Carcinoma of the Esophagus

April 01, 2005
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Carcinoma of the esophagus or the gastroesophageal junction is uncommon, accounting for approximately 1% of all malignancies in the United States [1]. An estimated 12,100 new cases and 10,900 deaths will occur in 1995.

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Carcinoma of the esophagus or the gastroesophageal junction is uncommon, accounting for approximately 1% of all malignancies in the United States [1]. An estimated 12,100 new cases and 10,900 deaths will occur in 1995 [1]. The diagnosis of esophageal cancer is often made late in the course of the disease in Western countries. Thus, according to the tumor-node-metastasis (TNM) system of staging, T3 or T4 and N-positive lesions are observed frequently. In fact, nearly 50% of patients have advanced incurable disease at the time of diagnosis. Therefore, the prognosis of patients with carcinoma of the esophagus remains poor, and the overall 5-year survival rates are still less than 10% [1].

The incidence of adenocarcinoma of the esophagus and proximal stomach in the Western world and especially in white males has increased in the past 15 years [2,3]. The proportion of adenocarcinomas has increased from the traditionally reported rate of 5% to 10% to 20% to 40% of all esophageal tumors [2]. It is our estimation that currently in the United States, adenocarcinoma occurs more frequently than does squamous-cell carcinoma.

Squamous-cell carcinoma of the esophagus has the greatest variation in geographical distribution, a fact that provides insight into its pathogenesis. Geographic variations in the incidence often exist within the same country. Unlike squamous-cell carcinoma, for which alcohol and tobacco (among other factors) have been implicated as risk factors, the risk factors for adenocarcinoma remain elusive. Coexistence of Barrett's esophagus does not yet explain this phenomenal rise in the frequency of adenocarcinoma.

Pathogenesis

A number of predisposing conditions have been identified in the pathogenesis of squamous-cell carcinoma of the esophagus. These conditions include achalasia, caustic injury, and esophageal diverticula and webs. Esophageal cancer may also develop as second primary tumors in patients with other primary tumors of the upper aerodigestive tract that are associated with tobacco consumption. In Barrett's esophagus, the normal stratified squamous epithelium of the esophagus is replaced by metaplastic columnar epithelium. It develops as a result of chronic gastroesophageal reflux and can lead to the development of adenocarcinoma through a multistep process characterized by a progression from metaplasia, to indefinite or low-grade dysplasia, to high-grade dysplasia, and ultimately to invasive cancer [4].

Over the past several years, intensive research into the molecular changes in carcinoma of the esophagus, premalignant lesions, and normal mucosa have identified a number of genetic events that play a major role in the pathogenesis of esophageal cancer. Both the loss of heterozygosity and replication errors have been identified as genetic alterations in esophageal cancer. Allelic losses at frequencies of at least 30% were observed at loci on chromosomal arms 3p, 3q, 5q, 7q, 9p, 9q, 10p, 10q, 13q, 17p, 17q, 18q, 19q, and 21q [5,6], suggesting that several putative tumor-suppressor genes may be associated with the development and/or progression of esophageal cancer.

MTS-1 (CDKN2) is a candidate tumor-suppressor gene on chromosome 9p21-22. This region is frequently observed to have a loss of heterozygosity in patients with esophageal squamous-cell
carcinomas and adenocarcinomas [7], and there is evidence of mutations of this gene in esophageal tumors [8]. It has been shown that 67% of esophageal squamous-cell carcinoma cell lines have deletions of both exons 1 and 2 of the \textit{MTS-1} gene, suggesting that it has a role in the pathogenesis of esophageal cancer [9].

Mutations in the \textit{p53} gene may be detected in a high proportion of esophageal squamous-cell carcinomas [10,11] and adenocarcinomas [11]. However, the overexpression of the \textit{p53} gene product did not correlate with either the TNM stage or the prognosis in these patients. These results suggest that \textit{p53} mutations occur early in the course of esophageal carcinogenesis. A recent study described the expression of \textit{p53} in 28 esophageal specimens that all contained Barrett's mucosa and a spectrum of low- to high-grade dysplasia and intramucosal and submucosal cancer [12]. Immunoreactivity to \textit{p53} was not detected in any of the Barrett's mucosa or low-grade dysplasia specimens. However, it was present in specimens of high-grade dysplasia, intramucosal cancer, and submucosal cancer. The conclusion of this study was that \textit{p53} mutations occurred late in the metaplasia-dysplasia-carcinoma sequence, during the transition to high-grade dysplasia.

