscopy

The high-magnification Exera® endoscope (Olympus Corp.) combines fiberoptic and videoendoscopic technologies to produce images of the bronchial wall at a magnification up to 110 times greater than that obtained with standard videoendoscopes. This enables the visualization of microvascular networks in the bronchial mucosa. Increased vessel density in the bronchial submucosa, which is often present in squamous dysplasia, might play an early role in cancer pathogenesis (23). Angiogenic squamous dysplasia is a potentially more aggressive preneoplastic lesion, characterized by a collection of blood vessels juxtaposed to and projecting into an area of epithelial dysplasia. In the majority of areas of abnormal autofluorescence, high magnification facilitates the identification of increased microvascular density, which makes it possible to discriminate between squamous dysplasia and mucosal inflammation.

Narrow-Band Imaging

Like high-magnification videoendoscopy, narrow-band imaging (NBI; Olympus Corp.) is a novel system that utilizes the changes seen in the microvascular network. This technique uses a narrow-band filter rather than the conventional, broad, red-green-blue (RGB) filter used in standard videoendoscopes. The conventional RGB filter uses bands of 400-500 nm (blue), 500-600 nm (green), and 600-700 nm (red), whereas NBI uses three narrow bands, of 400-430 nm (blue, covering hemoglobin absorption at 410 nm), 420-470 nm (blue), and 560-590 nm (green). Blue light has a short wavelength, reaches into the bronchial submucosa, and is absorbed by hemoglobin. As previously stated, this enables the detection of increased vessel growth and complex networks of tortuous vessels, dotted vessels, and spiral or screw type tumor vessels of the bronchial mucosa, which might reflect the onset of angiogenesis in the process of carcinogenesis (24). In the evaluation of airway lesions that are abnormal under autofluorescence imaging, this technique provides images of microvessels that are more accurate than are those obtained with high-magnification videoendoscopy using broadband RGB technology. The rate of detection of dysplasia/malignancy obtained with the NBI-WLB combination seems to be higher than that obtained with WLB alone, as demonstrated in one small study (25). There has been only one prospective study of early-stage squamous cell lung cancer comparing WLB, NBI, and AFB, in terms of their diagnostic yield (26). The re-

sults of that study suggest that NBI increases the specificity of bronchoscopy. Therefore, NBI and AFB might be complementary techniques in the future.

Optical Coherence Tomography

Optical coherence tomography (OCT) is an optical imaging method that offers microscopic resolution for visualizing structures at or below the tissue surface. Although OCT is similar to ultrasound, it uses near-infrared light (rather than sound waves), which is applied via a small probe inserted into the working channel of a bronchoscope. Because the velocity of light is far greater than is that of sound, the light reflected back from the structures within the tissue cannot be detected electronically, so it is detected with a technique known as low-coherence interferometry. An advantage of this technique is that light waves, unlike sound waves, do not require a coupling medium (liquid or gel), which makes OCT ideal for use in the airways. In addition, OCT creates images of cellular and extracellular structures by analyzing the backscattered light, with a spatial resolution of approximately 3-15 μm and a depth penetration of ~2 mm, to provide near-histological images of the bronchial wall. Early studies showed that OCT can distinguish dysplasia from metaplasia, hyperplasia, and normal tissue, as well as distinguishing between CIS and invasive cancer (27,28). The histopathological grade has been associated with epithelial thickness, as well as with other aspects, greater severity resulting in the darkening of cell nuclei and reduced light scattering. In cases of invasive carcinoma, the basement membrane becomes disrupted or disappears (28). To further advance this technology, systems with higher resolution, which can provide greater detail in images of tissue microstructures, and incorporating Doppler flowmetry, which can detect microvascular blood flow, could be useful. Doppler OCT systems that can detect very slow blood flow (< 20 μm/sec in blood vessels as small as 15 μm in diameter) already exist. The OCT technology could prove useful for structural and functional assessment of suspicious lesions, as well as for staging (based on invasion of the basement membrane) and feedback during bronchoscopic procedures. However, this promising technique requires further validation.

TREATMENT OF EARLY-STAGE SQUAMOUS CELL LUNG CANCER

Surgery is still the most widely accepted approach for the treatment of CIS, resulting in an 80-90% five-year survival rate. Unfortunately, such surgery often involves the removal of a significant amount of normal lung parenchyma. Up to 30% of patients with early-stage, centrally located lung cancer require bilobectomy or pneumonectomy, the remaining patients requiring lobectomy. In addition, such patients can present with synchronous tumors or develop additional primary tumors (field cancerization) after curative treatment. In these patients, comorbidities such as COPD often limit the amount of lung parenchyma that can be resected. Surgery is therefore not necessarily the only option and probably should not always be the treatment of first choice. There is significant interest in the use of bronchoscopic modalities to treat early-stage centrally located lung cancer. When bronchoscopic treatment fails or when the tumor is too far advanced, surgery can still be performed if the tumor remains local and operable. To date, there have been no trials comparing surgical and bronchoscopic techniques in terms of their effectiveness in treating early-stage squamous cell lung cancer. The reported outcomes of bronchoscopic treatment are comparable to those of surgical treatment. In one cost-effectiveness analysis, the cost of treatment and follow-up for small, inoperable stage IA tumors treated bronchoscopically was 30% of that of standard surgery in matched patients with comparable tumors that were operable, and, as expected, the surgical procedures were associated with greater morbidity (29).

As previously mentioned, successful bronchoscopic treatment strongly depends on accurate staging. Selected tumors should be limited primarily to flat squamous cell CIS and microinvasive carcinomas < 1 cm with clearly visible distal tumor margins under AFB examination, whereas tumor invasion of the airway wall can be reliably excluded by endoscopic ultrasound. In addition, tumors with nodal involvement obviously cannot be classified as early-stage, centrally located lung cancer.

