For Esophageal Cancer, Minimally Invasive Esophagectomy Yields Benefits

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Each year, more than 16,000 individuals in the United States are diagnosed with esophageal cancer—and the frequency is increasing dramatically at a rate surpassing any other cancer. Minimally invasive esophagectomy (MIE) improves the surgical standard of care by delivering decreased morbidity, shortened hospital stays and more rapid return to daily activities than open surgery. A technically elegant procedure with a steep learning curve, MIE encompasses thoracoscopic and laparoscopic surgery performed in three stages with as many as 600 separate steps.

In the first stage, the patient is placed in the left lateral decubitus position for minimally invasive mobilization of the intrathoracic esophagus, as well as lymphadenectomy, using video-assisted thoracoscopic surgery (VATS).

In the second stage, the patient is placed in a supine position for laparoscopic construction of the gastric conduit, placement of a feeding jejunostomy, and pyloroplasty.

The third stage consists of mobilization of the cervical esophagus via the left neck, removal of the surgical specimen and gastric pull-up, and construction of an esophagogastric anastomosis. This phase of the operation is performed as a continuation of the second stage, while the patient is still in the supine position.

If there is any concern that the patient may have disease not identified by conventional staging—such as endoscopic ultrasound, computed tomography (CT) or positron emission tomography (PET)—a staging laparoscopy is performed to confirm the stage of the patient by looking for tumor implants on the peritoneum and liver. This allows the surgeon to make an informed decision as to whether the patient is truly a surgical candidate. Surgery may be done on the same day as the staging laparoscopy if no suspicious lesions are found. However, biopsies are often necessary, and surgery is postponed until final pathology results are obtained.

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Comparing Top-Down to Step-Up Therapy for IBD

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The development of effective anti-tissue necrosis factor (anti-TNF) agents has substantially improved the treatment of inflammatory bowel disease (IBD), reducing hospitalizations and surgery for patients with Crohn’s disease or ulcerative colitis. In two important areas, symptom relief and mucosal healing, anti-TNFs have consistently produced higher success rates than conventional therapies. This has prompted a discussion of the potential role of an anti-TNF as an early treatment for IBD.

“Step-up” describes an approach in which gradual acceleration of therapy takes into consideration such factors as safety, cost and disease activity to help determine the order in which drugs are prescribed (Fig. 1). A “top-down” approach, on the other hand, starts therapy with biologic agents. Biologics are prescribed first in preference to steroids and/or immune-modulators under the rationale that anti-TNF agents will produce a better outcome while avoiding steroid side effects.

Most clinical trials have enrolled patients with active disease to placebo-controlled comparisons between an anti-TNF such as infliximab, adalimumab or certolizumab. These patients were symptomatic despite on-going treatment with mesalamine, steroids, thiopurines or methotrexate. Those drugs were continued during the clinical trial, so that differences in outcome could be seen as differences between an anti-TNF plus conventional therapy vs. conventional therapy alone. The trials represent the step-up approach: only after failure to respond to steroids and immunomodulators were patients given the anti-TNF.

One trial of the top-down approach has been reported (D’Haens, Lancet 2008). In this study, patients with Crohn’s disease for four years or less and no prior treatment with biologics, immunomodulators or steroids were randomized into two treatment arms:

- **Combined immune-suppression**: 5mg/kg bodyweight infliximab at 0, 2 and 6 weeks plus 2-2.5 mg/kg bodyweight azathioprine daily for duration of trial
- **Conventional corticosteroid therapy**: 32 mg methylprednisolone daily for 3 weeks or 9 mg budesonide daily for 8 weeks, then dosages tapered off for a total treatment period of 10 weeks

At the end of one year, 62 percent in the early combined immune-suppression group were in remission vs. 42 percent in the conventional therapy group. In addition, the patients receiving infliximab and azathioprine required none or minimal treatment with steroids that year.

The step-up approach has been the traditional way to escalate therapy in patients with IBD. Its advantages include the early use of safer and less expensive drugs with relatively rapid onset of action. However, while cost and safety are assets of 5-ASA drugs, they are generally only effective in ulcerative colitis. Prednisone, which is inexpensive and may work within days, is actually associated with a greater risk of death due to serious infection than biologic treatments. The major disadvantage of step-up treatment is the time lost trying ineffective therapies. The patient becomes more debilitated, leading to greater resistance to other medical treatments. Therefore, the severity of the condition at presentation should be an important factor in the selection of initial therapy.

The advantage of a top-down approach is that treatment better matches disease severity—and the earlier biologics are started, the better the response. There is also the potential for mucosal healing, which may result in fewer long-term complications. The disadvantages to early therapy with biologics are economic and logistical. The drugs are very expensive and obtaining third-party authorization can be a lengthy process. There is also the risk of serious infections associated with long-term biologic use. Finally, patients with a low risk for complications and/or surgery might never require biologic treatments in their lifetime.

Top-down therapy is probably best reserved for patients with complicated Crohn’s disease. This includes patients with ileitis and inflammatory narrowing, where the goal is to prevent stricture formation. Patients with fistulizing disease, especially those with complex perianal disease, are best treated with biologics rather than other therapies. A possible third group is women who experience flaring of their IBD symptoms early in pregnancy. For these women, the efficacy of biologics can be a distinct advantage over months of corticosteroids.