It has also been proposed that \textit{p53} expression may potentially be utilized as an intermediate biomarker in Barrett’s esophagus [13]. In addition to \textit{p53} mutations that may be induced by environmental chemical carcinogens, viruses such as the papillomavirus may inactivate the normal \textit{p53} function by the binding of the E6 protein to the \textit{p53} protein [14]. The tumor-suppressor gene \textit{APC} is infrequently mutated in esophageal cancer [15] despite the high frequency of allelic losses at the 5q locus [5], which suggests that other tumor-suppressor genes exist at this locus. Activation of oncogenes probably play an important role in the pathogenesis of esophageal cancer. Expression of growth factors and growth factor receptors facilitates autocrine or paracrine growth stimulation and may be important in the pathogenesis of esophageal cancers [16]. Epidermal growth factor receptor (EGFR) overexpression was detected in 71% of primary squamous-cell carcinomas of the esophagus and 88% of the lymph node metastases and was associated with a tendency for worse prognosis [17]. EGFR overexpression correlates with the degree of dysplasia and the frequency of lymph node metastases [18]. Overexpression of both epidermal growth factor and transforming growth factor-alpha, which are the normal ligands of EGFR, has been demonstrated in esophageal cancers [16].

Amplification of \textit{c-myc} has been frequently observed in esophageal cancer cell lines [19]. \textit{HER-2/neu} gene overexpression is observed in approximately 20% of esophageal adenocarcinomas and is an independent indicator of poor prognosis [20]. The \textit{hst-1} gene is also amplified in 30% of primary esophageal carcinomas but is without any prognostic significance [21]. However, \textit{ras} mutations that are common in several gastrointestinal tumors are infrequently found in esophageal cancers [22]. Genes involved in cell-cycle control have also been investigated in esophageal cancer [23]. In one report, amplification of the cyclin \textit{D1} gene was present in 32% of primary tumors and in two of four cell lines. Seventeen percent of tumor samples had no expression of the retinoblastoma (Rb) gene product. It was also noted that there was a correlation between \textit{D1} gene amplification and normal Rb protein levels, and by contrast absent expression of Rb correlated with the expression of low levels of cyclin D1 protein.

Prognostic Factors

Earlier studies have indicated that the length of the primary tumor predicted the duration of patients' survival [24,25]. Recently, however, the depth of wall penetration has been accepted as a better prognostic indicator than the length. Thus, T3 or T4 lesions impart a poorer prognosis than T1 or T2 lesions, irrespective of the length of the primary tumor. Patients with lymph node metastases have a poorer prognosis than those without lymph node metastases. Additionally, pretreatment weight loss of more than 10% carries a poor prognosis. At present, there are no molecular markers to reliably predict accurately the clinical behavior of esophageal carcinoma.

Staging

Accurate staging is required in validating and comparing the results of studies of multimodality therapy for esophageal cancer. The revised TNM system (1987) [25a] for staging esophageal cancer is determined by the depth of wall penetration by the primary tumor, metastases to the regional lymph nodes, and distant metastases (Table 1).
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**Regional lymph nodes (N)**

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**Distant metastasis (M)**

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**Stage grouping**

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The staging process should include a complete history and physical examination, a chest radiograph, pulmonary function studies, histologic confirmation, bronchoscopy in patients with lesions at or above the carina, blood tests to define hematology and organ functions, and computed tomographic scans of the chest and abdomen.

Improvements in staging techniques have been achieved with endoscopic ultrasonography (EUS), which is superior to computed tomography or magnetic resonance imaging in staging the primary tumor and in detecting small lesions (less than 5 mm in diameter) [26]. In patients with biopsy-proven esophageal cancer, local staging was 77% to 86% accurate for the T stage and 55% to 90% accurate for the N stage [27]. Nevertheless, limitations of this method have been recognized: EUS displays lymph nodes with high resolution but cannot distinguish inflammatory nodal changes from malignant adenopathy. Furthermore, EUS cannot be performed in patients with significant stenosis. Whether EUS will affect the outcome in patients with esophageal tumor is unclear, but accurate tumor staging and response to treatment is a critical part of any therapeutic protocol.
**Treatment**

**Single-Modality Therapy**

*Surgery:* Surgical resection is considered the standard approach for patients with stages I and II and even stage III carcinomas. Curative resection is feasible in only about 50% of patients because often the lesions are more extensive than judged by the routine clinical staging. A high rate of local relapse following resection has been reported in some series, and the median survival of patients with resected tumors is approximately 11 months. Over the past 10 years, surgical mortality has declined substantially and is well below 10% at centers where the procedure is frequently performed. Type of surgical resection does not seem to alter the long-term outcome of these patients.

