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From the Desk of Director Research

Esophageal cancer (EC) is a highly fatal malignancy. It is the eighth most common cancer worldwide, with 481 000 new cases (3.8% of the total) estimated in 2008, and the sixth most common cause of death from cancer with 406 000 deaths (5.4% of the total). These figures encompass both adenocarcinoma and squamous cell carcinoma (SCC) types. More than 80% of the cases and deaths occur in developing countries. Smoking and excessive alcohol consumption account for about 90% of the total cases of squamous cell carcinoma of the esophagus. By contrast, smoking, obesity, and gastroesophageal reflux disease are thought to be the major risk factors for adenocarcinoma. Over the past few decades, the incidence of adenocarcinoma of the gastroesophageal junction has risen dramatically in western countries.

The esophagus extends from the cricopharyngeal sphincter to the gastroesophageal (GE) junction and is commonly divided into the cervical, upper- to mid-thoracic, and lower thoracic portions. This can be important, because histology and optimal treatment approaches may vary considerably according to the site of the cancer. It may not be possible to determine the site of origin if the cancer involves the GE junction itself.

At diagnosis, nearly 50% of patients with esophageal cancer have cancer that extends beyond the locoregional confines of the primary. Fewer than 60% of patients with locoregional cancer can undergo a curative resection. Nearly 70% to 80% of resected specimens harbor metastases in the regional lymph nodes. Thus, clinicians often have to deal with advanced-stage carcinoma in newly diagnosed patients.

The treatment of esophagogastric cancer has been rapidly evolving in the past decade. New cytotoxic drugs and targeted agents have been integrated in the therapeutic paradigm. To better understand the tumor biology and to better utilize targeted agents, genetic alterations in esophagogastric cancer have been actively explored. Combination of trastuzumab with cytotoxic chemotherapy has demonstrated a survival advantage in patients with Her2/neu positive gastric cancer. However, the prognosis of advanced esophagogastric cancer remains poor. This is largely attributed to the tumor heterogeneity and poorly understood tumor biology. The integration of targeted therapies and development of predictive biomarkers to identify subgroups of patients who are likely to benefit will mark the future of neoadjuvant treatment in this disease.

This issue of Cancer News profiles the complexities and advancements in the field of Esophageal and GE Junction Cancer, and includes regular articles, such as “Special Feature”, “Guest Article”, “Perspective”, “Watch-Out”, “Research & Development”, “New Technologies”, “Clinical Trials”, “Globe Scan”, and “Cancer Control”.

We appreciate the contribution made by Dr Sanjay Sharma, Consultant, Surgical Oncologist, Asian Institute of Oncology, Mumbai, for providing the “Guest Article”on “Surgical Perspective in Esophageal & GE Junction Cancers”.

Suggestions / comments from the readers are welcome.

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SPECIAL FEATURE

NEWER ADVANCES IN CHEMOTHERAPY AND TARGETED THERAPY FOR ESOPHAGEAL & GE JUNCTION

Introduction

Cancers of the upper gastrointestinal (GI) tract are highly lethal malignancies. The five-year survival rates for esophagus and gastric cancers are among the worst reported for any malignancy. According to data from the National Cancer Institute Surveillance, Epidemiology and End Results (SEER) Program, the five-year survival for patients with esophageal and gastric cancer has improved only modestly over the last 50 years, from 4 percent in the years 1950 to 1954 to 17 percent during the period 1996 to 2003 for esophageal cancer, and from 12 to 22 percent for gastric cancer .Together, squamous cell carcinoma (SCC) and adenocarcinoma account for 93 percent of all esophageal carcinomas, but histologic and anatomic distribution has changed dramatically over the past 30 years. Adenocarcinomas of the distal esophagus, EGJ and proximal stomach share a common pathogenesis that is most likely different from that of proximal esophageal and distal gastric cancers.

Palliative treatments for advanced esophageal or gastric cancer can be either local or systemic. While cytotoxic chemotherapy is the most effective treatment modality for patients with metastatic disease and it may adequately palliate dysphagia, other symptoms such as nausea, pain, obstruction, perforation, or bleeding from a locally advanced or locally recurrent primary tumor often require multidisciplinary management using endoscopic, surgical, radiotherapeutic or other approaches.

Chemotherapy

Chemotherapy drugs that were tested for esophageal cancer at a time when SCC was the predominant histology (1970s and 1980s) were those initially developed for SCC of the head and neck, including 5-fluorouracil (5-FU), cisplatin, mitomycin, methotrexate, vindesine, and bleomycin. The combination of 5-FU plus cisplatin (FP) was adopted by many as a safe and effective standard regimen, and studies focused on the benefit of adding a third agent to the FP backbone. The response rates of these single agent chemotherapy drugs vary between 15-30% in different studies. The studies evaluating newer single agent chemotherapy in locally advanced and metastatic esophageal and gastric cancers did not result in improved responses.

Combination Chemotherapy and Newer Agents

In general, combination chemotherapy regimens provide higher response rates than do single agents, but this translates into only modestly longer durations of disease control and survival that are measured in weeks to a few months.

ECF and the Real Trial: The REAL trial was a landmark large randomized trial reported in 2008 that compared four different chemotherapy regimens in 1002 patients with advanced gastric cancer: ECF, EC plus the oral fluoropyrimidine capecitabine (ECX), and epirubicin plus oxaliplatin and either infusional 5-FU (EOF) or capecitabine (EOX, The study was sufficiently powered to demonstrate noninferiority.

As noted above, the trial showed that outcomes were comparable when capecitabine was substituted for infusional 5-FU in the ECF regimen, a finding that was reinforced in a subsequent meta-analysis of this and one other trial. They also showed (as did the meta-analysis that outcomes were comparable when oxaliplatin was substituted for cisplatin in the ECF regimen.

However, when the four groups were considered separately, median survival in patients treated with EOX was modestly longer compared to ECF (median 11.2 versus 9.9 months). These data have led some to conclude that EOX is preferred over ECF for first-line therapy.

Taxane-Based Combinations: Several taxane-containing regimens have been studied, none of which has emerged as clearly superior to any other or to modern cisplatin-based combinations because so few randomized trials have been carried out.

Paclitaxel Regimens: In two studies, an every two week or every three week regimen of cisplatin plus paclitaxel was associated with a response rates of 43 and 49 percent, and median survival durations of 9 and 13 months, respectively. The major toxicity encountered was neutropenia.

More recently, every other week paclitaxel plus short-term infusional 5-FU plus leucovorin yielded favorable antitumor activity and a better toxicity profile. A better tolerated combination may be paclitaxel plus carboplatin.

Docetaxel Regimens: Docetaxel combinations with cisplatin, 5-FU, capecitabine, or irinotecan are active in advanced gastric and esophageal squamous cell cancer.

DCF (TCF): Docetaxel plus cisplatin and 5-FU (the DCF or TCF regimen) was compared to cisplatin and 5-FU alone in a multinational TAX-325 trial that enrolled 457 patients with chemotherapy-naive advanced gastric cancer. Patients received either 21-day cycles of cisplatin (75 mg/m^2 on day 1) plus infusional 5-FU (750 mg/m^2 daily, days 1 to 5) and docetaxel (75 mg/m^2 on day 1) or 28-day cycles of cisplatin (100 mg/m^2 on day 1) plus infusional 5-FU (1000 mg/m^2 per day days 1 to 5). The group receiving docetaxel did significantly better in terms of response rates (37 versus 25 percent), time to tumor progression (TTP, 5.6 versus 3.7 months) and two-year survival (18 versus 9 percent). Although the incidence of grade 3 or 4 diarrhea (20 versus 8 percent) and neutropenia (30 versus 14 percent) was higher with triple therapy, rates of any grade 3 or 4 toxicity during therapy were high in both groups (81 and 75 percent, respectively). DCF showed significant improvement compared to cisplatin/5-FU in measures of clinical benefit, including time to definitive worsening of performance status (median 6.1 versus 4.8 months) and in the duration of preserved quality of life (as assessed by the time to 5 percent deterioration in global health status) There were also trends toward a better outcome with DCF, including longer time to definitive weight loss and time to definitive worsening of appetite.

Oxaliplatin Combinations: Although oxaliplatin combinations have been most extensively studied for metastatic colorectal cancer, they are also active in the treatment of esophagogastric cancer. A variety of different regimens have been studied in phase II trials (FOLFOX, EOF, XELOX [CAPOX], S1 plus oxaliplatin), all of which are associated with response rates in the range of 40 to 67 percent, with median survival durations between 8 and 15 months.

Irinotecan-containing Regimens: In a meta-analysis, the comparison of irinotecan-containing versus non-irinotecan-containing regimens (mainly5-FU/cisplatin) revealed a nonstatistically significant trend toward better survival with irinotecan.

