Review

Preoperative Concurrent Chemotherapy and Radiation Therapy Followed by Surgery for Esophageal Cancer

Masahiko Yano, MD,[1] Masatoshi Inoue, MD,[2] and Hitoshi Shiozaki, MD[3]

Currently, the most promising strategy to improve the prognosis of advanced esophageal cancer is preoperative chemoradiation (CRT) followed by surgery. The superiority of CRT over radiation therapy alone has been demonstrated by several randomized studies. Many phase II studies of CRT followed by surgery have shown that the pathologic complete response (CR) rate ranges from 17 to 40%, and the median survival time (MST) is 12 to 31.3 months. Five randomized trials have compared preoperative CRT followed by surgery with surgery alone for resectable esophageal cancer, and four of them did not find any significant survival benefit for the combined treatment group. There are several issues in interpreting these findings, such as the quality of the surgery, the accuracy of the preoperative staging, the statistical power and design of the trials. Until comprehensive evaluation can be done, the standard therapy for resectable esophageal cancer should be considered to be surgery alone. The histological response in the resected specimen correlates well with the prognosis. Patients with pathologic CR display significantly better survival than those with microscopic residual cancer cells in the resected specimens. These findings suggest that more potent regimens leading to higher pathologic CR rates should improve the prognosis. Chemotherapy or radiation therapy sensitivity testing needs to be established. If accurate prediction of the response is possible prior to therapy, non-responders can be excluded. Cell cycle-related genes, apoptosis-related genes, and drug metabolizing genes have been investigated in many pilot studies and need to be evaluated by large-scale clinical studies. At present, pathologic CR can not be accurately diagnosed before surgery. Endoscopic biopsy is also unreliable for the diagnosis. In the future, new diagnostic tools such as positron emission tomography scanning, a sensitivity test or molecular markers may enable accurate diagnosis of pathologic CR to guide the choice of treatment strategies for individual patients. (Ann Thorac Cardiovasc Surg 2002; 8: 123–30)

Key words: locally advanced esophageal cancer, squamous cell carcinoma, chemoradiation, neoadjuvant therapy, multimodal therapy

Introduction

Among the many gastrointestinal cancers, esophageal cancer has one of the poorest prognoses because it easily metastasizes to lymph nodes as well as to distant organs.[1,2] Even for submucosal tumors, lymph node metastasis is observed in about 40% of the cases, which is much more frequent than for gastric or colorectal cancers (about 10%).[3] Furthermore, esophageal cancer often infiltrates neighboring organs such as the aorta, trachea and bronchus, since the esophagus lacks serosa and is located in a very narrow mediastinal space. Once such organs are infiltrated, complete surgical resection of the tumors is very difficult, and even if it were possible, the prognosis of such patients is extremely poor.[4-6] One way of improving the prognosis of patients with locally advanced esophageal cancer is multimodal therapy. Radiation therapy

From the [1]Department of Surgery and Clinical Oncology, Graduate School of Medicine, Osaka University, Suita, the [2]Department of Surgical Oncology, Nara Hospital, Kinki University School of Medicine, Ikoma, and the [3]First Department of Surgery, Kinki University School of Medicine, Osaka-sayama, Japan

Received March 1, 2002; accepted for publication May 8, 2002.
Address for reprint requests to Masahiko Yano, MD: Department of Surgery and Clinical Oncology, Graduate School of Medicine, Osaka University, 2-2 Yamadaoka, Suita, Osaka 565-0871, Japan.

Table 1. Randomized trials of concurrent chemoradiation therapy compared with radiation therapy alone

Investigator	Regimen	RT	No. of patients	MST (mo)	Survival 2 years	Survival 3 years
Araujo[16]	5-FU/MMC/BLM	50 Gy	28	NS	38%	16%
	–	50 Gy	31	NS	22%	6%
Sischy[17]	5-FU/MMC	60 Gy	119[a]	14.8*	NS	NS
	–	60 Gy		9.1	NS	NS
Herskovic[18,19]	5-FU/CDDP	50 Gy	61	14.1	38%**	27%** (5 years)
	–	64 Gy	60	9.3	10%	0%

RT: radiation therapy, MST: median survival time, 5-FU: 5-fluorouracil, MMC: mitomycin C, BLM: bleomycin, CDDP: cisplatin, NS: not stated

[a]: total number of patients receiving chemoradiation and radiation alone

*: p=0.03, **: p<0.0001 vs. radiation therapy alone

alone may improve locoregional control but does not improve overall survival, whether given preoperatively or postoperatively. Increased incidence of clinically apparent distant organ metastasis during follow-up after radiation therapy suggests that systemic micrometastasis may have been present at the time of diagnosis, and thus systemic therapy is also required.[7-12] Adjuvant chemotherapy alone has not been reported to improve survival to date.[13,14] Recently, neoadjuvant chemoradiation therapy given prior to surgical resection has been anticipated to control both local recurrence and distant metastasis of esophageal cancer.