*Radiation Therapy:* Long-term results seen with radiation therapy as a single modality have been as disappointing as the results with surgery. However, irradiation as primary therapy is often used for patients who are medically unfit for operation or whose tumors are technically unresectable. Overall survival after radiation therapy is approximately 18% at 1 year and 6% after 5 years [28]. Radiation therapy might be equally effective against squamous-cell carcinoma and adenocarcinoma of the esophagus [29].

Most surgical series have reported better long-term results than have radiation therapy-only series [30]. However, such comparisons have limitations; for example, in some studies, patients with unresected tumors are not accounted for. Prospective randomized trials in accurately staged and stratified patients will be necessary to compare surgery with irradiation (or chemoradiation). Two such trials were launched—one in Europe [31] and another in the United States—but both trials were aborted, because of poor patient accrual. This problem was the result of reluctance on the part of physicians and patients to accept randomization. Thus, this issue poses a significant challenge and will require an enormous effort to resolve.

At present, there is no evidence that radiation therapy alone can achieve local control similar to that afforded by surgery. By some estimates, surgery offers more durable palliation of dysphagia than does irradiation [32]. However, contradictory statements have been made in the literature. Potential benefits of brachytherapy are being investigated at present [33,34].

*Chemotherapy:* Chemotherapy is not effective as a single modality in the treatment of locoregional esophageal carcinoma.

**Multimodality Therapy**

*Rationale:* Locoregional esophageal carcinoma, limited to the esophageal bed and regional lymph nodes, continues to be the dominant cause of morbidity in many patients. However, the natural history suggests that it is a systemic disease at the outset in the majority of patients. If locoregional disease can be effectively controlled, most patients eventually succumb to the metastatic disease [35]. Multimodality therapy has emerged as a result of the failures of single modalities against esophageal carcinoma.

Despite improving methods of clinical investigation, limitations are encountered, including small numbers of patients accrued in many studies, small proportions of patients with adenocarcinoma in some trials, the use of different chemotherapy regimens, and varying schedules and doses of chemotherapy and radiation therapy. Moreover, many studies have required several years to complete accrual.

When discussing multimodality therapy of esophageal carcinoma, the following issues warrant consideration: (1) radiation therapy alone vs chemoradiation therapy to improve local control, (2) impact of chemotherapy on distant metastases, and (3) cost of therapy, which continues to gain importance.

*Chemotherapy:* Systemic therapy is an important cornerstone of multimodality therapy because more than 75% of the patients harbor occult metastases at presentation [36,37]. Sixteen cytotoxic drugs have been investigated in depth in phase II trials in patients with metastatic disease [38], and the majority of these agents have been evaluated in patients with the squamous-cell carcinoma histologic subtype.

Cisplatin (Platinol) is one of the most active agents, with a single-agent response rate that is consistently around 20% [39]. With cisplatin-based combination chemotherapy, superior response rates of 30% to 50% have been reported but only a few complete responses [39-42]. Furthermore, responses are typically brief (usually less than 4 months).

Although it has been predominantly investigated in squamous-cell carcinomas, cisplatin continues to form the backbone of combination therapy for both histologic subtypes [43]. Pilot studies suggest that adenocarcinoma would probably respond to chemotherapy with a frequency similar to that of
Carcinoma of the Esophagus

Extensively studied cisplatin-based chemotherapy regimens have included bleomycin (Blenoxane), the investigational agent vindesine (Eldisine), and fluorouracil in various combinations. The most popular combination has been infusional fluorouracil and cisplatin. Fractionating the dose of cisplatin over several days can result in less nausea and vomiting than occurs with a single total dose.

Bleomycin, once a popular component of combination chemotherapy regimens, has now been dropped because of the significant perioperative pulmonary morbidity associated with its use. The optimum duration and dose intensity of chemotherapy in esophageal carcinoma has not been determined. It is logical to assume that more than two treatment cycles are required, based on the results achieved in sensitive tumor types (eg, germ-cell tumors and lymphomas). The age range of patients who develop carcinoma of the esophagus (60 years and older) often limits the cumulative cisplatin dose to approximately 500 mg/m² because of neurotoxic and ototoxic effects.

