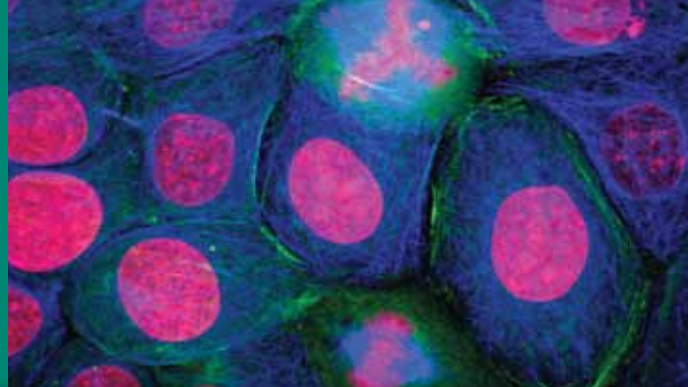




CEDARS-SINAI

Samuel Oschin Comprehensive Cancer Institute



ADVANCES IN CANCER

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Case Study: Transoral Laser Microsurgery for Head and Neck Cancer

Babak Larian, MD

Transoral laser microsurgery (TLM) uses a flexible, hollow-core fiber to transmit CO₂ laser energy, enabling precision surgery around intricate anatomy and critical structures. TLM can result in reduced post-operative pain, shorter rehabilitation, shorter hospital stays and better outcomes compared to traditional "open" surgery.

Presentation

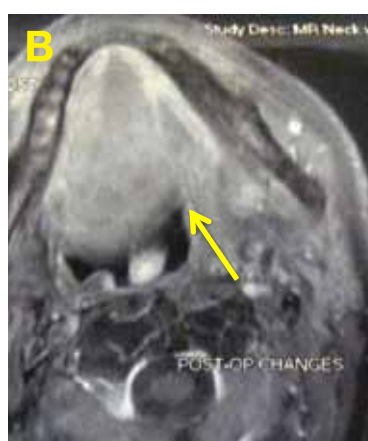
A non-smoking male in his mid-fifties presented with a lump in his neck he assumed was due to infection. He had been previously treated with antibiotics to no benefit. A needle biopsy was immediately performed, revealing a squamous cell cancer of the lining of the mouth, and MRI confirmed the presence of a tumor at the base of the tongue that had spread to his neck.

In a 12-hour procedure, the surgical team employed a precision laser to remove the spreading tumor without sacrificing large sections of adjacent normal tissue. One of the primary benefits of TLM is that it can provide tissue margins tailored to the exact shape and dimension of the tumor for an extraction that is precise and less invasive.

A traditional surgery for this patient would have required completely separating the tongue from its surrounding tissue, removing the tumor, then bringing all of the parts of the mouth back together. Because nerves are cut, such a procedure can result in the loss of sensation in the tongue, with negative consequences for both eating and speech. With TLM, however, enough normal tissue is left in the area to leave nerves intact and allow good blood flow to the tongue. Sensation is usually retained and the surgical incisions can heal more quickly.



(A) Preoperative MRI. Arrow indicates mass at the base of the patient's tongue.



(B) Postoperative MRI. Arrow indicates area from which tumor was removed.

Since radiation therapy and chemotherapy need good blood flow to be most effective, TLM may also be advantageous for patients' postoperative therapy.

Prognosis

The patient's prognosis is very good. He is undergoing six weeks of radiation therapy and his recovery to date has been spectacular. He was able to leave the hospital three days after surgery, began eating 10 days after surgery, has perfect speech and no breathing problems. A swallow study has shown no issues. Not only did pathological examination show that the tumor had been removed with safe margins of normal tissue, the one node in his neck that was cancerous had not spread beyond the capsule of the lymph.



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Staging of Advanced Esophageal Cancer

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The American Cancer Society estimated that there were 15,560 new U.S. cases and 13,940 deaths from esophageal cancer in 2007. Esophageal cancer is three to four times more common among men, and 50 percent more common among African-Americans. In some countries such as Iran, northern China, India and South Africa, esophageal cancer rates are 10 to 100 times higher than those of the United States. In Western countries, the incidence of esophageal adenocarcinoma in white men has been increasing at a rate of about two percent per year.

