ACTA BIO MEDICA 2003; 74; Suppl. 2: 15-20

CONFERENCE REPORT

Surgery for esophageal carcinoma and the role of neoadjuvant therapy

Luigi Bonavina, Davide Bona, Alberto Luporini, Nicoletta Navoni, Roberto Zucali

Department of Medical and Surgical Sciences, Division of General Surgery, Istituto Policlinico San Donato, University of Milan

Abstract. Esophagectomy is a major surgical procedure. Due to the related morbidity and mortality, this operation should be carried out in high-volume referral centers by expert surgeons. Only patients in whom a complete resection is predictable at preoperative staging can consistently benefit from the operation. Chemoradiation therapy should be the first-line approach in patients with locally advanced tumors. A pathological complete response to neoadjuvant therapy is associated with a significantly improved long-term survival.

Key words: Esophagus, esophagectomy, lymphadenectomy, neoadjuvant chemoradiation therapy

Resection of esophageal carcinoma with intent to cure is based on the concept that if all neoplastic tissue can be removed (R0 resection according to TNM), a worthwhile period of survival and possible cure might be achieved. Surgical therapy is the only treatment that has repeatedly been shown to provide prolonged survival, albeit in only around 20% of cases (1). However, when the disease is detected early, the results of surgical resection in the Western hemisphere can be excellent, both for squamous-cell carcinoma and adenocarcinoma. Five year rates are over 80% when tumours are confined to the mucosa and between 50% and 80% when the submucosa is involved (2, 3). Conversely, resection has no place in patients with haematogenous metastases (4). It is essential that esophagectomy should be undertaken with an acceptably low hospital mortality and morbidity. In this respect, case selection, case volume, and surgical expertise play an important role. Preoperative risk analysis can reduce postoperative mortality in elderly patients (5, 6). A negative correlation between the number of resected patients and hospital mortality has clearly been demonstrated (7, 8). A team based approach and increasing expertise within that team has also demonstrated a significant decrease in the mortality of esophagectomy over time (9-12).

Choice of the operative approach

The choice of most appropriate surgical strategy is determined by the histological tumour type, its location and the extent of the proposed lymphadenectomy. Transmediastinal esophagectomy is usually unsuitable for squamous cell carcinoma. A left thoracoabdominal approach is limited proximally by the aortic arch, which may compromise the proximal limit of resection. Tumours which lie at the level of the arch are difficult to deal with from the left side and this approach should be avoided when the tumour lies at this level or higher. The combined abdominal and right chest approach allows an adequate oncological resection of most infracarinal esophageal tumors (12).

Appropriate extent of resection

All operations should be designed to reduce the risk of local recurrence and permit an adequate lymphadenectomy, which will minimise the risk of staging error (13). The extent to which lymphadenectomy minimises the risk of symptomatic local recurrence is unknown. The evidence that a more extended

lymphadenectomy is associated with better survival may simply reflect more accurate staging. Longitudinal submucosal spread is characteristic of all types of esophageal carcinoma. This accounts for a high rate of resection margin positivity, when limited longitudinal resections are employed, even with negative frozen section biopsy margins. Several studies support the view that the proximal extent of resection should ideally be 10 cm above the macroscopic tumour and 5 cm distal to it, when the oesophagus is in its natural state (14-16). Adenocarcinoma of the lower oesophagus commonly infiltrates the gastric cardia, fundus and lesser curve. Some degree of gastric resection is essential to accomplish an adequate lymphadenectomy in the abdomen. It is interesting to note that positive distal resection margins in adenocarcinoma are often found in patients with locally advanced disease, where the resection in retrospect was unlikely to be curative. Most of these patients do not die from symptomatic locoregional recurrence (17). Adequate radial margins should also be considered, particularly in patients with infracarinal tumors, where continguous excision of the crura and diaphragm need to be considered (18).