Dose-intensive chemotherapy has not demonstrated an advantage. Ajani et al [45] reported a pilot study in 26 patients who received high doses of etoposide (VePesid), doxorubicin (Adriamycin, Rubex), and cisplatin, with granulocyte-macrophage colony-stimulating factor (GM-CSF, sargramostim [Leukine]). Fifty percent of the patients achieved a major response, and 65% of the patients were able to undergo curative resection for their tumors. None of the patients had a pathologically complete response, and significant toxicity was associated with this regimen. Therefore, higher doses result in poor patient tolerance.

Preoperative Radiation Therapy: Preoperative radiation therapy can potentially increase the resectability rate and local control. The majority of pilot studies using preoperative radiation therapy have reported a decent rate of pathologically complete responses, curative resections, and survival, but only in comparison with historical parameters [46]. Another weakness is the influence of patient selection in some of these studies.

Several prospective randomized trials have investigated survival duration following preoperative radiation therapy. Launois et al [47] compared patients who underwent irradiation preoperatively with those who did not and found no difference in the rate or duration of survival between the groups. Gignoux et al [48] reported a trial involving 192 patients who were randomized to receive preoperative radiation therapy (33 Gy) or immediate surgery. Here again, no survival benefit was observed, but in the irradiated group there was a longer median time to recurrence as well as fewer local recurrences than in the control group.

Wang et al [49] investigated 206 patients with tumors less than 8 cm in length who had a good performance status and dysphagia only to solid foods. The dose of preoperative radiation was 40 Gy. The 5-year survival durations were similar in both arms of the study. Another reported randomized study showed no benefit of low-dose (20 Gy) radiation therapy in prolonging the survival duration of patients with squamous-cell carcinoma or adenocarcinoma of the esophagus [50]. It would appear that despite 60% to 70% “response rates,” including up to 25% pathologically complete responses in some studies, there has not been a statistically significant survival advantage with the use of preoperative radiation therapy [51]. Thus, preoperative radiation therapy alone cannot be recommended for routine use.

Postoperative Radiation Therapy: Postoperative radiation therapy is aimed at improving local control. In addition, better delivery of radiotherapy may be possible if the surgical bed is demarcated by clips. Occasional limitations may be attributed to the distorted anatomy and enhanced toxicity to the stomach, when it is used for reconstruction.

When resection is incomplete, postoperative radiation therapy is usually recommended to prevent morbidity from locoregional disease [52,53]. Results of a randomized study that involved 221 patients who had curative resection of esophageal carcinoma showed only a slight reduction (85% vs 70% at 5 years) in local relapse among patients who received postoperative radiation therapy [54]. A statistically significant difference in local relapse was achieved only in node-negative patients, but there was no survival advantage. Thus, postoperative radiation therapy alone does not alter the natural history of the disease even if the surgical margins contain tumor.

Preoperative Chemotherapy (Neoadjuvant): According to the Goldie and Coldman hypothesis, chemotherapy early in the natural history of a malignancy potentially delays the emergence of drug-resistant malignant clones [55]. The benefit of preoperative chemotherapy in the eradication of micrometastatic disease is also supported by data from studies in animal tumor models [56,57]. With preoperative chemotherapy, optimum drug delivery may be achieved because of the intact vasculature. In addition, preoperative chemotherapy allows an assessment of in vivo chemosensitivity and can guide postoperative therapy.

A number of pilot studies have reported 40% to 60% response rates, but few have shown
pathologically complete responses [58,59]. Roth et al [60] reported on a small prospective study in which patients were randomized to undergo either immediate surgery (20 patients) or to receive two cycles of cisplatin, vindesine, and bleomycin preoperatively (19 patients). Major responses were achieved in 47% of the patients but with only one pathologically complete response. Resectability and survival were similar regardless of whether patients received preoperative chemotherapy.

A second prospectively randomized study compared the effectiveness of preoperative chemotherapy (cisplatin, vindesine, and bleomycin) with preoperative radiation therapy (55 Gy) [61]. Ninety-six patients with resectable squamous-cell carcinoma of the esophagus were enrolled. Postoperatively, patients with positive lymph nodes were crossed over (to receive either radiation therapy or chemotherapy). Response rates, survival duration (limited by the crossover design), resectability, and surgical morbidity were similar [61].

Earlier trials used only one or two courses of systemic chemotherapy in the combined-modality setting, but it is possible to administer five cycles of chemotherapy [35,45,62]. In the current Intergroup trial, a total of five courses of chemotherapy are being administered to patients before and after surgery, and the results will be compared with those of patients receiving surgery alone. The value of preoperative chemotherapy in patients with carcinoma of the esophagus remains unproved; the current trial may help to define the role of this strategy.