Irinotecan has been combined with cisplatin, docetaxel, and fluoropyrimidines. There are no phase III trials comparing an irinotecan-based combination with a cisplatin-based triplet regimen such as ECF, DCF (TCF), or EOX.

Biologic Agents

***Agents Targeting HER2*:** Approximately 7 to 22 percent of esophagogastric cancers overexpress the type II EGFR (HER2), a similar percentage to that seen in breast cancer.

The benefit of trastuzumab in advanced HER2-positive adenocarcinoma of the stomach or esophagogastric junction (EGJ) was addressed in the phase III ToGA trial, which compared standard chemotherapy (six courses of cisplatin plus either infusional 5-FU or capecitabine) with and without trastuzumab (8 mg/kg loading dose, then 6 mg/kg every three weeks until disease progression). The objective response rate was significantly higher with trastuzumab (47 versus 35 percent). At a median follow-up of 17.1 to 18.6 months, median overall survival (the primary endpoint) was significantly better with trastuzumab (13.8 versus 11.1 months).

Lapatinib: Lapatinib, an orally active small molecule inhibitor of both epidermal growth factor receptor (EGFR) type I and II (HER2), is under study in combination with weekly paclitaxel versus paclitaxel alone in patients with previously treated advanced gastric cancer.

Agents Targeting EGFR: Tumor overexpression of EGFR correlates with poor prognosis.

Cetuximab and Panitumumab: The benefit of adding cetuximab to cisplatin plus 5-FU was addressed in a randomized phase II German trial of 66 previously untreated patients with metastatic squamous cell cancer (SCC). The objective response rate was only slightly higher (19 versus 13 percent), and there was a trend toward longer median PFS (5.7 versus 3.6 months) and overall survival (9.5 versus 5.5 months) when cetuximab was added to the CF backbone. Conclusions regarding the clinical utility of cetuximab in patients with advanced esophagogastric cancer await data from randomized phase III trials.

In the REAL3 trial, 553 patients with previously untreated advanced unselected esophagogastric cancer were randomly assigned to EOC (epirubicin 50 mg/m^2 on day 1, oxaliplatin 130 mg/m^2 on day 1, and capecitabine 1250 mg/m^2 per day), or modified EOC (with a reduction in oxaliplatin to 100 mg/m^2 and capecitabine to 1000 mg/m^2 per day) plus panitumumab. In a preliminary report presented at the 2012 ASCO meeting, the addition of panitumumab was associated with a similar response

rate but a significantly worse overall survival (median 8.8 versus 11.3 months). The authors postulated that the lower chemotherapy doses and/or higher toxicity rates in the panitumumab arm may have compromised outcomes in this group.

Small Molecule Tyrosine Kinase Inhibitors: Another means of interfering with EGFR signaling is through the use of orally active tyrosine kinase inhibitors (TKIs), small molecules that block the binding site of the EGFR TK. Small molecule TKIs that have been tested as single agents in phase II and III trials in esophagogastric cancers are gefitinib and erlotinib. However these agents have not resulted in any significant benefit.

Bevacizumab (Agents Targeting VEGF): A phase III AVAGAST trial for adding bevacizumab to capecitabine plus cisplatin could not show a survival benefit. In this trial 774 patients with previously untreated locally advanced unresectable or metastatic (98 percent) gastric or EGJ cancer were randomly assigned to capecitabine (1000 mg/m^2 twice daily for 14 of every 21 days) plus cisplatin (80 mg/m^2 on day 1) with either bevacizumab (7.5 mg/kg day 1) or placebo. Cycles were repeated every three weeks for a maximum of six cycles of cisplatin; thereafter, capecitabine plus either bevacizumab or placebo was continued until disease progression. Although the addition of bevacizumab to chemotherapy significantly improved both objective response rate (46 versus 37 percent) and median progression-free survival (6.7 versus 5.3 months), there was no significant survival benefit (median 12.1 versus 10.1 months).

Future Perspective

- The use of HER2 status as predictor of prognosis and response to anti-HER2 drugs changes the design of future trials. All new trials should define by recruitment whether patients with GEJ or gastric cancer have a HER2-positive or -negative disease before randomization to induction or postoperative chemoradiation with an anti-HER2 drug in HER2-positive cancer.
- Histone methylation and miRNA expression have gained attention as potential therapeutic targets.

NCCN Guidelines for Systemic Treatment in Esophageal and Esophagogastric Cancers

First Line Treatment

- Trastuzumab with Cisplatinum and 5-FU
- DCF chemotherapy
- ECF chemotherapy or modifications of ECF like EOF, ECX, EOX.

Subsequent Treatment

- Irinotecan + Platinum
- Irinotecan + Fliropyrimidine
- Irinotecan + Docetaxel
- Single agent Irinotecan, Gemcitabine

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GUEST ARTICLE

SURGICAL PERSPECTIVE IN ESOPHAGEAL & GE JUNCTION CANCERS

Introduction

Globally, esophageal cancer is the eighth most common malignancy and sixth most common fatal with approximately 4, 60,000 new diagnosis and >3, 80,000 deaths annually [1]. In a disease where many deaths occur as new cases reported, thorough search has been and is being done in recent years to offer optimal therapeutic interventional strategy for its management. The advances in technology combined with understanding of genomics and biology of esophageal cancer has allowed introduction of an era of multimodality treatment. Despite several standards of care influenced by geographical location, patient status and institutional bias, surgery is the gold standard and radical three-field esophagectomy for most patients and still remains the mainstay as primary curative option for localised resectable esophageal cancers or as secondary to achieve R0 resection after down staging disease with neoadjuvant chemotherapy or after chemoradiation to confirm pathologic response at primary tumor and nodal level and to eradicate residual disease [2].

Surgical Options

The goal of surgery is to achieve local control by curative (R0) resection, comfortable alimentation, improve outcome in terms of diseasefree survival (DFS) and overall survival (OS), minimise morbidity and improve quality of life (QOL). The optimal surgical approach, extent of lymphadenectomy, selection of conduit and location of anastomosis depends on tumor location, stage of the disease, risk profile of the patient, route of conduit placement, experience and preference of a surgeon and institutional policy. The various surgical options available are: endoscopic mucosal resection (EMR), Mckeowns esophagectomy, transhiatal esophagectomy, Ivor Lewis esophagectomy, extended (enbloc) esophagectomy, minimal invasive esophagectomy (MIE), vagus sparing esophagectomy and left thoracoabdominal (Garlocks) approach. The extent of lymph node dissection (LND) can be two field or thre field. The conduit can be stomach, colon or jejunum. Anastomosis can be handsewn, stapled; single or double layer; continuous or interrupted; end to end or end to side.

Surgical Management of Premalignant and Early Esophageal Cancers

Arrays of therapeutic options have been studied for Barretts esophagus (BE) with high grade dysplasia (HGD) and superficial cancers of the esophagus. These include photodynamic therapy, radiofrequency ablation, argon beam plasma coagulation, EMR and esophagectomy with or without vagal sparing. The arguments in favour of esophagectomy are: *(i)* It completely eradicates mucosa at risk and precludes the development of recurrent and metachronous lesions that may occur with other options. *(ii)* It has been widely published that 30-50% of patients undergoing esophagectomy for high grade dysplasia are found to have an occult invasive cancer in the resected specimen [3]. *(iii)* The surgery is less morbid because extensive lymphadenectomy is not required as the chance of lymph node involvement in mucosal cancers is <5%[4]. *(iv)* An endoscopically visible region within Barretts mucosa cannot be assumed to be confined to mucosa no matter how much small. Such lesions may penetrate into the sub mucosa where the risk of nodal involvement is 25% [5]. *(v)* It is an ideal option for anxious patients with allied difficult to correct pathophysiologies, e.g., motility disorders, poorly controlled gastroesophageal reflux disease, large hiatus hernia and delayed gastric emptying. *(vi)* Various studies have shown cumulative incidence of progression from HGD to esophageal cancers ranging from 16% to 59% over 5 to 8 year period of surveillance [6], thus serving an excellent option for patients who can't return for frequent follow ups. Keeping the above arguments in consideration, the NCCN guidelines recommend esophagectomy (MIE, vagal sparing or not), EMR and ablation therapy for T1s (HGD), T1a (lamina propria) lesions and radical esophagectomy with lymphadenectomy for T1b (sub mucosa) lesions.

EMR, a minimal invasive technique popular in Japan is indicated in BE with HGD and <2cms, non ulcerated, well or moderately differentiated esophageal cancers confined to lamina propria without any lymphovascular invasion or nodal metastasis. EMR serves as a valuable staging procedure that can identify patients with lesions confined to the mucosa that have a low risk of nodal involvement and for whom there is no need to perform lymphadenectomy at the time of esophagectomy. The limitations of EMR are the lack of randomised trials comparing it with standard surgical techniques, requirement of and expertise in endoscpic ultrasonography to determine depth of tumor and guided biopsies from periesophageal nodes, risk of occult nodal metastasis and chance for recurrent or metachronous lesions[7].