Concurrent Chemoradiation for Esophageal Cancer

The rationale behind preoperative chemoradiation therapy is as follows: 1) preoperative therapy permits higher resectability in the subsequent surgery; 2) chemoradiation therapy is more tolerable before surgery than after it; 3) simultaneous treatment with chemotherapy and radiation may control not only local but also occult distant disease; 4) 5-fluorouracil and cisplatin, most frequently used in chemoradiation regimens, both act as radiation sensitizers.[15] On the other hand, the disadvantages of this strategy is that a substantial percentage of patients who do not respond to it may lose the chance of surgery and that the toxicity of the preoperative treatment may increase operative morbidity and mortality.

The superiority of concurrent chemoradiation therapy over radiation therapy alone has been demonstrated by several randomized studies as shown in Table 1. Araujo et al. compared treatment using 5-fluorouracil (5-FU)/mitomycin C (MMC)/bleomycin (BLM) plus 50 Gy of radiation therapy with treatment using radiation therapy (50 Gy) alone for 59 patients. They reported that although survival was not improved by the combined therapy, local (46.5% vs. 74%) and distant (9% vs. 22%) failure rates decreased in the chemoradiation therapy group.[16] Sischy et al. in 1990 for the Eastern Cooperative Oncology Group (ECOG) reported the results of their randomized trial comparing 5-FU/MMC plus 60 Gy of radiation therapy with radiation therapy (60 Gy) alone in 119 patients with squamous cell carcinoma. The median survival time (MST) for chemoradiation therapy was 14.8 months, which was significantly longer than the 9.1 months for radiation therapy alone (p=0.03).[17] Herskovic et al. in 1992, with an update in 1997 for the GI Intergroup, randomized 121 patients with localized disease of 15 cases of adenocarcinoma and 106 cases of squamous cell carcinoma to treatment using either 5-FU plus cisplatin (CDDP) with 50 Gy of radiation therapy or treatment using radiation therapy (64 Gy) alone. The MST was 9.3 months for the radiation therapy alone group, compared with the 14.1 months for the chemoradiation therapy group. The 2- and 5-year survival rates in the former group were 10% and 0%, respectively, whereas those for the combined therapy group were 38% and 27% (p<0.0001). Both the local (44% vs. 65%) and distant (12% vs. 26%) recurrences were significantly fewer in the chemoradiation therapy group.[18,19] At present, it is generally accepted that concurrent chemoradiation therapy has a significant advantage over radiation therapy alone. Therefore, recent studies recommend chemoradiation therapy as an adjuvant or definitive treatment.

Concurrent Chemoradiation without Surgery

Many phase II trials of concurrent chemotherapy and radiation therapy as definitive therapy without surgery have

Table 2. Phase II studies of concurrent chemoradiation without surgery

Investigator	Regimen	RT	No. of patients	Major response	MST (mo)	Survival
Leichman[20]	5-FU/CDDP+MMC/BLM	30+20 Gy	20	NS	22	NS
Coia[21]	5-FU/MMC	60 Gy	57 (Stage I, II)	NS	18	29% (3 yrs), 18% (5 yrs)
John[22]	5-FU/CDDP/MMC+MTX/5-FU/LV	41.5-50.4 Gy	30	77%	15	29% (2 yrs)
Le Prise[23]	5-FU/CDDP	60 Gy	50	NS	13	63% (1 y), 36% (2 yrs)
Minsky[24]	5-FU/CDDP (NAC)+5-FU/CDDP (CRT)	64.8 Gy	37	NS	20	NS[a]

RT: radiation therapy, MST: median survival time, 5-FU: 5-fluorouracil, CDDP: cisplatin, MMC: mitomycin C, BLM: bleomycin, MTX: methotrexate, LV: leucovorin, NAC: neoadjuvant chemotherapy, CRT: chemoradiation, NS: not stated

[a]: The trial was terminated because of toxicity.