Postoperative Chemotherapy: The role of adjuvant chemotherapy after resection has not been investigated adequately. Currently there is no evidence that it is useful, and thus, it cannot be recommended as a routine clinical practice.

Concurrent Chemotherapy and Radiation Therapy Followed by Surgery: In terms of design, the earliest trials of chemotherapy with radiation therapy in esophageal cancer [63] were based on the successes in treating anal cancer. The goal has been to control local and systemic disease simultaneously, with a greater emphasis on the local disease. Drugs such as fluorouracil, cisplatin, and mitomycin (Mutamycin) are also radiation enhancers and may potentially improve local tumor control.

Several pilot studies with small numbers of selected patients have reported clinical response rates up to 70% and a pathologically complete response rate of up to 37% [64,65]. Poplin et al [66] from the Southwest Oncology Group reported a study of 113 patients who received fluorouracil plus cisplatin and radiation therapy followed by esophagectomy. Median survival duration was 12 months, with a 2-year survival rate of 28% and an operative mortality rate of 11%. The median survival duration was 32 months for those attaining a pathologically complete response [66].

Mercke et al [67] reported the use of preoperative fluorouracil plus cisplatin followed by radiation therapy in 60 patients, which resulted in effective palliation in 50% of patients and a pathologically complete response rate of 15%. In another study, 43 patients received concurrent hyperfractionated radiation therapy (37.5 to 45 Gy) and an intensive 21-day inpatient course of cisplatin, vinblastine, and fluorouracil before undergoing trans-hiatal esophagectomy [68]. Thirty-six (84%) patients had a curative surgical resection and 10 (24%) had a pathologically complete response. Myelosuppression and severe esophagitis were the major toxic effects. Two patients died of treatment-related causes before undergoing surgery. The median survival time was 29 months; 34% of patients are alive at 5 years. The best survival results were observed in 6 of the 10 patients who achieved the pathologically complete response. A follow-up study is comparing concurrent preoperative chemoradiotherapy plus surgery with surgery alone and will be most helpful in evaluating the role of intensive chemoradiotherapy.

Naunheim et al [44] investigated 47 patients, with either histologic subtype of esophageal cancer, treated simultaneously with radiation therapy (30 to 36 Gy) and cisplatin plus fluorouracil. Of the 39 patients taken to surgery, 83% (or 66% of the entire group) had a curative resection. Eight patients (21%) had a pathologically complete response. Siewart et al [69] reported a significant improvement in survival compared with their historical controls in 58 patients with adenocarcinoma treated concurrently with cisplatin, fluorouracil, and leucovorin (folinic acid) and radiation therapy (76% of patients remain alive at 24 months) [69].

Gill et al [70] compared the patterns of failure after preoperative (fluorouracil plus cisplatin and 36-Gy radiation) with those of chemotherapy and radiation therapy (54 to 60 Gy) without surgery and found the local failure rates to be similar (17% vs 12%) whether or not surgery was performed. Distant metastases were the predominant sites of failure. In addition, there was a higher rate of complete durable relief of dysphagia in patients receiving radiation therapy and chemotherapy than in those who also had surgery.

Concurrent radiation therapy and chemotherapy results in substantial morbidity and up to a 15% therapy-related mortality rate [44,68,71], with the respiratory distress syndrome being a major
complication [72]. This strategy might prove highly effective in the future, but more emphasis is required on the development of less toxic combinations with newer radiation enhancers. The other important option to consider is sequential chemotherapy and radiation therapy. The role of preoperative concurrent chemotheraphy and radiation therapy remains to be defined, but this strategy seems to result in a higher rate of pathologically complete responses than does preoperative chemotheraphy alone.

**Definitive Radiation Therapy and Chemotherapy:** Promising pilot study results with concurrent chemotherapy and radiation therapy [73-76] prompted prospectively randomized trials. The Eastern Cooperative Oncology Group studied 130 patients who had unresectable squamous-cell carcinomas treated with radiation therapy (40 Gy) with or without fluorouracil and mitomycin [77]. A survival advantage was observed in patients who received the combined-modality therapy (14.9 vs 9 months). To some extent, however, the results might have been influenced by the surgical salvage accomplished in some patients. This study has not yet been published.