Surgical Management of Invasive Esophageal Cancer

Esophagectomy is the mainstay of treatment for localised or locally advanced resectable carcinomas of esophagus either as sole therapy or as the key component in multimodality treatment. There is no issue that engenders more debate among experts than the optimal surgical approach of esophagectomy and the extent of lymphadenectomy. Proponents of transhiatal esophagectomy (THE) emphasize the benefit of shorter operative procedure, fewer pulmonary complications, longer proximal margins of resection and a cervical rather than an intrathoracic anastomosis. Opponents suggest that THE ignores basic principles of oncology with less exposure, inferior tumor and lymph node clearance, less hemostasis and risk of complications like anastomotic leaks, thoracic duct or recurrent laryngeal nerve injury. Advocates of transthoracic esophagectomy (TTE) discuss the oncologic superiority of this approach in terms of thorough exposure and benefit of dissection under vision and extended lymphadenectomy to more accurately stage the disease and provide local control. The opponents argue that TTE increases risk of mediastinitis, sepsis and not ideal for patients with co morbidities. The results of two large meta-analysis by Rindani and Hulscher didn't show any statistically significant difference in median DFS and OS between the two surgical approaches [8]. The proponents of three field lymphadenectomy argue that more local control, disease free and overall survival as lymphatic spread is bidirectional in mid-esophageal cancers and in one-third cases of lower esophageal cancers, upper thoracocervical nodes are involved. The opponents believe it causes more morbidity and is indicative of a systemic disease.

Various studies have now shown that circumferential margins, total number of lymph nodes removed, ratio of metastatic to total nodes retrieved and blood loss are the major prognostic factors. Higher the lymph node count (>30) and negative lymph node count (>15) are associated with best overall survival [9]. The Japanese concept of enbloc esophagectomy with lymphadenectomy does seem to overpower the minimalist Western approach as it shows better rates of RO resections, negative circumferential margins and adequate lymphadenectomy, less blood loss, all contributing to benefit in long term survival. Possible reasons of better results and less morbidity in Japan than West may be the patient profile [thin built vs obese in West], histology [SCC in Japan vs AC in West], more expertise and experience in Japanese surgeons. The NCCN guidelines recommend at least 10 lymph nodes to be resected in T1 lesion, 20 in T2 and 30-40 lymph nodes in T3, 4 lesions. For all practical purposes, at least minimum 15 lymph nodes in 2-field LND and 25-30 in 3-field LND dissection are considered adequate for accurate staging.

Technical Considerations in the Performance of Esophagectomy

Radical esophagectomy with lymphadenectomy in spite of being a technically challenging surgery, lately there has been a significant improvement in post esophagectomy results in comparison with the past. Based on current literary references, the mortality rate now is within 1.0 to 5.8% and morbidity 17.9 to 58% with a considerable improvement in overall survival and decreased loco regional recurrences [10]. The data results from our study [11] and other recent studies have shown that specific measures when taken preoperatively, intra operatively and post-operatively have improved results (Table I).

Preoperative Measures

The focus has to be on better case selection. Preoperatively risk factors have to be taken into account to reduce morbidity and mortality as has been shown by

Table I: The Mortality and Mobidity of Our Study as Compared with Other Studies in Literature

STUDIES COMPARED	MORTALITY %	MORBIDITY %			
		PULMONARY	RLN PALSY	LEAK	TRACHEOSTOMY
Aikyam 1994	2	31	10	0	-
Fujita et al 1995	2	6	70	11	21
Kato 1991	2.6	9	14	33	-
Nishi Hara 1998	3.1	19	56	6	53
Altorki 2002	15	26	9	11	4
Ando 2000	1.7	22	-	13	-
Verba et al 2012	8	20	10.6	6.6	-
Nakamura et al. 2008	3.3	19.6	1.6	9.2	-
Sharma et al. 2010	2.75	16	12.5	2.4	8.2

Table II: Ca Esophagus -Modified Risk Factor Analysis

ORGAN	FUNCTION TEST	RISK CLASSES	POINTS	RELEVANT FINDINGS
LUNG	PFT (FVC, PaO2, FEV1)	Normal Increased High	1 2 3	FVC>90% 2 PaO2 70 mmhg FVC<90% 1PaO2 70 mmhg FVC<90% PaO2 70 mmhg
HEART	Cardiac Normal Pari clinic opinion	Normal Increased High	1 2 3	No apparent cardiac risk Increased risk Rcent myocardial infarction
LIVER	Serum parameters	Normal Increased High	1 2 3	
GENERAL	Karrofsky index PT Co-operation	Normal Increased High	1 2 3	>80%, Good co-operation = 80%, Bad co-operation <80%, Bad co-operation

Siewert. We have modified the assessment to a modified TMH (SS) risk scoring system (Table II). This has reduced our morbidity considerably in patients with low and intermediate scores. Patients with high scores have been treated with other modalities rather than surgery.

Various patient factors implicated to increase cardio pulmonary morbidities include advancing age, history of smoking, diabetes, cirrhosis, poor LFT'S, FEV1<65%, poor nutritional status, pre-existing lung diseases (COPD or infection). Measures taken are optimization of comorbidities, nutritionally replenish patient, cessation of smoking, adequate hydration and antibiotics. Preoperative chest physiotherapy and incentive spirometry are the key.

Intra Operative Measures

There are various principles and measures taken to reduce morbidity and mortality and improve results. The most important pre-requisites are effective synchronization and jelling of team members, good anaesthesia delivery with epidural catheter placement and single lung ventilation and standardisation of surgical techniques and principles. Aim should be monobloc meticulous R0 resection safeguarding RLN, bronchial artery with end to side esophagogastric anastomosis. The monobloc R0 resection prevents tumor implantation and decreases loco regional recurrence rates [12]. R+ resections have been shown to have bad prognosis and thus avoided. Meticulous dissection in surgical planes leads to decreased blood loss and thereby decreased rate of transfusions. Increased blood loss has been shown to be associated with an increased incidence of pulmonary complication and hospital deaths after esophagectomy [13].

Preservation of azygous vein, bronchial artery which lies beneath it and RLN helps in decreasing pulmonary complications. RLN should be dissected meticulously by avoiding traction, compression, blunt dissection and use of bipolar cautery preferred to avoid thermal injury. The principles of anastomosis are - end to side, between two vascular ends, mucosa involved tension free, no redundancy and effective decompression. This technically reduces chance of leak. The transposed gastric conduit should reach neck in a tension free manner with proper lie to avoid ischemia of the conduit. There should be minimal handling of lung to reduce risk of postoperative atelectasis or pressure on heart to avoid arrhythmias. Avoid traction injury to vessels arising from aorta and supplying esophagus. Use of harmonic and metal clips eases the job. It is better to spare thoracic duct in patients with deranged LFT's or comorbid patients. Proper feeding jejunostomy and drain placement should be done.

Postoperative Measures

The patient after surgery needs to be properly oxygenated and put on elective ventilation for 12 -24 hrs. To avoid pulmonary events aim is to prevent fluid overload and thus JT feeds are started within 24 hrs and increased gradually. Early ambulation, bronchial toileting, intense physiotherapy, prophylactic anticoagulant therapy, proper antibiotics, analgesics are pertinent. Retained secretions or vocal cord palsy may require repeated bronchoscopies or tracheostomy. Post-operative pain control by epidural analgesia has significantly improved outcome. Patients should be monitored on daily basis for any signs of complications like anastomosis leaks, chyle leaks, sepsis, and thromboembolism and conduit necrosis.

Role of Surgery in the Multimodality Therapy Era

In the era of multimodality treatment, many have questioned value of surgery and suggested diminished role for radical resection. However, this conclusion is at best premature and irrational. The data strongly suggest that residual microscopic or gross tumor is associated with poor outcome and that proper oncologically sound esophagectomy is an important component of a long term disease free state [14]. Several benefits of preoperative chemotherapy and concurrent chemo-radiation have been proposed which include early

treatment of micro-metastasis, down-staging of tumor to facilitate RO surgical resection, better loco regional control and complete pathological responses. On the other hand, chemotherapy and radiotherapy related toxicity, morbidity and mortality have been a matter of concern. Non-compliance and intolerance are worrisome as the general health and nutritional status of those with esophageal carcinoma are usually already poor at presentation. Delay in starting definitive treatment (surgery) and more importantly disease progression in non-responders is a major setback for patients who would have otherwise been resectable. There is also a fear amongst surgeons that perioperative morbidity and mortality would be higher after neoadjuvant chemo radiotherapy.