Importance of staging

Esophageal cancer staging is guided by the tumor-node-metastasis (TNM) system of the American Joint Committee on Cancer and the International Union Against Cancer. Since management decisions are heavily affected by the initial disease staging, accuracy is critical. Endoscopic ultrasound (EUS) with fine needle aspiration (FNA) is the most accurate modality in the initial tumor (T) and node (N) staging of esophageal cancer, while computed tomography (CT) and positron emission tomography (PET) scans are the most useful to detect metastatic disease.

CT and PET for initial staging, detection of metastasis

A CT scan of the chest and upper abdomen is usually performed once a diagnosis of an esophageal cancer is made, both to evaluate the region of the primary tumor and to search for distant metastatic disease. PET scans are even more sensitive than CT for detecting metastatic disease, and are now widely used for preoperative staging in patients who lack evidence of distant disease on CT.

Endoscopic ultrasound becomes standard practice

In recent years, EUS has replaced CT as the standard investigation in the T and N staging of esophageal cancer, and is considered the locoregional staging modality of choice. Using a dedicated radial echoendoscope, the physician captures ultrasound images from within the esophagus that allow assessment of the tumor's size and location. Once a tumor penetrates all the way through the wall of the esophagus (T3) or is node-positive, it is considered to be advanced disease, and long-term survival is uniformly poor. The optimal treatment for these patients is controversial; in many institutions, initial chemoradiotherapy is preferred over immediate surgery for patients with T3 and/or regional node-positive (N1) disease.



Figure 1: Endoscopic view of the upper margin of a lower esophageal tumor.

The accuracy of EUS for T staging ranges from 61 percent to 76 percent and for N staging from 64.5 percent to 89 percent, compared to postsurgical pathological staging. EUS can accurately stratify patients into "early" (T0-2 or N0) or "advanced" (T3-4 or N1) disease categories in 83 percent of patients, providing information that is highly predictive of treatment outcome and patient survival.

In fact, EUS changes patient management in about one-third of cases, with the majority (85 percent) moving toward nonsurgical and palliative treatments after identification of advanced disease. To avoid overstaging, EUS-guided FNA of suspicious lymph nodes is critical – since up to 80 percent of N0-pathology staged tumors may be overstaged as N1 by EUS alone.

Esophageal stricture and EUS

Some advanced esophageal tumors are challenging to evaluate using EUS because the tumor creates a stricture of the esophagus too narrow to be traversed by echoendoscopes, which are 12.7 mm in diameter. A non-traversable stricture can significantly decrease the accuracy of standard echoendoscope T-staging.

In such cases, a non-optic esophagoprobe (a slightly narrower instrument used for esophageal imaging) may be used as an alternative to the echoendoscope. The esophagoprobe is comparable in T-staging accuracy to the echoendoscope in patients with traversable tumors.

Dilating the esophageal stricture may also allow an echoendoscope or esophagoprobe

to traverse the constricted segment of the esophagus. Gradual dilation in a series of procedures over several days may be safer than dilating the stricture all at once.

EUS in multimodality imaging

The strength of EUS in a multimodality staging strategy – used in conjunction with CT and PET – is in identifying patients with locally advanced disease and guiding the need for preoperative neoadjuvant therapy.

In a study of 56 patients who concomitantly underwent examination with EUS, CT and PET in a multimodality staging program, EUS was the only imaging test that identified all primary tumors and provided tumor staging (note 1). EUS identified a significantly greater number of patients (58.9 percent) with locoregional nodes than CT

Continued on Page 4 (see "Esophageal")

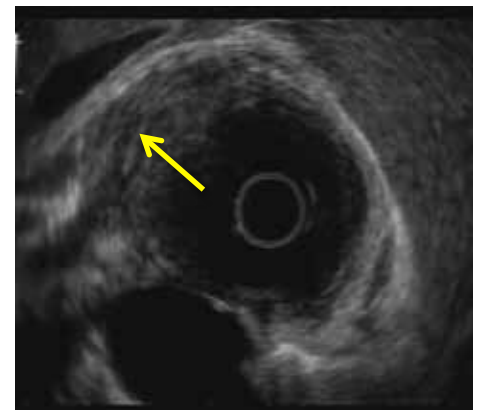


Figure 2: Endoscopic ultrasound showing invasion of a tumor beyond the muscularis propria.