Araujo et al [78] compared radiation therapy with a combination of fluorouracil, mitomycin, and bleomycin plus radiation therapy in a small number of patients and found no differences in statistical survival between the two arms. Hatlevoll et al [79] also compared radiation therapy alone with two sequential courses of bleomycin and cisplatin followed by radiation therapy in 97 patients with squamous-cell carcinoma and demonstrated no statistically significant survival advantage with either treatment.

A study conducted by the Radiation Therapy Oncology Group [80] demonstrated a statistically significant but modest survival advantage (12.5 vs 8.9 months) favoring combined-modality treatment over radiation therapy alone in patients who had unresectable tumors or were medically unfit for surgery. Sixty patients were randomized to receive radiation therapy (50 Gy) alone and 61 patients to receive combined-modality therapy consisting of four courses of fluorouracil and cisplatin given concurrently with radiation therapy (45 Gy).

In this trial, 40% of patients receiving radiation therapy alone had persistent local disease; an additional 24% developed local relapse after a short median follow-up. In contrast, the combined-modality arm had a 43% local failure rate ($P = .005$). However, the local failure rate at longer follow-up will be more meaningful. The modest improvement in survival among patients who received chemotherapy and radiation therapy was associated with substantial morbidity because of severe myelosuppression and mucositis. In addition, less than 60% of the patients completed the planned combined-modality therapy.

The combination of chemotherapy and radiation therapy suggests benefit for both local control and, albeit modest, overall survival. This approach may be appropriate for patients with either unresectable squamous-cell carcinoma or those who are medically unfit to undergo surgery [81]. A relatively high local failure rate remains a concern, as does patient compliance and morbidity. Overall, there seems to be increasing interest in studying concurrent chemotherapy and radiation therapy, either as preoperative therapy or definitive therapy. Patients with adenocarcinoma histology have not yet been adequately studied.

The challenges lie ahead for investigators to develop less toxic chemoradiotherapy regimens. In addition, there is growing momentum to develop strategies to compare the effectiveness of chemoradiotherapy with that of surgery in patients with locoregional carcinoma of the esophagus.

**Palliative Therapy**

Surgical bypass to alleviate dysphagia is no longer recommended on a routine basis. There are a number of appropriate palliative approaches, but discussion of these is beyond the scope of this chapter. Significant palliation for a limited time may be obtained with radiation therapy in approximately 50% of patients [80]. In addition, the use of concurrent fluorouracil with less than 45 Gy of radiation therapy might produce the most effective palliation without prohibitive morbidity [81].

**Cost**

The cost of cancer therapy is a growing concern in the current milieu of health-care reform. Treatment cost for patients with carcinoma of the esophagus is high, and long-term benefits have not yet been demonstrated. There will be increasing scrutiny of our standard treatment and research approaches as related to the cost of care. At the present time, available information is scanty and remains to be validated, but more data are likely to appear in the next 2 years.

**Current Options, Future Directions**

Significant advances have been made in the management of patients with carcinoma of the
esophagus. Improvements in short-term outcome have resulted from advances in all disciplines. Combined-modality therapeutic approaches have taken the central stage in the management of carcinoma of the esophagus. The major limitations at present include the lack of more effective cytotoxic therapy and less toxic chemoradiotherapy. Substantial efforts are underway to improve combined-modality therapy for carcinoma of the esophagus.

With regard to the current therapeutic options for locoregional carcinoma of the esophagus:

1. For severe dysplasia with or without Barrett's esophagus and with or without aneuploidy, consider chemoprevention protocols, frequent close observations, or surgical resection as a last resort.
2. For the above conditions with carcinoma in situ (with or without invasion), consider surgical resection.
3. For a T1 or T2 primary tumor with N0 and M0 status, consider surgical resection or chemoradiotherapy for patients medically unfit for surgery.
4. For a T2 or T3 primary tumor with N1 and M0 status, consider investigational studies, surgical resection, or chemoradiotherapy for the medically unfit.
5. For a T4 primary tumor with any N and M0 status, consider chemoradiotherapy or investigational studies and other palliative options as appropriate.

The aim of preoperative therapy must be to increase the rate of pathologically complete responses. Hyperfractionated radiation therapy, the search for new radiation enhancers, and sequential therapy must also be investigated. Nevertheless, the combined-modality therapy has demonstrated short-term benefit for patients with locoregional carcinoma of the esophagus, and we remain optimistic that further research efforts will translate into long-term benefits for our patients. The search must continue for novel therapeutic agents, novel approaches, and exploitation of the unique biologic features of precancerous and cancerous tissues. Analyses of molecular events underlying the development of esophageal cancer may yield new strategies for diagnosis, prevention, and therapy.

References:


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