Surgical Treatment for Gastroesophageal Junction Tumors

These tumors possess distinct behaviour pathophysiologic characteristics. The pliability of the gastric cardia, as well as the deep location of the gastroesophageal junction, often masks the vague symptoms caused by early-stage lesions. Furthermore, due to the strategic location at the crossroads of two major body cavities, lymphatic spread occurs in two directions-proximally into the mediastinum and distally to the celiac lymph node. Type I tumors are a distinct entity that should be treated as a distal esophageal cancer. Most of these tumors arise from areas of intestinal metaplasia in Barrett's epithelium as a consequence of chronic gastroesophageal reflux. Increased surveillance programs have led to the diagnosis of these tumors at an earlier stage, and they can occasionally be managed by limited surgical or endoscopic treatment. In contrast, type III tumors represent proximal gastric cancer and should be approached in accordance with gastric cancer guidelines. The characterization of type II tumors, however, remains controversial. Most evidence suggests that these tumors behave more like proximal gastric tumors than distal esophageal adenocarcinoma. For example, in contrast to patients with type I tumors, only 10% of these patients have intestinal metaplasia in the distal esophagus. Furthermore, the lymphatic drainage pathways are such that type I tumors tend to drain more toward the mediastinal nodes, as well as to the celiac axis, whereas type II and type III tumors preferentially spread to the celiac axis nodes. The various surgical approaches include abdominothoracic en bloc esophago gastrectomy, subtotal esophagectomy with resection of the proximal stomach, total gastrectomy with transhiatal resection of the distal esophagus, and resection of the proximal stomach and distal esophagus with esophagogastrostomy. Patient factors, such as body habitus, prior surgery, and pulmonary function are important in selecting the appropriate surgical approach.

Although each approach has its advantages and disadvantages, no option has demonstrated a clear survival benefit over the others provided that adequate margins are obtained and an adequate lymphadenectomy is performed. Locally advanced tumors are treated with neoadjuvant chemotherapy for down staging and eradication of micro metastases and adjuvant chemo radiation following surgery is given in margin or node positive disease.

Conclusion

Surgery is still the best option with potential to improve survival and decrease loco-regional recurrences. The advances in preoperative diagnostic staging and patient selection, good instruments, good team work (anaesthetist, surgeon, nurses, ICU), good knowledge of fluid and electrolytes, refinements in surgical techniques have considerably decreased complication rates. A considerable progress has been made to manage complications of radical esophagectomy. However, in locally bulky disease as we see in India, we believe that neoadjuvant chemotherapy followed by surgery is the best option which is less morbid than preoperative chemoradiation followed by surgery which has a high morbidity at our hand, hence is not a preferred option. Surgical techniques using minimal intensive thoraco laparoscopic and recently introduced robotic esophagectomy have been tried, but the short and long term results needs to studies for future.

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PERSPECTIVE

PAST PRESENT AND FUTURE FOR RADIOTHERAPY IN ESOPHAGEAL CARCINOMA AND GASTROESOPHAGIC JUNCTION

Introduction

Oesophageal carcinoma is a highly malignant disease. It is the eighth most common cancer and the sixth leading causes of cancer-related deaths worldwide. It affects more than 450 000 people worldwide and the incidence has been rising rapidly (GLOBOCAN 2008. Int J Cancer 2010).

Squamous cell carcinoma is the commonest histological type. But the incidence of adenocarcinoma is also increasing and now exceeds that of squamous-cell in Australia, the UK, the USA, and some western European countries. The overall 5-year survival of patients with oesophageal carcinoma is poor uniformly, ranging from 15% to 25%. Less than 40% of patients present with localized and resectable disease.

Treatment: Changing Role of Radiation Therapy

The treatment options depend on **the site, the histological types and stage of esophageal cancers. Surgery** has been the cornerstone of esophagus and GEJ cancer management. Squamous cell carcinoma of the cervical esophagus poses a difficult management situation. Surgery demands resection of portions of the pharynx, the entire larynx, thyroid gland, and the proximal esophagus, along with radical neck dissection. Because of the significant morbidity and loss of organ function with surgery, chemoradiation alone has been frequently delivered to cancers of cervical esophagus. The survival probability with **definitive chemoradiotherapy** is comparable to surgery, minus the major functional impairments, morbidity, and mortality associated with surgery. On the other hand, surgery has been an important modality of curative treatment for lesions of the mid- to lower third of the thoracic esophagus and gastro esophagic junction (GEJ) cancers. The term gastro-esophagic junction cancer usually includes adenocarcinomas of the lower esophagus and gastric cardia as well as the true junction between the two. But even after a radical surgery, survival has been seen to be bleak because of high local recurrences. Contemporary randomized trials with surgery-alone arms have reported locoregional failure rates of **32% to 45%.** As a result, over the past three decades combined modality treatment has been investigated in a number of studies with an aim to improve long term results.

The role of radiotherapy in carcinoma of esophagus and gastroesophagic junctions is diverse, with either (A) Curative intent-as Adjuvant, Neoadjuvant, and Definitive or (B) Palliative intent to relieve symptoms.

Adjuvant Chemotherapy, Radiation, or Chemoradiation

The main advantage of adjuvant radiation treatment is the knowledge of the pathological staging, that helps to appropriately select patients with high risk for recurrences. Potential disadvantages of postoperative radiation include limited tolerance of normal tissues following surgery and presence of a devascularized tumor bed. Several randomized trials have evaluated surgery alone and surgery with adjuvant radiation treatment. A French trial, a study conducted by the University of Hong Kong, and a study conducted by Xiao et al, all showed that postoperative radiation therapy may decrease local recurrence, particularly in patients **with involved margins**, although the impact of this adjuvant treatment on overall survival is not clear. Randomised trials of adjuvant radiation without chemo-therapy have not consistently shown benefits, and its indication is today for positive margins or residual tumor.

Adjuvant Chemotherapy Alone for Oesophageal Carcinoma

In a **phase 2 trial (ECOG E8296)** of adjuvant cisplatin and paclitaxel in patients with completely resected oesophageal adenocarcinoma, despite N1 disease, 2-year survival was found 60%. This and similar studies suggest that this approach is beneficial in oesophageal adenocarcinoma (*N Engl J Med* 2001;345: 725–30). For patients with adenocarcinoma of the stomach and GE junctions, the role of adjuvant chemotherapy and radiotherapy was defined in 2001 in a large randomized **Intergroup trial**. The treatment here consisted of one cycle of 5-FU and leucovorin, followed by 45 Gy external beam irradiation concurrent with 5-FU, followed by two additional cycles of 5-FU and leucovorin. A significant survival advantage was seen in the adjuvantly treated group (median survival 36 months vs. 27 months; $p = 0.005$).

Therefore, in patients with stage Ib to IV, nonmetastatic GE junctional carcinoma, it is appropriate to advise adjuvant chemoradiotherapy in efforts to potentially improve upon local control and ultimate survival.

Definitive Chemoradiation or Chemoradiation Followed by Surgery?

This question has been addressed by a few randomized trials. A French trial showed no significant difference in 2-year survival (34% vs 40%; p = 0.44) or median survival (18 vs 19 months) between the groups, chemoradiation followed by surgery and chemoradiation alone. The death rate at 3 months following treatment was 9% in the surgery group versus 1% in the combined modality therapy-alone group. Additionally, patients undergoing surgery were found to have a worse quality of life. However, the rate of stent and dilatation requirement was higher in the nonsurgical arm. The results of this trial suggest that surgery following chemoradiation in responding patients does not further enhance survival. In a study from Germany, 172 patients with potentially resectable squamous cell carcinoma of the esophagus, concluded that surgery following combined modality therapy improves local control but has no impact on overall survival. Non responders to induction chemotherapy may benefit from surgery, and it may be quite apt to individualize therapy based on response to induction treatment. Neoadjuvant concurrent radiation and cisplatin and 5-FU-based chemotherapy can produce a pathological complete response (pCR) rate of approximately 25%, and patients who achieved pCR had improved treatment outcome (Stahl et al. 2005; Walsh et al. 1996).

In summary, preoperative radiation therapy was intended to improve local control by reducing tumor bulk and sterilizing involved nodes. Although surgery following combined chemoradiation for esophageal cancer appears to improve local control of disease, its impact on ultimate survival remains controversial.

The RTOG 85-01 trial with esophageal carcinoma in 1980s, documented that concomitant radiotherapy and chemotherapy was superior to radiation therapy alone in the treatment of locally advanced esophageal cancers, and is considered the gold standard. A follow-up trial (RTOG 94-05) compared chemoradiotherapy regimens with radiation doses of 64·8 Gy or 50·4 Gy. The study was closed prematurely because of a lack of improved locoregional control and increased mortality in the high-dose radiotherapy group. On the basis of these results, 50·4 Gy has been accepted as the standard dose used in carcinoma esophagus (*J Clin Oncol* 2005; **23:** 2310–17). A meta-analysis by Wong including 19 (11 concomitant radiochemotherapy, 8 sequential) trials that studied chemoradiotherapy versus radiotherapy alone concludes that concomitant chemoradiotherapy is better than sequential chemoradiotherapy in regards to overall survival, disease-free survival and local control.