been conducted, with selected studies outlined in Table 2. Leichman et al. conducted a pilot nonoperative study on 20 patients with squamous cell carcinoma. Surgery was not planned after chemoradiation therapy based on their early studies showing high operative mortality after chemoradiation therapy and an uncertain contribution of surgery to survival benefit. The regimen consisted of two cycles of 5-FU and CDDP given concurrently with 30 Gy of radiation followed by an additional two cycles of chemotherapy with MMC and BLM. An additional boost of radiation therapy (20 Gy) was given after completion of chemotherapy. The MST in this series was 22 months.[20] Coia et al. reported the results of 57 patients with squamous cell and adenocarcinoma treated with chemoradiation therapy alone. Patients were treated with 5-FU and MMC given concurrently with 60 Gy of radiation therapy. The MST was 18 months with 3-year and 5-year survival rates of 29% and 18%, respectively. Local control was achieved in 70% of the patients. Of the 29 patients with recurrences, local and distant failures occurred in 48% and 72%, respectively.[21] John et al. reported the results of 30 patients treated with 5-FU, MMC and CDDP given concurrently with 41.5 to 50.4 Gy of radiation therapy. Chemotherapy combining methotrexate (MTX), 5-FU and leucovorin (LV) was given for three cycles after chemoradiation therapy. The MST was 15 months and 2-year survival rate was 29%.[22] Another two investigators combined 5-FU and CDDP with radiation therapy, with similar prognoses.[23,24]

Whether surgery after chemoradiation therapy actually does contribute to survival remains unknown and needs to be proven by randomized study. However, in theory, concurrent chemoradiation followed by surgery seems to offer the highest curability for patients. Local control should be better than that from a non-surgical approach because residual cancer cells in the esophagus and regional lymph nodes can be removed by surgery. Thus, until further evidence is obtained, chemoradiation therapy without surgery should not be used for the treatment of patients with localized, surgically curable disease. Chemoradiation therapy alone should only be used when the tumors are unresectable.

Concurrent Chemoradiation Followed by Surgery

Phase II studies of concurrent chemotherapy and radiation therapy followed by surgery are summarized in Table 3. The first report of preoperative chemoradiation therapy for esophageal cancer came from Franklin et al.[25] They had obtained successful results for anal cancer and applied it to the treatment for esophageal cancer. Their regimen consisted of 30 Gy of radiation with 5-FU and MMC followed by surgery. Of the 30 patients enrolled in their study, resection was done for 23. Six of these 23 patients (26%) had no evidence of cancer cells in the resected specimens. The MST was 18 months. All the patients with residual tumor in the resected esophagus showed recurrence during the follow-up, whereas four of the six pathologic complete response (CR) patients were alive at 95 to 190 weeks. Many subsequent studies modified this protocol and used CDDP in place of MMC because CDDP was reported to be effective in combination with 5-FU for advanced esophageal cancer.[26-31] As shown in Table 3, the pathologic CR rate of these phase II studies ranged from 17 to 40%, and the MST was 12 to 31.3 months. These encouraging results have made neoadjuvant chemoradiation therapy followed by surgery one of the most promising strategies for locally advanced esophageal cancer.

To clarify whether preoperative chemoradiation offers survival benefits for patients with esophageal cancer, randomized trials are absolutely needed. Thus far, five ran-

Table 3. Phase II studies of concurrent chemoradiation followed by surgery

Investigator	Regimen	RT	No. of patients	Resectability	Operative mortality	Path CR	MST (mo)	Survival
Franklin[25]	5-FU/MMC	30 Gy	30	76%	13%	20%	18[a]	30% (3 yrs)[a]
Leichman[26]	5-FU/CDDP	30 Gy	21	71%	27%	24%	18	NS
Poplin[27]	5-FU/CDDP	30 Gy	106	49%	11%	17%	12	16% (3 yrs)
Seydel[28]	5-FU/CDDP	30 Gy	41	66%	4%	20%	13	8% (3 yrs)
Forastiere[29]	5-FU/VBL/CDDP	37.5-45 Gy	43	91%	2%	24%	29	34% (5 yrs)
Wolfe[30]	CDDP/VCR (Sq)	45 Gy	104	53%	5%[b]	40%	25.5[a]	25% (5 yrs)[a]
	5-FU/CDDP (Adeno)	45 Gy	45	67%		20%	29.1[a]	20% (5 yrs)[a]
Forastiere[31]	5-FU/CDDP	44 Gy	50	90%	0%	40%	31.3	58% (2 yrs)

RT: radiation therapy, Path CR: pathologic complete response, MST: median survival time, 5-FU: 5-fluorouracil, MMC: mitomycin C, CDDP: cisplatin, VBL: vinblastine, VCR: vincristine, Sq: squamous cell carcinoma, Adeno: adenocarcinoma, NS: not stated