Treatment Modalities

Commonly used bronchoscopic treatment techniques include electrocauterization, APC, cryotherapy, neodymium:yttrium-aluminum-garnet (Nd:YAG) laser therapy, PDT, and intraluminal brachytherapy.

Electrocauterization and APC

Electrocauterization is the application of heat produced by electrical current and transferred to the target tissue with the use of a specifically designed probe or hook. Electrocauterization can be applied with a rigid or flexible bronchoscope and under local or general anesthesia, depending on the experience of the bronchoscopist, the risk assessment, and the availability of instruments. In APC, a specially designed flexible catheter is used in order to apply a flow of argon around a high frequency electrode. This produces a plasma jet that transfers the energy homogeneously to the tissue. Although the coagulative necrosis that occurs after standard electrocauterization is similar to that occurring after APC, the latter causes more acute superficial tissue destruction, which makes APC less efficient in cases of bulky tumors.

Cryotherapy

Cryotherapy causes tissue death by repetitive freezing. Cryotherapy systems use the expansion of a pressurized gas (e.g., nitrous oxide) to generate cold, which is subsequently transferred to the target tissue by a special flexible probe (Figure 3). The goal of cryotherapy is to damage pathologic tissue but spare healthy tissue. The maximum effect is achieved by rapid freezing and slow warming. Repeated cycles of freezing increase the amount of tissue destruction. Cryotherapy inflicts minimal damage on surrounding structures, because collagen, cartilage, and poorly vascularized tissues are highly resistant to freezing, which makes this an extremely safe method. Cryotherapy is still a relatively new tool for treating early-stage squamous cell lung cancer, and further studies are therefore needed in order to determine its effectiveness.

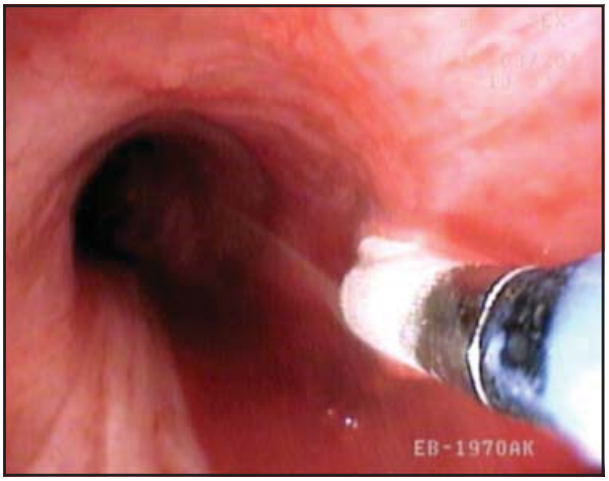

Figure 3 - Cryotherapy for a lesion in the left main bronchus using a flexible probe. Note the clear demarcation of the frozen tissue.

Laser Therapy and Irradiation

The laser most suitable for use in bronchoscopic treatment is the Nd:YAG laser, because of its high power, reliability, and durability. The most common use of Nd:YAG laser therapy is the debulking of centrally located tumors, although it might also come to be of use in early-stage squamous cell lung cancer. Although Nd:YAG laser light is commonly applied with a rigid scope, it can also be applied with a flexible scope.

In PDT, the interaction between tumor-selective photosensitizers and laser light results in selective cell death (of tumor cells only). Interactions among the photosensitive molecules, light of a specific wavelength, and tissue oxygen lead to the formation of active forms of oxygen that induce cellular necrosis.

Finally, intraluminal brachytherapy involves irradiating tissue by placing a radioactive source at the site of the bronchial tumor.

FINAL CONSIDERATIONS

The choice of the treatment modality depends largely on the availability of the technical equipment, as well as on the skill and experience of the bronchoscopist. In general, the cure rate after bronchoscopic treatment of early-stage squamous cell lung cancer is 43-97%. Many studies of these techniques have included larger stage 1A tumors rather than limiting the selection to CIS or microinvasive carcinomas. In addition, many were conducted without the aid of newer technologies, such as endoscopic ultrasound, AFB, and positron emission tomography, to assess tumor suitability. The success is clearly dependent on the application of stringent selection criteria for appropriate tumors, better responses being reported for smaller tumors (30). Electrocauterization has been shown to cause less airway scarring and stenosis than do PDT and Nd:YAG laser therapy (31).

Because the majority of cases of early-stage, centrally located lung cancer are diagnosed on the basis of incidental findings, previous studies have dealt with relatively small numbers of patients treated with bronchoscopic techniques. Such tumors are often diagnosed during the clinical surveillance of high-risk individuals with any of various smoking-related illnesses, as well as in individuals having been treated for and cured of aerodigestive cancer. This in itself is a valid argument for the careful assessment of alternative treatment options prior to the consideration of surgical resection. Bronchoscopic techniques are clearly less morbid and less toxic than are surgical procedures. Even bronchoscopic techniques involving radiation appear to be less detrimental than is conventional radiation therapy. For selected early-stage, centrally located lung cancers, simple techniques such as electrocauterization, APC, and cryotherapy can be conducted safely and quickly under local anesthesia in an outpatient setting, thus providing greater cost-effectiveness.

In conclusion, there is sufficient technology available for the detection and treatment of early-stage squamous cell lung cancer. The greatest challenge ahead is to determine whether the screening of high-risk populations for the detection and treatment of early-stage squamous cell lung cancer improves patient survival and whether such a strategy is cost-effective.

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