Brachytherapy: The use of brachytherapy as intraluminal boost, along with external beam radiotherapy in curative approach does not appear to significantly improve results achieved with combined external beam radiation therapy with chemotherapy alone. On the other hand, incidence of acute toxicities and appearance of fistulas are increased. But it has been used in palliative setting giving a local control rate of 25 to 35% and median survival of 5 months.

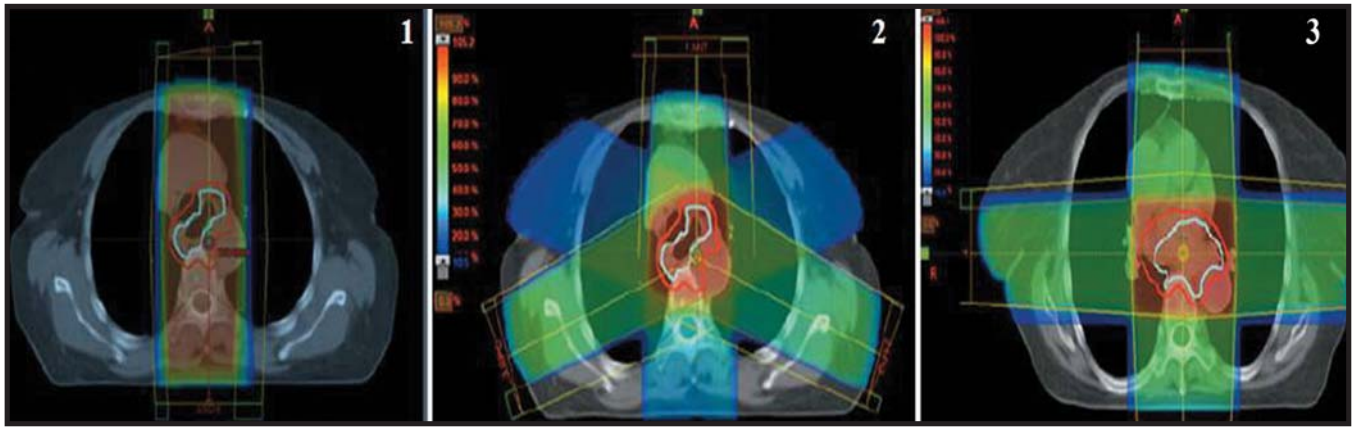

Figure: Conformal beam arrangements for carcinoma of the thoracic oesophagus. (1) Plan with anterior and posterior beams minimal lung dose but high dose to the cord and heart, (2) Three-beam plan for the same volume-low cord dose, and lung dose, (3) Four-beam plan for the same volume-minimum cord and lung dose

Radiation Technique: Radiation is preferably done by 3D conformal radiotherapy or intensity modulated radiotherapy (IMRT) to reduce the dose to the nearby normal organs. An immobilization device, along with CT simulation is encouraged.

More recently, the fusion of CT-PET has been used for more precise delineation of the gross tumor volume (GTV) and planning target volumes (PTV) in a majority of patients. GTV adjustment was required in more than 50% of cases with the utilization of FDGPET and CT fusion in a small prospective trial (Moureau-Zabotto et al; 2005). The main advantage of FDG-PET for esophageal cancer patients is the detection of unrecognized lymph nodes or distal metastases. Strict normal tissue constraints to the normal lung, heart, especially the left ventricle, liver , kidneys and spinal cord, are maintained in these techniques to prevent unnecessary damage to these vital organs.

Toxicities of Radiotherapy: The acute toxicities of radiation therapy include esophagitis, erythema, fatigue, and weight loss in most patients. Nausea and vomiting are common, particularly in patients with lower esophageal and gastroesophageal junction tumors. Pneumonitis and perforation are rare in today's era of conformal therapy. Addition of chemotherapy may increase the acute toxicities. But most of the toxicities subside in 1-2 weeks. The most common late effects following radiation therapy are stenosis and stricture formation. Stenosis can occur in more than 60% of patients. Stricture requiring dilatation has been reported to occur in at least 15% to 20% of treated patients. Dysphagia may be relieved with two to three dilatations.

Recommended Treatment Summery: Surgical resection is considered as the best option for stage I and IIA esophageal carcinomas. Neoadjuvant chemotherapy (for adenocarcinomas) or chemoradiotherapy (for squamous cell or adenocarcinomas) plus surgery is advised for resectable stage IIB esophageal carcinomas. For locally advanced potentially resectable oesophageal cancer (stage III), neoadjuvant chemoradiotherapy should be followed by surgery in patients with adenocarcinomas or those patients with SCC without morphological response after chemoradiotherapy. For responders with SCC, definitive chemo radiotherapy may be considered as an appropriate treatment option.

(Dr Swarupa Mitra, Consultant, Dept of Radiation Oncology)

WATCH-OUT

Biomarkers for Response of Esophageal Cancer

The inventors Pei-Chun Chen et. al of National Taiwan University have filed a patent application for their invention entitled "Biomarkers for predicting response of esophageal cancer patient to chemoradiotherapy". Their patent application No. US 20130017961 A1 was published by USPTO on 17th January 2013. Esophageal cancer (ECa) has become the 6th leading cause of cancer deaths in the world, and its incidence rate continues to increase worldwide. Unfortunately, most patients with esophageal cancer have advanced disease at the time of initial diagnosis and ineligible for curative surgical resection. Recently, multimodality therapies have been attempted to improve the resectability of tumors and the long-term survival of patients. The invention claims a method of predicting an increased likelihood of response of a human patient with esophageal cancer to radiochemotherapy and subsequent esophagectomy, wherein the radiochemotherapy comprises radiation in conjunction with cisplatin, 5-fluorouracil and/or paciltaxel.

(usgene.suqencebase.com/Patent, June 22, 2013)

Methods for Treating Esophageal Cancers

Patent application number 20130116226 entitled "Method for Treating Esophageal Cancer" filed by Hoboken et al of Nikki Pharma Inc. NJ, US was published by USPTO on 9th May 2013. The invention provide methods and compositions for treating gastric and esophageal cancers. In one aspect, the present invention provides a method of treating, preventing or delaying the onset of, gastric cancer and esophageal cancer comprising administering to a patient having gastric cancer or esophageal cancer a therapeutically or prophylatically effective amount of a compound. The compound here being used is tris(8-quinolinolato) gallium(III). The treatment method optionally also comprises a step of diagnosing or identifying a patient as having gastric or esophageal tumor. The identified patient is then treated with or administered with a therapeutically effective amount of a compound of the present invention, e.g., tris(8-quinolinolato) gallium(III).

(USPTO, May 23, 2013)

RESEARCH & DEVELOPMENT

CT Texture Analysis of Tumors

Scientists have identified that CT texture analysis of primary tumors may be a potential imaging biomarker in localized esophageal cancer following neoadjuvant chemotherapy. This study evaluated the tumoral texture analysis on baseline and post-treatment CT scans of 31 patients with localized resectable esophageal cancer and with a median age of 63 and who received neoadjuvant chemotherapy between 2007 and 2010. CT scans were performed before and after the use of chemotherapy and prior to surgery. All patients received platinum and fluorouracil-based chemotherapy followed by surgery. Texture analysis of the CT scans is a post-processing step, which was done utilizing proprietary software (TexRAD) that enhances the images in ultra-fine detail not visible to the human eye. Certain tumoral features changed consistently following chemotherapy, and some features were associated with overall survival. As a biomarker for treatment efficacy, this technique could save patients from unnecessary surgery and provide more definitive guidance in developing patient treatment plans with improved outcomes.

(Science Daily, Feb 8, 2013)

DNA Copy Number in Esophageal Adenocarcinoma

According to the results of a study conducted in China, there may be an association of mitochondrial DNA (mtDNA) copy number in peripheral blood leukocytes (PBLs) with risk of esophageal adenocarcinoma (EAC). Alterations of mtDNA have been associated with the risk of a number of human cancers. A total of 18 EAC cases and 218 frequency-matched controls was determined. mtDNA copy number was significantly lower in these cases than in controls (mean± SD, 1.16 ±0.30 vs 1.27±0.43, P=0.002). Dichotomized at the median value of mtDNA copy number in the controls, low mtDNA copy number was significantly associated with an increased risk of EAC (OR=1.55, 95% CI: 1.05-2.29). A significant dose-response relationship was observed between mtDNA copy number and risk of EAC in quartile analysis. Therefore, the results suggest that low mtDNA copy number in PBLs is associated with increased susceptibility to EAC.