[a]: data for resected cases, [b]: operative mortality for both Sq and Adeno

Table 4. Randomized trials comparing concurrent chemoradiation followed by surgery with surgery alone

Investigator	Regimen	RT	No. of patients	Resectability	Operative mortality	Path CR	MST (mo)	3 y-survival
Nygaard[32]	CDDP/BLM	35 Gy	53	88.7%	23.5%	NS	9	17%
	Surgery alone		50	82.0%	13.2%		8.4	9%
Le Prise[33]	5-FU/CDDP	20 Gy	41	85.0%	8.5%	10%	NS	19.2%
	Surgery alone		45	93.0%	7.0%		NS	13.8%
Walsh[34]	5-FU/CDDP	40 Gy	58	100%	6.9%	25%	16*	32%*
	Surgery alone		55	100%	3.6%		11	6%
Bosset[35]	CDDP	37 Gy	143	96.5%	12.3%	26%	18.6	37%
	Surgery alone		139	98.6%	3.6%		18.6	35%
Urba[36]	5-FU/VBL/CDDP	45 Gy	50	94.0%	2.0%	28%	16.9	30%
	Surgery alone		50	100%	4.0%		17.6	16%

RT: radiation therapy, Path CR: pathologic complete response, MST: median survival time, 5-FU: 5-fluorouracil, BLM: bleomycin, CDDP: cisplatin, VBL: vinblastine, NS: not stated

*: p=0.01 vs. surgery alone

domized trials which compared preoperative chemoradiation followed by surgery with surgery alone have been conducted for resectable esophageal cancers.[32-36] (Table 4) Only one study reported by Walsh et al. demonstrated a significantly better median survival time and 3-year survival for the chemoradiation group.[34] However, criticism of their paper work pointed out that their control group showed very poor survival (3-year survival of 6% and MST of 11 months), which might have led to a significant difference in their results. The other four studies failed to show any significant survival benefit for the combined treatment group.

From these findings, the question arises of whether preoperative chemoradiation is necessary. When interpreting these literature findings, attention must be paid to several points. First, the quality of the surgery is a critical factor. High operative mortality (2.0-23.5%) and the choice of surgical procedure (transhiatal esophagectomy or esophagectomy with lymphadenectomy through right thoracic and abdominal routes) may affect the outcome. Second, the accuracy of the preoperative staging of the disease is important. Since nodal involvement is an important prognostic factor for esophageal cancers, the number and extent of lymph node metastases must be accurately diagnosed for even randomization. Therefore, well-designed trials of high quality which overcome these problems are needed to prove the significant survival benefit of preoperative chemoradiation. Until this is done, standard therapy for resectable esophageal cancer should be considered to be surgery alone.

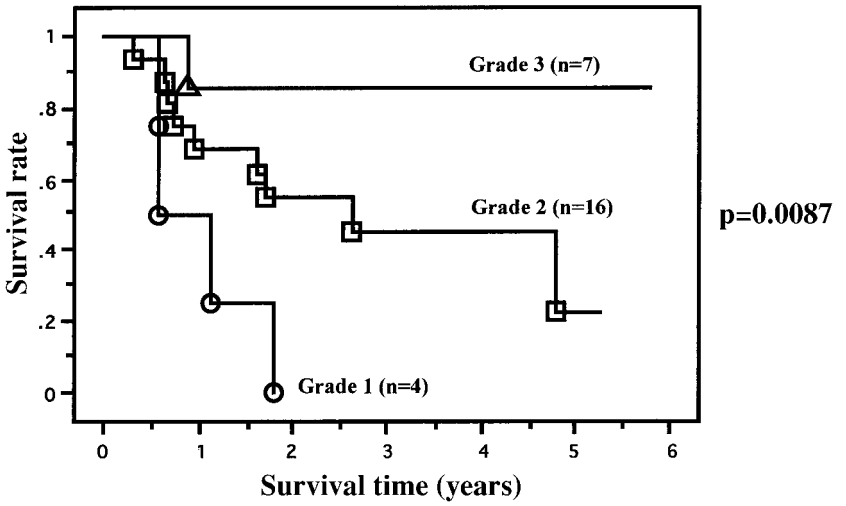

Fig. 1. Relationship between survival rates and histologic effect of the main tumors. Histologic effect is defined as follows: grade 3, complete disappearance of cancer cells; grade 2, more than 2/3 disappearance; grade 1, less than 2/3 disappearance.