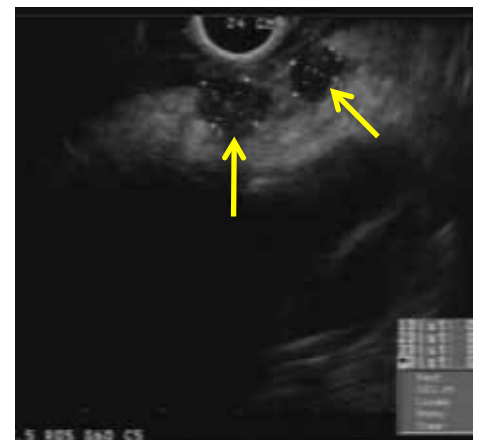


Figure 3: Endoscopic ultrasound showing malignant-appearing lymph nodes in the right upper paratracheal area.

Staining for Laminin in Glioma Biopsies

Serguei I. Bannykh, MD, PhD

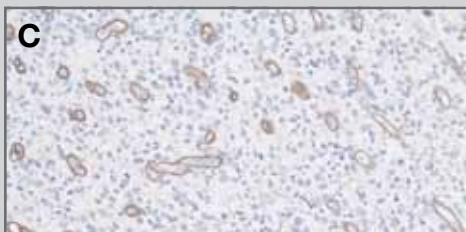
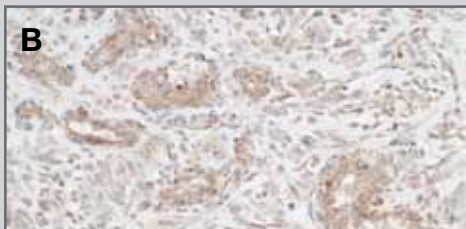
Cedars-Sinai pathologists now routinely employ immunohistochemical staining for $\beta 1$ and $\beta 2$ chains of laminin in order to better gauge the position of gliomas on the tumor progression scale (see related article on this page).

Examples of expression of laminin $\beta 1$ and $\beta 2$ in patients with glioblastoma multiforme are shown in figures A-D below. Loss of staining for laminin $\beta 2$ (A) and up-regulation of laminin $\beta 1$ (B) correlates with the most aggressive tumors and the worst clinical outcomes. Up-regulation of laminin $\beta 2$ (C) correlates with progression from the low-grade gliomas to the anaplastic variants. Anaplastic gliomas (WHO grade III) tend to have a relatively low expression of laminin $\beta 1$ (D).

Laminin testing helps to predict patients' survival – and can potentially be useful in differentiating between gliomas of WHO grade II and III.



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The Future of Chemotherapy: Molecularly Targeted Treatments

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As researchers gain new knowledge of the basic biology of cancer, this understanding is making a real difference to the success rate of new anticancer drug development. Recent adoption of anti-cancer drugs such as Gleevec®, Herceptin® and Avastin® clearly demonstrates the benefits of developing molecularly targeted treatments. Further achievements are likely to depend on the continued discovery and investigation of relevant molecular targets.

New molecular targets for brain tumors

In 2001-2004, an expression-profiling study on low- and high-grade gliomas conducted at Cedars-Sinai (IRB #s 3646, 14263) revealed a biochemical structural change in newly formed tumor vessels. It was shown that normal and malignant vessels express different proteins. Normal vessels predominantly express laminin 421, whereas malignant ones express laminin 411. Laminins are a group of basement membrane (BM) proteins that are all coded by three different genes each, and consist of three corresponding peptides, α , β and γ .

High-grade gliomas are vascular tumors, with vascularity increasing as tumors progress from low- to high-stage. Published data from the Cedars-Sinai study showed that laminin 411 ($\alpha 4\beta 1\gamma 1$) is mainly expressed in vascular BMs of an especially aggressive form of brain tumor, glioblastoma multiforme. Another alpha 4 chain containing laminin 421 ($\alpha 4\beta 2\gamma 1$) is mainly expressed in the blood vessel walls of low-grade, less aggressive tumors and in normal brain tissue.