(Carcinogenesis, Jun 26, 2013)

Newly Identified Biomarkers

A new study has reported a series of microRNA expression signatures that may help to define progression of the precancerous condition Barrett's esophagus into esophageal adenocarcinoma. The researchers compared hundreds of microRNAs in normal esophageal epithelia and in Barrett's esophagus and esophageal adenocarcinoma tissues of different histological grades with distinct progression risks. They identified a number of differentially expressed microRNAs at each histological stage. The expression of microRNAs in Barrett's esophagus and esophageal adenocarcinoma tissues was remarkably similar, indicating that the microRNA aberrations were very early events in the development of Barrett's esophagus. The researchers also identified a small number of microRNAs that were significantly different from Barrett's esophagus and esophageal adenocarcinoma. Specifically, downregulation of the microRNA miR-375 and upregulation of five microRNAs of the miR-17-92 and homologue family seemed to differentiate Barrett's esophagus and esophageal adenocarcinoma. Defining the protein-coding genes targeted by the differentially expressed microRNAs may provide significant biological insights into the development of esophageal adenocarcinoma.

(AACR, Mar 6, 2013)

Socio-demographic and Geographical Factors

Researchers at Karolinska Institute, Sweden, have conducted a population-based cohort study including Swedish residents aged 30–84 years in 1990–2007 to study the role of socio-demographic factors and area of residence in the development of esophageal and gastric cancer. Cox regression yielded hazard ratios (HR) adjusted for potential confounding. Among 84 920 565 person-years, 5125 and 12 230 deaths occurred from esophageal cancer and gastric cancer, respectively. Higher educational level decreased the HR of esophageal cancer and gastric cancer. Being unmarried increased HR of esophageal cancer but not of gastric cancer. Living in densely populated areas increased HR of esophageal cancer, but not of gastric cancer. These socio-demographic inequalities in cancer mortality warrant efforts to investigate possible preventable mechanisms and to promote and support healthier lifestyles among deprived groups.

(PLoS One, Apr 18, 2013)

NEW TECHNOLOGIES

Molecular Signature

Using new genetic sequencing techniques, US scientists have revealed some of the key underlying gene mutations behind the most common type of esophageal cancer known as adenocarcinoma. The researchers sequenced specific portions of DNA in cells from 149 tumor tissue samples, reading all the individual letters of the genetic code within those sections. A pattern of DNA changes was discovered that had not been seen earlier in any other cancer type. The pattern involved a slight swap in one of the four nucleobases that form the rungs of the DNA double helix. It was realized that in many places where an A nucleobase was followed by another A nucleobase, the second one was replaced by a 'C'. Overall, about one-third of all the mutations discovered within these cells involved this type of transversion and accounted for almost half of all mutations in some tumor samples. In addition to the mutational "signature" of AA becoming AC, 26 genes were identified that were frequently mutated in the tumor samples. Among the genes not previously linked to esophageal adenocarcinoma (EAC) were *ELMO1* and *DOCK2*, mutations that can switch on a gene called *RAC1*, which may cause cancer cells to invade surrounding tissue. The discovery of mutated *ELMO1* and *DOCK2* in many tumor samples may indicate that the invasive process is particularly active in EAC and thereby promoting metastasis. Identifying the mutated genes within these tumors would help to understand the underlying biology of disease. In future, the known genetic abnormalities can be used to diagnose the disease at an early stage, classify tumors by the particular mutations within EAC cells, and ultimately develop treatment precisely for those mutations.

(Science Daily, Mar 24, 2013)

Novel Drug Improves Survival

Findings of a new study indicate that patients with previously treated gastric cancer get a modest survival benefit with the anti-VEGF monoclonal antibody, ramucirumab. The novel drug ramucirumab is a fully human immunoglobulin G1 monoclonal antibody that targets VEGFR-2. The study evaluated ramucirumab versus best supportive care in 355 patients with metastatic gastric or gastroesophageal junction adenocarcinoma progressed after receiving first-line platinum- and/or fluoropyrimidine-containing combination therapy. The drug was well tolerated, with grade 3/4 adverse events occurring only in 8% of patients. The median overall survival was observed to be 5.2 months in 238 patients who received ramucirumab and 3.8 months in 117 patients who received placebo. Ramucirumab significantly reduced mortality by 22% compared with placebo (hazard ratio [HR] for overall survival, 0.78; $P = 0.0473$). There was a 52% reduction in disease progression with ramucirumab (HR, 0.48; $P < 0.0001$). The median progression-free survival was 2.1 months with ramucirumab and 1.3 months with placebo. The toxicity of drug was found to be trivial and essentially the same as placebo. The researchers concluded that this represented the first single-agent biologic therapy that has improved survival in gastric and gastroesophageal junction cancer and would eventually be a new standard of care in advanced disease.

(Medscape Medical News, Apr 09, 2013)

Targeted Imaging with Fluorescent Peptide

The incidence of esophageal adenocarcinoma is increasing rapidly. It usually develops from Barrett's esophagus, a precursor condition commonly found in patients with chronic acid reflux. This increases the risk of developing esophageal adenocarcinoma 30-fold, but premalignant lesions are difficult to detect using conventional endoscopy. The scientists at University of Michigan, United States, have developed a fluorescently labeled peptide for the early detection of cancer in patients with Barrett's esophagus. The peptide was first applied ex vivo to esophageal specimens from 17 patients to validate specific binding. Further, confocal endomicroscopy was performed in 25 human subjects after topical peptide administration. This showed 3.8-fold greater fluorescence intensity for esophageal neoplasia compared with Barrett's esophagus and squamous epithelium with 75% sensitivity and 97% specificity. One of the advantages of peptide is its ability to illuminate flat cancerous lesions. Unlike large tumors, flat lesions do not have any distinguishing features that make them project among normal tissue. No toxicity was attributed to the peptide in either animal or patient studies. The first-in-human results of the study show that this molecular probe enabled visualization of neoplasia in, the oesophagus using in vivo endomicroscopy and might be proved useful in the early detection of esophageal adenocarcinoma.

(Sci Transl Med, May 8, 2013)

CLINICAL TRIAL

Docetaxel & Cetuximab as a Second Line Treatment

According to the results of ATTAX2 trial of the Australian Gastro-Intestinal Trial Group, cetuximab can also be used in combination with docetaxel as a second-line treatment in docetaxel-refractory oesophagogastric cancer patients. Overall 38 patients were recruited in the trial who received docetaxel 30 mg/m^2 on days 1 and 8, every 3 weeks and cetuximab 400 mg/m^2 on day 1, then 250 mg /m^2 weekly. Biomarker mutation analysis was the performed. Response evaluation showed partial response 6% (95% CI 2–19%), stable disease 43% (95% CI 28–59%). Median progression-free and overall survival were 2.1 and 5.4 months, respectively. Grade 3/4 toxicities were febrile neutropenia, anorexia, nausea, diarrhoea, stomatitis and acneiform rash. No KRAS, BRAF or PIK3CA mutations were observed. The data indicates that combination of cetuximab and docetaxel attain modest response rates, with low rates of toxicity.

(Br J Cancer, Mar 2013)

Neoadjuvant Radiochemotherapy for GE Junction

Researchers from Germany performed a prospective, open, multi-centre phase I/II trial to assess safety and efficacy of neoadjuvant radiochemotherapy (RCT) with docetaxel and oxaliplatin in patients with adenocarcinoma of the oesophagogastric junction. A total 24 patients was included who received neoadjuvant radiotherapy (50.4 Gy) together with weekly docetaxel (20 mg/m^2 at dose level (DL) 1 and 2, 25 mg/m^2 at DL 3) and oxaliplatin 40 mg/m(2) at DL 1, 50 mg/m^2 at DL 2 and 3 over 5 weeks. Four patients were treated at DL 1, 13 patients at DL 2 and 7 patients at DL 3. The primary endpoint was to assess the dose limiting toxicities and maximum tolerated dose (MTD). Results showed that the MTD of the RCT was DL 2 with docetaxel 20 mg/m^2 and oxaliplatin 50 mg/m^2. Patients treated at DL 2 had a median overall survival of 29.5 months. The median PFS for all patients (n= 24) was 6.5 months and overall survival was 16.3 months. Through this study it could be concluded that neoadjuvant RCT with docetaxel 20 mg/m^2 and oxaliplatin 50 mg/m^2 was effective and also showed a good toxicity profile.