Future Directions

Most studies have shown that patients with pathologic CR displayed significantly better survival than those with a pathologic partial response (PR). Forastiere et al. reported that pathologic CR patients had a median survival duration of 70 months and 60% were alive at 5 years, while those with residual tumors in the resected specimen had a median survival duration of 26 months and 32% were alive at 5 years.[29] Previously, we reported the results of neoadjuvant chemoradiation therapy followed by surgery for 43 patients with primary inoperable T4 esophageal cancer. Pathologic CR was found in 8 (28.6%) of 28 surgical specimens. As shown in Fig. 1, the histological response in the resected specimen correlated well with the prognosis. Most of the long-term survivors (more than 5 years) were in the pathologic CR group, whereas there were few 5-year survivors among those with microscopic residual cancer cells in the resected specimens.[37] Mandard et al. demonstrated that pathologic CR was the only significant predictor of disease-free survival for patients with esophageal cancer by multivariate analysis.[38] These findings suggest that more potent regimens having higher pathologic CR rates should improve the prognosis of patients and make preoperative chemoradiation followed by surgery a standard therapy for esophageal cancer in the future.

Paclitaxel is a candidate drug which leads to a higher pathologic CR rate in combination with radiation therapy since it is a potent radiosensitizer and has an antitumor effect against esophageal cancer. Preliminary results suggest that preoperative concurrent paclitaxel-based combination chemotherapy with radiation therapy is very effective for esophageal cancer.[39,40] In addition, a new radiosensitizer which enhances the radiation effect or an agent which reduces cytotoxicity should also be developed. Cytoprotective drugs such as amifostine are under investigation for clinical use.[41] Hyperfractionated radiation is another approach to increasing the pathologic CR rate. Kim et al. conducted a phase II study of preoperative hyperfractionated radiation (48 Gy/40 fr/4 weeks) with concurrent chemotherapy (5-FU/cisplatin) followed by surgery for 94 resectable esophageal cancer patients. The pathologic CR rate was 49% for 53 resected patients, which was better than the historical control.[42]

Chemotherapy or radiation therapy sensitivity testing is another important issue. If accurate prediction of response becomes possible pretherapeutically, non-responders who would receive no benefit from the treatment can be excluded. Cell cycle-related genes, apoptosis-related genes, and drug metabolizing genes have been investigated in many pilot studies. Miyata et al. reported that p53 mutation seems to be correlated with resistance to the treatment and that CDC25B, one of the cell cycle regulators involved in G2/M arrest, is also a candidate for a predictor.[43,44] Imdahl et al. demonstrated that a higher proliferation index (>39%) as determined by MIB-1 positivity indicates a responder to the treatment.[45] Yamamoto et al. reported that metallothionein expression in tumor tissue correlated well with the pathologic response.[46] Metallothionein is an intracellular metal-binding protein and is involved in detoxification of heavy metals including cadmium, copper and mercury. Immunohistochemical analysis of pretherapeutic biopsy specimens revealed that 13 out of 14 patients with metallothionein-negative tumor cells were responders, whereas 10 out of 16 pa-

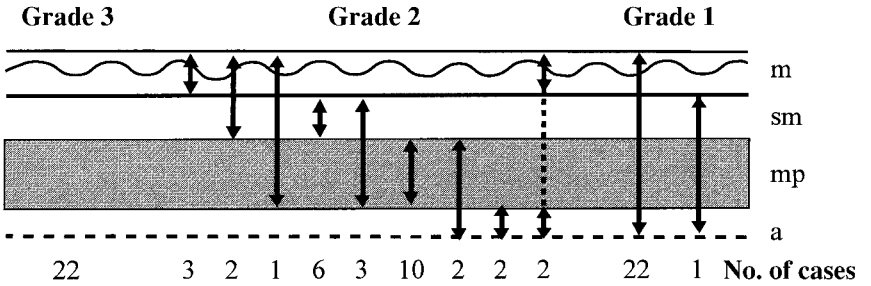

Fig. 2. Localization of residual cancer cells after preoperative chemoradiation therapy. A total of 76 patients were treated with preoperative chemoradiation followed by surgery. The localization of residual cancer cells in the resected esophagi is indicated as a line with bilateral arrowheads. The histologic effect is shown at the top and the number of cases at the bottom. m: mucosa, sm: submucosa, mp: muscularis propria, a: adventitia.

tients with metallothionein-positive tumor cells were non-responders. Large-scale clinical study is necessary for evaluation of these factors.