As a result of this pioneering work, the Medical Center's neurosurgeons are using laminin testing to evaluate the biological behavior of gliomas with the goal of providing better, individualized therapeutic treatment and follow-up regimens for each patient (IRB #s 3646, 14263). Cedars-Sinai pathologist Dr. Serguei Bannykh successfully developed a new clinical test for laminin 411 evaluation (see related article on this page).

Using nanotechnology to block laminin 411

Cedars-Sinai researchers have blocked laminin 411 expression using a compound (antisense oligonucleotides) to significant-

ly reduce the spread of human glioma cells in cell culture. However, there were no methods available to prevent synthesis of this complicated structural protein for the purpose of human treatment. A new approach, employing the latest knowledge about drug delivery, tumor biology, chemistry and cancer therapy, was used to develop a novel, nanomedicine-based cancer treatment delivery system.

The resulting new drug, called Polycefyn, is a nanobiopolymer engineered to interrupt the changes in blood vessels and prevent tumor growth. Polycefyn specifically targets genes coding for laminin 411, the structural component of cancer blood vessels. In animal studies, Polycefyn was able to cross the blood-tumor-brain barrier and accumulate in cancer cells, suggesting that it may be used for targeting brain tumors without affecting normal surrounding tissue. Study results have documented an increased length of survival by 60 percent in laboratory animals following drug administration. Polycefyn may offer the first therapeutic approach designed to produce blood vessel changes involving multiple chain proteins such as laminins and collagens (*Nanomedicine*, 2008).

Future directions in nanomedicine to treat brain tumors

Polycefyn, which is 20 to 30 nanometers in size, acts as an anti-cancer drug – and can also be engineered to transport other therapeutic molecules. In ongoing laboratory work at Cedars-Sinai, researchers have successfully attached antisense oligonucleotides or siRNA monoclonal antibodies and chemotherapeutic drugs to Polycefyn molecules for transport directly into tumor cells. The technique, which was found to reduce drug side effects in laboratory animals, could eventually lead to the creation of highly potent, patient-specific treatment options.



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Esophageal: continued from Page 2

(26.8 percent, $P = .0006$) or PET (37.5 percent, $P = .02$). CT alone identified the need for preoperative neoadjuvant therapy in 15.2 percent of patients, PET alone identified this need in 28.3 percent and EUS – the most effective of the three modalities – identified this need in 34.8 percent.

Laparoscopic staging

Some centers use laparoscopic staging for esophageal cancer given the increasing prevalence of distal esophageal adenocarcinoma. This approach can potentially detect more nodes and distant metastases.

In a study of 125 patients with potentially resectable cancer of the distal esophagus or stomach, laparoscopic staging changed TNM classification in 46 cases (37 percent). This resulted in up-staging of the N-factor ($n = 15$) and M-factor ($n = 28$). Downstaging of the T-factor was recorded in three cases (note 2).

Another study compared laparoscopy to EUS for esophageal staging in 47 patients. EUS-FNA was 90 percent accurate compared to laparoscopic staging. Overall, staging accuracy of EUS compared to laparoscopic staging was 72 percent. Accuracy was 76 percent for patients with complete EUS staging compared with 64 percent for patients with incomplete EUS examinations. Staging differences were mostly reflected in distant metastases detected by laparoscopy (17 percent) (note 3).

PET with fluorodeoxyglucose

The role of fluorine-18 fluorodeoxyglucose PET (FDG-PET) in esophageal cancer stag-

ing continues to evolve. This technology is not indicated in the staging of superficial esophageal cancer. And while FDG-PET is better at detecting infiltrating lymph nodes and distant metastases than CT, it can lead to some false positive results. For this reason, CT is commonly the first choice for detecting metastatic disease. When CT shows no evidence of distant disease, FDG-PET is then used preoperatively to verify the absence of metastases.

There may be a role for FDG-PET to estimate the tumor metabolic length in untreated esophageal cancer, providing a noninvasive delineation of the superior and inferior extent of viable tumor involvement using computer-generated metabolic length measurements.

Magnetic resonance imaging

The role of magnetic resonance imaging (MRI) in esophageal cancer staging has not been thoroughly evaluated. Riddell et al were able to develop imaging criteria for local staging using high-resolution T2-weighted (T2W) MRI. Their success using this technique in a small group of patients demonstrated the value of continued study of MRI as a possible alternative, non-invasive method of local staging for esophageal cancer.