(BMC Cancer, Feb 11, 2013)

Panitumumab in Advanced Oesophagogastric Cancer

A team of scientists in London conducted a randomized, open label, phase III trial to observe the effects of anti-EGFR antibody panitumumab given along with epirubicin, oxalipaltin and capacitabine (EOC). Researchers enrolled 553 patients with untreated, metastatic or locally advanced oesophagogastric adenocarcinoma at 63 centres. Patients were randomly distributed (1:1) to receive up to eight 21-day cycles of open-label EOC (epirubicin 50 mg/m^2 and oxaliplatin 130 mg/m^2 on day 1 and capecitabine 1250 mg/m^2 per day on days 1-21) or modified-dose EOC plus panitumumab (mEOC+P; epirubicin 50 mg/m^2 and oxaliplatin 100 mg/m^2 on day 1, capecitabine 1000 mg/m^2 per day on days 1-21, and panitumumab 9 mg/kg on day 1). As per the results, median overall survival in 275 patients in EOC group was 11.3 months (95% CI 9.6-13.0) compared with 8.8 months (7.7-9.8) in 278 patients allocated mEOC+P (hazard ratio [HR] 1.37, 95% CI 1.07-1.76; p=0.013). Patients in mEOC+P group had grade 3-4 diarrhoea, mucositis and hypomagnesaemia. Due to less survival period and severe adverse events, trial recruitment was halted and panitumumab withdrawn. Therefore, the study did not recommend addition of panitumumab to EOC chemotherapy.

(Lancet Oncol, May 2013)

Recommended Dose of DNF Based Chemotherapy

A phase I trial was conducted to find the recommended dose of chemotherapeutic regimen of docetaxel, nedaplatin, and 5-fluorouracil (DNF) in patients with unresectable or recurrent esophageal cancer. This open label, prospective study was conducted at Gunma University Hospital, Japan and 14 patients were enrolled in the study. Recruited patients received DNF based combined therapy at different dose levels according to the treatment and examination plan. The regimen was repeated every 4 weeks for up to 2 cycles unless progressive disease or unacceptable toxic effect occurred. The recommended doses (level 3) of DNF were 60 mg/m^2 (day 1), 70 mg/m (2) (day 1), and 700 mg/m^2 (days 1-5) respectively, given at 3-week intervals. Dose-limiting toxicities were febrile neutropenia and thrombocytopenia. The findings suggested that DNF combined chemotherapy for advanced esophageal cancer could be safely administered at the recommended dose levels and it was also sociated with relatively minor adverse events.

(Cancer Chemother Pharmacol, Apr 2013)

GLOBE SCAN

Effect of Early Enteral Nutrition

A study was done to explore the effect of early enteral nutrition (EN) on postoperative nutritional status, intestinal permeability, and immune function in elderly patients with esophageal cancer. A total of 96 patients with esophageal cancer or cardiac cancer who underwent surgical treatment in the hospital were enrolled in this study. They were divided into EN group (n=50) and parenteral nutrition (PN) group (n=46) based on the nutrition support modes. The body weight, time to first flatus/defecation, average hospital stay, complications and mortality after the surgery as well as the liver function indicators were recorded and analyzed. Peripheral blood samples were collected on days 1, 4 and 7 after surgery. After the surgery, the time to first flatus/defecation, average hospital stay, and complications were significantly less in the EN group than those in the PN group ($P<0.05$), whereas the EN group had significantly higher albumin levels than the PN group ($P<0.05$). The EN group had significantly higher IgA, IgG, IgM, and CD4 levels than the PN group ($P<0.05$) but significantly lower IL-2, IL-6, and TNF-α levels ($P<0.05$). In elderly patients with esophageal cancer or cardiac cancer, early EN after surgery can effectively improve the nutritional status, protect intestinal mucosal barrier (by reducing plasma endotoxins), and enhance the immune function.

(China: Chin J Cancer Res, Jun 2013)

Survival after Esophageal Cancer Surgery

There is limited knowledge on how diabetes and other comorbidities influence the survival of patients undergoing curative esophageal cancer surgery. A population-based and prospective cohort study included patients who underwent surgical resection for esophageal or cardia cancer in Sweden from 2001 to 2005, with follow-up until 2011. Associations between diabetes and other comorbidities in relation to postoperative mortality were analyzed using Cox proportional-hazards regression with adjustment for potential confounding factors. Among 609 patients, 67 with diabetes had no increased risk for mortality compared with those without diabetes (hazard ratio, 0.81; 95% confidence interval, 0.60 to 1.09). Compared with patients without any predefined comorbidities, those with 1 (hazard ratio, 1.15; 95% confidence interval, 0.93 to 1.43) or $\geq$2 comorbidities (hazard ratio, 1.05; 95% confidence interval, 0.83 to 1.33) had no statistically significant increase in risk for mortality. This study revealed no perceptible increased risk for mortality in patients with diabetes or other comorbidities selected for esophageal cancer surgery.

(Sweden: Am J Surg, Jun 2013)

New Clinical Guidelines

The Society of Thoracic Surgeons (STS) has released a set of clinical-practice guidelines to assist in the diagnosis and treatment of localized esophageal cancer. One of the key recommendations is that endoscopy with biopsy is the diagnostic test of choice for esophageal cancer. Another key recommendation is that staging should be done with computed tomography (CT) and positron emission tomography (PET)/CT. For the diagnosis of esophageal cancer, flexible endoscopy with biopsy is the primary method. Staging for early-stage esophageal cancer, chest CT is an optional test. For locoregionalized esophageal cancer, CT of the chest and abdomen is a recommended test for staging. For early-stage esophageal cancer, PET is also an optional test is recommended for staging locoregionalized esophageal cancer. The goals of endoscopy are to determine the presence and location of esophageal cancer and to biopsy any suspicious lesions. The location of the tumor relative to the teeth and gastroesophageal junction, the length of the tumor, the extent of circumferential involvement, and degree of obstruction should be noted. In addition, the location and extent of Barrett's esophagus should be documented, if observed in the patient. More than one biopsy should be performed to obtain sufficient material for histology analysis. The optimal treatment for localized esophageal cancer remains one of the most widely debated topics in oncology although esophagectomy is considered the gold standard for localized disease. However, while patients with early localized disease do benefit from surgery, the evidence is increasing that neoadjuvant chemotherapy or radiation therapy, or both, followed by esophagectomy, has a survival benefit in advanced disease, when compared with surgery alone. Future clinical-practice guidelines will cover Barrett's esophagus, the role of multimodality therapy, and the choice of esophageal resection techniques.

(USA: Ann Thoroc Surg, July 2013)

CANCER CONTROL

Dietary Fiber and Esophageal Cancer

Scientist at Queen's University, Belfast, Northern Ireland have quantified the association between dietary fiber and the risk of esophageal cancer by investigating histological subtypes of esophageal cancer and the stage at which fiber may influence the carcinogenic pathway. Ten relevant case-control studies were identified within the timeframe searched. Pooled estimates from eight studies of esophageal adenocarcinoma revealed a significant inverse association with the highest fiber intakes (OR 0.66; 95% confidence interval [CI] 0.44-0.98). Two studies also identified protective effects of dietary fiber against Barrett's esophagus. Similar, though nonsignificant, associations were observed when results from five studies of fiber intake and risk of squamous cell carcinoma were combined (OR 0.61; 95% CI 0.31-1.20). Dietary fiber is associated with protective effects against esophageal carcinogenesis, most notably esophageal adenocarcinoma. Potential methods of action include modification of gastroesophageal reflux and/or weight control.

(Nutr Rev, Jul 2013)

Folic Acid, Vitamin B2 and Esophageal Cancer

Researchers at the Southeast University, China, have studied the relationship between serum folic acid and vitamin B2 levels and esophageal cancer. The enzyme-linked immunosorbent assay was used to observe the serum folic acid and vitamin B2 levels of the 1:1:1 paired of 106 groups, which included 106 cases of esophageal cancer, 106 cases of esophageal precancerous lesions and 106 cases of normal control group. The levels of folic acid and VB2 in serum of esophageal cancer group and esophageal precancerous lesions group were significantly lower than normal control group ($P<0.05$); the level of folic acid in serum of esophageal cancer group was significantly lower than esophageal precancerous lesions group ($P<0.05$), but the difference of the serum VB2 of esophageal cancer group and esophageal precancerous lesions group was not statistically significant ($P>0.05$). The folic acid and vitamin B2 deficiency has the relationship with the esophageal cancer occurrence and development.

(Pubmed, May 2013)

Meat, Fish and Risk of Esophageal Cancer

Researchers at Mashhad University of Medical Sciences, Iran have conducted a large meta analysis that shows that low levels of red and processed meat consumption and higher levels of fish intake may reduce esophageal cancer (EC) risk. To help elucidate the role of particular dietary components, databases were searched (1990-2011) on associations between EC risk and consumption of various types of meat and fish. Random-effects models and dose-response meta-analyses were used to pool study results. Subgroup analyses were conducted by histological subtype, study design, and nationality. The overall pooled relative risk (RR) of EC and the confidence intervals (CIs) for the groups with the highest versus the lowest levels of intake were as follows: 0.99 (95% CI: 0.85-1.15) for total meat; 1.40 (95% CI: 1.09-1.81) for red meat; 1.41 (95% CI: 1.13-1.76) for processed meat; 0.87 (95%CI: 0.60-1.24) for poultry; and 0.80 (95% CI: 0.64-1.00) for fish. People with the highest levels of red meat intake had a significantly increased risk of esophageal squamous cell carcinoma. Processed meat intake was associated with increased risk of EAC. These results suggest that low levels of red and processed meat consumption and higher levels of fish intake might reduce EC risk.