The next question that arises is whether surgery can be omitted if pathologic CR is accurately diagnosed after chemoradiation therapy. The answer is probably "yes". Non-surgical, definitive chemoradiation trials summarized in Table 2 show substantial percentages of long-time survivors, which seems to correspond to the pathologic CR rates reported in phase II trials of preoperative chemoradiation followed by surgery as shown in Table 3. Patients who truly need surgery after chemoradiation and can benefit from it may be only those with microscopic residual tumors. However, conventional methods such as CT scan and endoscopic ultrasound can not correctly evaluate pathologic CR.[47-50] As shown in Fig. 2, endoscopic biopsy is also unreliable because most residual tumor cells after the treatment are located not in the mucosal layer but in the muscular and deeper layers of the esophageal walls.[51] Positron emission tomography (PET) scan was reported to be more sensitive than CT in the detection of nodal involvement of esophageal cancer.[52] Brucher et al. reported that the pathologic tumor response after preoperative chemoradiation therapy can be evaluated by tumor uptake of FDG.[53] The diagnostic power of PET for microscopic residual tumors remains unknown, but PET alone or in combination with other tools such as a sensitivity test may enable accurate diagnosis of pathologic CR in the future.

Advances in molecular biology are contributing to elucidating the mechanism of esophageal tumorigenesis, metastasis, and response to treatment. Findings from such work should guide the choice of future treatment strategies.

References

1. Sugimachi K, Inokuchi K, Kuwano H, et al. Patterns of recurrence after curative resection for carcinoma of the thoracic part of the esophagus. *Surg Gynecol Obstet* 1983; **157**: 537–40.
2. Goseki N, Koike M, Yoshida M. Histopathologic characteristics of early stage esophageal carcinoma. *Cancer* 1992; **69**: 1088–93.
3. Watanabe H, Kato H, Tachimori Y, et al. Necessity of cervical lymph node dissection by retrospective analysis of submucosal cancer in mid- and lower thoracic esophagus. *Ann Thorac Cardiovasc Surg* 1995; **1**: 49–53.
4. Iizuka T. Surgical treatment for A3 esophageal carcinoma. *Kyobu Geka* 1980; **80**: 822–7. (in Japanese)
5. Ancona E, Ruol A, Castoro C, et al. First-line chemotherapy improves the resection rate and long-term survival of locally advanced (T4, any N, M0) squamous cell carcinoma of the thoracic esophagus: final report on 163 consecutive patients with 5-year follow-up. *Ann Surg* 1997; **226**: 714–23.
6. Takagi I, Karasawa K, Kunishima K, et al. Surgical treatment of esophageal carcinoma infiltrated to the adjacent organs. *Jpn J Gastroenterol Surg* 1981; **14**: 1141–6. (in Japanese)
7. Launois B, Delarue D, Campion JP, Kerbaol M. Preoperative radiotherapy for carcinoma of the esophagus. *Surg Gynecol Obstet* 1981; **153**: 690–2.
8. Gignoux M, Roussel A, Paillot B, et al. The value of preoperative radiotherapy in esophageal cancer: results of a study of the E.O.R.T.C. *World J Surg* 1987; **11**: 426–32.
9. Wang M, Gu XZ, Yin WB, et al. Randomized clinical trial on the combination of preoperative irradiation and surgery in the treatment of esophageal carcinoma: report on 206 patients. *Int J Radiat Oncol Biol Phys* 1989; **16**: 325–7.
10. Arnott SJ, Duncan W, Kerr GR, et al. Low dose preoperative radiotherapy for carcinoma of the esophagus:

results of a randomized clinical trial. *Radiother Oncol* 1992; **24**: 108–13.
11. Teniere P, Hay JM, Fingerhut A, Fagniez PL. Postoperative radiation therapy does not increase survival after curative resection for squamous cell carcinoma of the middle and lower esophagus as shown by a multicenter controlled trial. *Surg Gynecol Obstet* 1991; **173**: 123–30.
12. Fok M, Sham JST, Choy D, et al. Postoperative radiotherapy for carcinoma of the esophagus: a prospective, randomized controlled study. *Surgery* 1993; **113**: 138–47.
13. Roth JA, Pass HI, Flanagan MM, et al. Randomized clinical trial of preoperative and postoperative adjuvant chemotherapy with cisplatin, vindesine, and bleomycin for carcinoma of the esophagus. *J Thorac Cardiovasc Surg* 1988; **96**: 242–8.
14. Schlag P. Randomized trial of preoperative chemotherapy for squamous cell cancer of the esophagus. *Arch Surg* 1992; **127**: 1446–50.
15. Ilson DH, KelsenDP. Combined modality therapy in the treatment of esophageal cancer. *Semin Oncol* 1994; **21**: 493–507.
16. Araujo CM, Souhami L, Gil RA, et al. A randomized trial comparing radiation therapy versus concomitant radiation therapy and chemotherapy in carcinoma of the thoracic esophagus. *Cancer* 1991; **67**: 2258–61.
17. Sischy B, Ryan L, Haller D, et al. Interim report of EST 1282/phase III protocol for the evaluation of combined modalities in the treatment of patients with carcinoma of the esophagus, stage I and II (abstract). *Proc Am Soc Clin Oncol* 1990; **9**: 105.
18. Herskovic A, Martz K, Al-Sarraf M, et al. Combined chemotherapy and radiotherapy compared with radiotherapy alone in patients with cancer of the esophagus. *N Engl J Med* 1992; **326**: 1593–8.
19. Al-Sarraf M, Martz K, Herskovic A, et al. Progress report of combined chemoradiotherapy versus radiotherapy alone in patients with esophageal cancer: an intergroup study. *J Clin Oncol* 1997; **15**: 277–84.
20. Leichman L, Herskovic A, Leichman CG, et al. Nonoperative therapy for squamous cell cancer of the esophagus. *J Clin Oncol* 1987; **5**: 365–70.
21. Coia LR, Engstrom PF, Paul AR, Stafford PM, Hanks GE. Long-term results of infusional 5-FU, mitomycin-C, and radiation as primary management of esophageal carcinoma. *Int J Radiat Oncol Biol Phys* 1991; **20**: 29–36.
22. John MJ, Flam MS, Mowry PA, et al. Radiotherapy alone and chemoradiation for nonmetastatic esophageal carcinoma. A critical review of chemoradiation. *Cancer* 1989; **63**: 2397–403.
23. Le Prise EA, Meunier BC, Etienne PA, et al. Sequential chemotherapy and radiotherapy for patients with squamous cell carcinoma of the esophagus. *Cancer* 1995; **75**: 430–4.
24. Minsky BD, Neuberg D, Kelsen DP, et al. Neoadjuvant chemotherapy plus concurrent chemotherapy and high-dose radiation for squamous cell carcinoma of the esophagus: a preliminary analysis of the phase II intergroup trial 0122. *J Clin Oncol* 1996; **14**: 149–55.
25. Franklin R, Steiger Z, Vaishampayan G, et al. Combined modality therapy for esophageal squamous cell carcinoma. *Cancer* 1983; **51**: 1062–71.
26. Leichman L, Steiger Z, Seydel HG, et al. Preoperative chemotherapy and radiation therapy for patients with cancer of the esophagus: a potentially curative approach. *J Clin Oncol* 1984; **2**: 75–9.
27. Poplin E, Fleming T, Leichman L, et al. Combined therapies for squamous-cell carcinoma of the esophagus, a Southwest Oncology Group Study (SWOG-8037). *J Clin Oncol* 1987; **5**: 622–8.
28. Seydel HG, Leichman L, Byhardt R, et al. Preoperative radiation and chemotherapy for localized squamous cell carcinoma of the esophagus: a RTOG Study. *Int J Radiat Oncol Biol Phys* 1988; **14**: 33–5.
29. Forastiere AA, Orringer MB, Perez-Tamayo C, et al. Preoperative chemoradiation followed by transhiatal esophagectomy for carcinoma of the esophagus: final report. *J Clin Oncol* 1993; **11**: 1118–23.
30. Wolfe WG, Vaughn AL, Seigler HF, et al. Survival of patients with carcinoma of the esophagus treated with combined-modality therapy. *J Thorac Cardiovasc Surg* 1993; **105**: 749–56.
31. Forastiere AA, Heitmiller RF, Lee DJ, et al. Intensive chemoradiation followed by esophagectomy for squamous cell and adenocarcinoma of the esophagus. *Cancer J Sci Am* 1997; **3**: 144–52.
32. Nygaard K, Hagen S, Hansen HS, et al. Pre-operative radiotherapy prolongs survival in operable esophageal carcinoma: a randomized, multicenter study of pre-operative radiotherapy and chemotherapy. The second Scandinavian trial in esophageal cancer. *World J Surg* 1992; **16**: 1104–10.
33. Le Prise EA, Etienne PL, Meunier BC, et al. A randomized study of chemotherapy, radiation therapy, and surgery versus surgery for localized squamous cell carcinoma of the esophagus. *Cancer* 1994; **73**: 1779–84.
34. Walsh TN, Noonan N, Hollywood D, et al. A comparison of multimodal therapy and surgery for esophageal adenocarcinoma. *N Engl J Med* 1996; **335**: 462–7.
35. Bosset JF, Gignoux M, Triboulet JP, et al. Chemoradiotherapy followed by surgery compared with surgery alone in squamous-cell cancer of the esophagus. *N Engl J Med* 1997; **337**: 161–7.
36. Urba SG, Orringer MB, Turrisi A, et al. Randomized trial of preoperative chemoradiation versus surgery alone in patients with locoregional esophageal carcinoma. *J Clin Oncol* 2001; **19**: 305–13.
37. Yano M, Tsujinaka T, Shiozaki H, et al. Concurrent chemotherapy (5-fluorouracil and cisplatin) and radiation therapy followed by surgery for T4 squamous cell carcinoma of the esophagus. *J Surg Oncol* 1999; **70**: 25–32.
38. Mandard AM, Dalibard F, Mandard JC, et al. Pathologic assessment of tumor regression after preopera-