Future tests on FNA samples

There is growing evidence of the need for new forms of pathological testing of FNA samples. For example, there is reason to suspect the presence of micrometastases in lymph nodes that cannot be detected by standard pathological methods. Furthermore, the addition of methylation analysis to conventional cytology may have resulted in increased sensitivity to the presence of cancer while sacrificing accuracy in identifying

the type of cancer.

Digital image analysis (DIA) and fluorescence *in situ* hybridization (FISH) are two promising new forms of testing. One early study looked at DIA/FISH versus routine cytology (RC) examination on upper EUS-FNA samples, including samples from lymph nodes and esophageal malignancy. The sensitivity, specificity, and accuracy of DIA/FISH versus RC for detecting malignancy were 97 percent, 100 percent and 98 percent, versus 87 percent, 100 percent and 90 percent respectively. In one patient where RC was negative, DIA/FISH diagnosed squamous cell cancer.

Conclusion

For advanced esophageal cancer, locoregional staging is best performed with EUS-FNA, while a CT scan of the thorax and abdomen and FDG-PET should be used to detect metastatic disease. The role of laparoscopic staging is evolving and seems to complement EUS staging, while the role of MRI in esophageal cancer staging has not been well-studied.



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Note 1: Pfau PR et al. The role and clinical value of EUS in a multimodality esophageal carcinoma staging program with CT and positron emission tomography. *Gastrointest Endosc* 2007; 65:377-384.
Note 2: Kaiser GM, et al. Value of staging laparoscopy for multimodal therapy planning in esophago-gastric cancer. *Int Surg* 2007; 92:128-132.
Note 3: Kaushik N, et al. Endoscopic ultrasound compared with laparoscopy for staging esophageal cancer. *Ann Thorac Surg* 2007; 83:2000-2002.

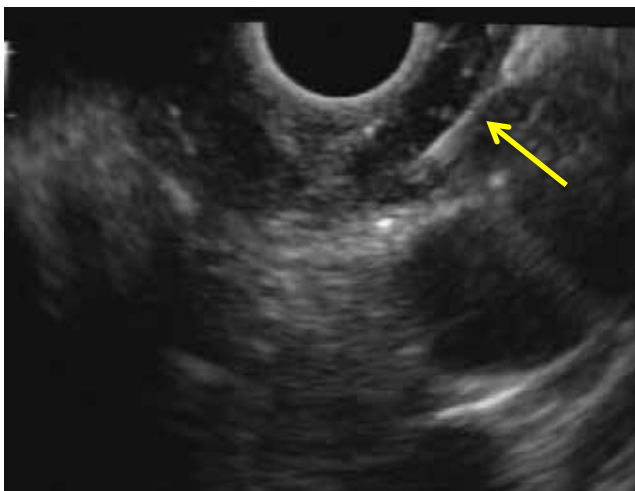


Figure 4: Endoscopic ultrasound-guided fine-needle aspiration. Yellow arrow indicates needle.

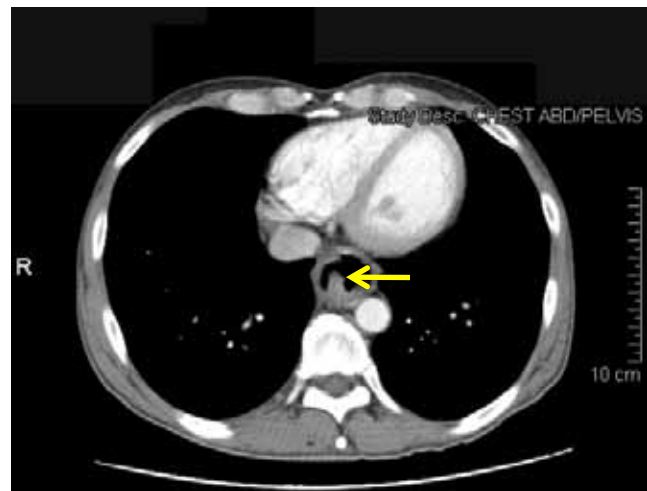


Figure 5: CT scan showing an esophageal tumor.