(Nutr Rev, May 2013)

Sunlight Reduces Risk of Esophageal Cancer

Scientists at the Queensland Institute of Medical Research, Australia, have shown link between esophageal cancer and UV rays in sunlight. In their study, they investigated the link between moles, freckles and environmental exposure to sunlight and UV over a lifetime to the risk of contracting esophageal cancer. Researchers compared the estimated lifelong UV dose of almost 1,000 esophageal cancer sufferers with a control group of 1,500 persons. They discovered an inverse relationship between the amount of sunlight/UV exposure a person receives during their lifetime in the area where they live and the risk of contracting esophageal cancer. UV exposure from sunlight and sunbeds has many positive effects on human health. Scientists recommend moderate exposure, as this is proven to increase vitamin D levels. It is also interesting to note that the study was carried out in Australia. This is a country where increased UV exposure as a result of the hole in the ozone layer is considered extremely dangerous for human health.

(Medical News Today, Feb 08, 2013)

IN FOCUS

ESOPHAGEAL CARCINOMA- IMAGING

Esophageal cancer is among the 10 most prevalent cancers worldwide. The overall mortality from this disease is extremely high with the overall 5-year survival rate in patients amenable to definitive treatment ranging from 5% to 30%. The occasional patient with very early disease has a better chance of survival. As with all other tumors, the outcome for patients with esophageal cancer is strongly associated with the stage at initial diagnosis. Surgical resection is currently the best curative treatment for patients without distant metastases or locally advanced tumor growth. However, patients with locally advanced disease have a poor prognosis despite aggressive attempts at resection, and patients with distant metastatic disease are considered to have an incurable disease. Consequently, accurate preoperative staging and assessment of response to neoadjuvant therapy are crucial in determining the most suitable therapy and avoiding inappropriate attempts at curative surgery.

Staging

The two most important prognostic indicators for esophageal cancer are depth of tumor penetration and nodal involvement. T1 tumors invade the lamina propria or submucosa, T2 tumors invade the muscularis propria, T3 tumors involve the adventitia, and T4 tumors directly invade adjacent structures. N stage considers the number of regional lymph nodes involved by metastases. The TNM staging of esophageal cancer is summarized in Table I.

Table 1. TNM Staging of Esophageal Cancer

a) Primary Tumor (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	High-grade dysplasia
T1	Tumor invades lamina propria, muscularis mucosae, or submuco sa
T1a	Tumor invades lamina propria or muscularis mucosae
T1b	Tumor invades submucosa
T2	Tumor invades muscularis propria
T3	Tumor invades adventitia
T4	Tumor invades adjacent structures
T4a	Resectable tumor invading pleura, pericardium, or diaphragm
T4b	Unresectable tumor invading other adjacent structures, such as aorta, vertebral body, trachea, etc.

b) Regional Lymph Nodes (N)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastases in 1-2 regional lymph nodes
N2	Metastases in 3-6 regional lymph nodes
N3	Metastases in ≥7 regional lymph nodes

c) Distant Metastasis (M)

M0	No distant metastasis
M1	Distant metastasis

Radiologic Evaluation

Although computed tomography (CT) has been the mainstay for staging esophageal cancer, the increasing use of endoscopic ultrasonography (EUS) and positron emission tomography (PET) with fluoro-2-deoxy-D-glucose (FDG) has improved the staging algorithm for newly diagnosed esophageal cancer. Currently, the combined use of CT, endoscopic US, and PET is advocated to determine whether a patient should be treated with surgery, chemotherapy, or a combination of chemotherapy and radiation therapy. As with many malignancies, the staging criteria for esophageal cancer include depth of local invasion, regional lymph node involvement, and distant metastases. The aforementioned imaging modalities have different strengths and weaknesses with respect to each of these criteria.

Barium Studies: These are often used to detect esophageal carcinomas in patients with dysphagia. Superficial spreading lesions tend to show a nodular mucosal pattern without a well-defined mass. Early esophageal cancers may have subtle findings on barium studies, and therefore endoscopic follow-up of any suspected abnormality should be performed. Once a diagnosis of esophageal malignancy has been established, barium studies may be used to evaluate the morphology and size of tumors before and after treatment. Complications, such as trachea-esophageal fistula formation from locally advanced disease, are well shown on barium studies.

CT Scan: The main purpose of cross-sectional imaging studies in patients with known esophageal carcinoma is

to stage the disease as accurately as possible and to determine which patients may be suitable candidates for surgical resection. CT is considered complementary to endoscopy and barium studies and may be used to stage and follow up esophageal tumors. With the advent of multidetector CT, along with significant advances in three-dimensional imaging techniques, CT has become more valuable in the evaluation of T staging of esophageal cancer. CT estimates of tumor length made with multiplanar reformatted images are more accurate than those made with axial scans alone. Multiplanar reformatted images are also useful in evaluating esophageal cancer at the esophagogastric junction, which is difficult to evaluate with axial scans alone. An important limitation of CT in staging esophageal cancer is its lack of sensitivity for detecting lymph node metastases, since even a normal-sized lymph node might contain microscopic metastatic foci that are beyond the level of detection offered by CT. Despite its limitations in assessing T and N stages, CT has become the most commonly used modality in the initial staging of newly diagnosed esophageal cancer. The identification of distant metastases at CT permits immediate triage of these patients to systemic therapy or other multimodality treatments. However, CT is not accurate for the assessment of treatment response to neoadjuvant therapy.

Endoscopic US: Endoscopic US is considered to be the most accurate imaging modality currently available for primary tumor staging (T staging) in patients with esophageal cancer. Endoscopic sonography has been used to define the layers of the esophageal wall and thereby distinguish the depth of tumor penetration. The frequency of most endoscopic sonography transducers is 7.5 or 12 MHz. The overall accuracy of endoscopic sonography is greater than CT and is reported to be between 85% and 90%. Endoscopic US can accurately help differentiate between T1-T3 disease, which is important for neoadjuvant treatment. Recently, endoscopic US performed with high-frequency US probes has shown promising results in helping distinguish mucosal from submucosal invasion, which is critical to the identification of tumors that are amenable to local ablative therapy, such as photodynamic therapy or endoscopic mucosal resection. Endoscopic US has been shown to be superior to CT in detecting lymph node metastases. The accuracy of preoperative endoscopic US for N staging ranges from 72% to 80%, whereas the accuracy of CT ranges from 46% to 58%. Endoscopic US has limited value in the assessment of distant metastases, except for celiac lymph node metastases. Therefore, CT or FDG PET is the first-line study for the detection of distant metastases, which, if present, make loco regional staging assessment unnecessary. Endoscopic US has been shown to be less accurate for restaging after neoadjuvant chemotherapy-radiation therapy than for initial staging. Overstaging is the most common error, since at endoscopic US the fibrosis and inflammation associated with chemotherapy-radiation therapy are indistinguishable from residual tumor.

FDG PET: Although PET has been shown to have a higher sensitivity than CT in the detection of primary esophageal cancer, it is of limited value in assessing T stage because it provides little information on the depth of tumor invasion. Sensitivities as high as 90% have been reported in the detection of metastatic lymph nodes at distant sites, including cervical and abdominal locations. Several comparative studies have demonstrated that FDG PET is more accurate than CT in detecting distant metastases. Furthermore, recent studies have suggested that FDG PET can help detect metastatic diseases in 15% of patients who were thought to have localized esophageal cancer on the basis of findings at conventional diagnostic procedures. Therefore, FDG PET may be cost effective in the prevention of non-curative surgery by helping detect metastases not identified with other imaging modalities. FDG PET currently seems to be the best imaging modality for the assessment of response to neoadjuvant therapy in patients with esophageal cancer. Recent studies suggest that the quantitative decrease in FDG uptake seen after neoadjuvant therapy correlates closely with patient survival and with pathologic response to therapy.

CT, endoscopic US, and PET, all play important roles in the staging of patients with esophageal cancer. CT is a good initial screening modality for determining whether the patient may undergo resection or has distant metastases. CT can also help detect enlarged lymph nodes in the mediastinum and celiac regions. Endoscopic US is the best modality for determining the depth of tumor invasion and the presence of regional lymph node involvement. Combined use of fine-needle aspiration and endoscopic US can improve the assessment of lymph node involvement. PET is useful for assessing distant metastases as well as restaging after neoadjuvant therapy. Each modality has its advantages and disadvantages; therefore, CT, endoscopic US, and PET should be considered complementary modalities for the staging of esophageal cancer.

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