tive chemoradiotherapy of esophageal carcinoma: clinicopathologic correlations. *Cancer* 1994; **73**: 2680–6.
39. Blanke CD, Choy H, Teng M, et al. Concurrent paclitaxel and thoracic irradiation for locally advanced esophageal cancer. *Semin Radiat Oncol* 1999; **9**: 43–52.
40. Choy H. Taxanes in combined modality therapy for solid tumors. *Oncology* 1999; **13**: 23–38.
41. Dunst J, Semlin S, Pigorsch S, Muller AC, Reese T. Intermittent use of amifostine during postoperative radiochemotherapy and acute toxicity in rectal cancer patients. *Strahlenther Onkol* 2000; **176**: 416–21.
42. Kim JH, Choi EK, Kim SB, et al. Preoperative hyperfractionated radiotherapy with concurrent chemotherapy in resectable esophageal cancer. *Int J Radiat Oncol Biol Phys* 2001; **50**: 1–12.
43. Miyata H, Doki Y, Shiozaki H, et al. CDC25B and p53 are independently implicated in radiation sensitivity for human esophageal cancers. *Clin Cancer Res* 2000; **6**, 4859-65.
44. Miyata H, Doki Y, Yamamoto H, et al. Overexpression of CDC25B overrides radiation-induced G2-M arrest and results in increased apoptosis in esophageal cancer cells. *Cancer Res* 2001; **61**: 3188–93.
45. Imdahl A, Jenkner J, Ihling C, Ruckauer K, Farthmann EH. Is MIB-1 proliferation index a predictor for response to neoadjuvant therapy in patients with esophageal cancer? *Am J Surg* 2000; **179**: 514–20.
46. Yamamoto M, Tsujinaka T, Shiozaki H, et al. Metallothionein expression correlates with the pathologic response of patients with esophageal cancer undergoing preoperative chemoradiation therapy. *Oncology* 1999; **56**: 332–7.
47. Kelsen DP, Heelan R, Coonley C, et al. Clinical and pathological evaluation of response to chemotherapy in patients with esophageal carcinoma. *Am J Clin Oncol* 1983; **6**: 539–46.
48. Andelstein DJ, Rice TW, Becker M, et al. Use of concurrent chemotherapy, accelerated fractionation radiation, and surgery for patients with esophageal carcinoma. *Cancer* 1997; **80**: 1011–20.
49. Isenberg G, Chak A, Canto MI, et al. Endoscopic ultrasound in restaging of esophageal cancer after neoadjuvant chemoradiation. *Gastrointest Endosc* 1998; **48**: 158–63.
50. Zuccaro G, Rice T, Goldblum J, et al. Endoscopic ultrasound cannot determine suitability for esophagectomy after aggressive chemoradiotherapy for esophageal cancer. *Am J Gastroenterol* 1999; **94**: 906–12.
51. Yamamoto M, Doki Y, Shiozaki H, et al. Evaluation of the histologic effect of chemoradiation therapy for squamous cell carcinomas of the esophagus by assessing morphologic features of surgical specimens. *Dis Esophagus* 2000; **13**: 293–300.
52. Kim K, Park SJ, Kim BT, Lee KS, Shim YM. Evaluation of lymph node metastases in squamous cell carcinoma of the esophagus with positron emission tomography. *Ann Thorac Surg* 2001; **71**: 290–4.
53. Brucher BL, Weber W, Bauer M, et al. Neoadjuvant therapy of esophageal squamous cell carcinoma: response evaluation by positron emission tomography. *Ann Surg* 2001; **233**: 300–9.