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The American Association for the Study of Liver Diseases (AASLD) guidelines for the management of chronic hepatitis B virus (HBV) were recently updated. Although many of the core recommendations remain the same, several changes were made from previous versions.

**Background**

Chronic HBV, when acquired via vertical transmission, is generally divided into four phases (Fig. 1). It needs to be emphasized that these phases, although chronological, do not always proceed in a linear, progressive manner.

The initial phase of infection is termed the “immune-tolerance phase.” This usually occurs early in life and is characterized by very high viral loads and normal alanine transaminase (ALT) levels. The lack of immune response will eventually give way to the “immune-clearance” phase. During this second phase, the immune system starts to attack the virus. As a result, viral loads tend to fluctuate and ALT levels often flare as infected hepatocytes are killed. This may culminate in e-antigen seroconversion and a third phase termed the “inactive carrier state,” during which the immune system exerts some degree of control over the virus. Patients in this phase have low viral loads and normal ALT levels. However, even at low levels of replication, the virus will often find ways to escape immune surveillance, resulting in a fourth phase of “reactivation.”

**What remains unchanged**

Treatment for patients with compensated liver disease continues to be reserved for those with elevated viral loads above 20,000IU and ALT levels at least twice the upper limit of normal. The goal of maintaining these criteria is to limit treatment to those who are either in the immune-clearance or reactivation phases of chronic HBV. These groups are characterized by higher ALT levels and necroinflammatory scores, which can be thought of as surrogate markers for immune activity. A number of clinical trials have shown these groups are more likely to benefit from therapy than those who are immune-tolerant.

**What has changed**

One of the most significant changes to occur concerns the definition of an abnormal ALT level. This is now accepted as anything above 30 U/mL for a man and above 19 U/mL for a woman. For those who have persistently normal levels, the follow-up interval for lab checks should be every three to six months. Liver biopsy should be considered for these individuals above the age of 40.

Another change involves an expansion of those who should be screened for HBV. The new guidelines recommend screening anyone who originates from a country of intermediate or high prevalence for HBV, defined by a prevalence of 2 percent or more. This essentially includes many more countries than it excludes. Close contacts of individuals from these countries should be screened as well.

Other groups that should be screened include those who have abnormal liver enzymes and anyone who will be receiving immunosuppressive therapy. The third area that has been modified concerns the first-line choices for therapy in treatment-naïve individuals. These should include entecavir, tenofovir and pegylated interferon alfa-2a. The rationale for starting with these choices is based on their low resistance rates.

Interferon is an injectable, while entecavir and tenofovir are oral therapies. The oral therapies seem to exert their antiviral effects irrespective of genotype, whereas interferon-based therapy appears to work best in well-compensated patients with genotype A HBV. Also, use of the orals as monotherapy in patients coinfected with HIV should be avoided due to the risk of inducing drug resistance.
Case study

A 60-year-old, slightly obese, Caucasian male with a history of Barrett’s esophagus that had developed into high-grade dysplasia and then into adenocarcinoma was referred to Cedars-Sinai Medical Center. Since the cancer had not been properly staged, an endoscopic ultrasound was performed to evaluate tumor depth and penetration. The stage was determined to be T2, N0.

A PET scan and CT scan were performed to look for metastatic disease, and pulmonary function tests were undergone to ensure the patient could tolerate the operation. Last, laparoscopic staging to look for micronodules on the diaphragm, liver and peritoneum was performed. All tests were normal, so the decision was made to proceed with MIE.

In the first stage of the procedure, the entire esophagus was mobilized using VATS. Under direct visualization, all visible lymph nodes were removed, the periesophageal tissues were cleaned, and the carina was evaluated. Next, the subcarinal lymph node packet was removed, as were lymph nodes all the way up to the thoracic inlet. At the completion of the thoracoscopy, a Penrose drain was left in the thoracic inlet, chest tubes were put in place, and the area was closed.

In the second stage of the procedure, the patient was placed in a supine position. Trocors were placed into the abdomen, as was a feeding jejunostomy. Once gastric mobilization was complete, a laparoscopic pyloroplasty was performed. Next, the stomach was de-vascularized, and care was taken to preserve the right gastric vessels. The stomach was then stapled into a gastric tube five cm in diameter. Once the tube was created, it was attached to the esophagogastric specimen.

In the last stage of the procedure, the esophagus was divided 2 cm below the cricopharynx, and the esophagogastric specimen was pulled out of the wound. The entire specimen with proximal and distal margins was sent to pathology to make sure clear margins were established. An anastomosis was then performed between the esophagus and gastric tube. Next, any redundant gastric conduit was pulled back into the abdomen under direct visualization. The gastric tube was then sutured to the right and left crura in proper orientation. Finally, instrumentation was withdrawn, a toilet broncoscopy was performed, and the port sites were closed.

The patient spent one day in the intensive care unit and began tube feeds on postoperative day 1. He was transferred to a regular bed on postoperative day 2. On day 4, a barium swallow was performed to ensure there was no leak and no evidence of aspiration. The patient was started on a liquid diet and advanced to full liquids and then a soft diet. He was discharged home on postoperative day 7.

The patient’s final surgical pathology was T2, N0. All margins were clear and all 33 lymph nodes were negative for malignancy. The patient felt well and went home with minimal pain and discomfort. On follow-up in clinic, the patient is recovered and performing activities of daily living. This patient’s prognosis is very good.

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