Appropriate extent of lymphadenectomy

The majority of patients who undergo surgery for either adenocarcinoma or squamous cell carcinoma of the esophagus will have lymph node metastases (1). Occult lymph node micrometastases detected by immunohistochemical analysis may have a prognostic impact in patients with adenocarcinoma (19). The principal aims of lymphadenectomy should be to minimise staging error, reduce locoregional recurrences and by increasing the number of patients undergoing a R0 resection, potentially improve cure rates (20). In squamous cell carcinoma, when a methodical approach to lymphadenectomy is applied, the number of lymph nodes involved are of prognostic significance (21), as is the ratio of invaded to removed nodes (22). Although there is considerable enthusiasm in Japan for the performance of lymphadenectomy in three fields (abdomen, thorax and neck), this approach has not been adopted widely by Western surgeons. It is clear, however, that methodical lymph node dissection contributes to the accuracy of the final staging of the disease (4, 21). Studies have shown that when no residual tumour is left behind, there is an improved five year survival compared to patients where this has not occurred (4, 22). A formal one field lymph node dissection is confined to the abdomen. This involves dissection of the right and left cardiac node, the nodes along the lesser curvature, left gastric, hepatic and splenic artery territories. Two field dissection additionally embraces a thoracic lymphadenectomy and includes the para-aortic nodes along with the thoracic duct, paraesophageal nodes, right and left pulmonary hilar nodes, those at the tracheal bifurcation and in Japan, paratracheal nodes including those along the left recurrent laryngeal nerve. Three field dissection extends the lymphadenectomy to the neck to clear the brachiocephalic, deep lateral and external cervical nodes and the deep anterior cervical nodes adjacent to the recurrent laryngeal nerve chains in the neck. A number of studies have shown that two field lymphadenectomy can be carried out without any significant increase in operative morbidity or mortality (23,24). The reported benefits of the three field operation (25), widely advocated in Japan, may simply reflect the reduction in staging error, as nearly a quarter of all Japanese patients will have cervical lymph node metastases (21). There is no evidence that three field lymphadenectomy improves survival in patients with adenocarcinoma and it must be accepted that the operation is associated with a higher postoperative morbidity.

Choice of conduit, route and anastomosis

Foregut continuity is commonly restored using a gastric tube as an esophageal substitute. The function of the intrathoracic stomach as an esophageal replacement has been extensively studied (26, 27). A prospective randomised trial demonstrated that the addition of a drainage procedure did not affect gastric emptying or clinical outcome (28). When stomach is not available, the left colon is the next most suitable conduit. Again, functional performance has been studied in detail (29). Most surgeons favour a prevertebral route for reconstruction and this was shown to be

superior to an anterior reconstruction in one randomised study (30), although another small prospective randomised comparison with a retrosternal gastric tube showed no differences in technical complications or functional outcome (31). Both retrospective and prospective studies comparing manual versus mechanical esophagogastric anastomosis, have shown no difference in leak rates or other complications (32, 33). Fewer strictures are demonstrated with single layer anastomoses (34). A semimechanical anastomosis in the neck using an endoscopic linear stapler may markedly reduce the incidence of leaks (12, 35).

Role of minimally invasive surgery

Minimally invasive surgery may play a role in selected patients with esophageal carcinoma. The most appropriate candidates seem to be those with preoperative diagnosis of high-grade dysplasia or T1 carcinoma. The operation can be performed without opening the chest. The procedure consists of laparoscopy to mobilize the stomach and dissect the lower mediastinum plus blunt dissection or videomediastinoscopy through a left cervical incision (12). Esophagectomy can also be performed through a right thoracoscopy (36). However, the role of minimally invasive esophagectomy for carcinoma still remains a debated issue.

Postoperative management and complications

Meticulous attention to the maintenance of fluid balance and respiratory care are essential in the immediate postoperative period. Pain control and pulmonary physiotherapy are crucial. A double-lumen nasogastric tube should be left in place under moderate suction until a gastrographin swallow study performed on day 7-9 shows anastomotic integrity. Although some authors advocate the routine use of a feeding jejunostomy, no prospective trials have examined its value (37). Early mobilisation is important in the prevention of venous thrombosis and pulmonary embolism.

Respiratory complications. These represent the most common source of morbidity following esophagectomy. Pain from extensive incisions can be a major contributor to decreased ventilation and atelectasis, leading to pneumonia and respiratory failure. Incisions of the diaphragm may impair its movement and extensive lymphadenectomy can cause poor lymphatic drainage and pulmonary edema (38-40).

Anastomotic leakage. Early disruption (within the first 72 hours) reflects technical error. Once confirmed, if the general condition of the patient is good, then re-exploration and correction of the technical fault is appropriate. The majority of disruptions occur later (up to two weeks) and probably reflect local ischaemia and/or tension in the anastomotic site. A high index of clinical suspicion is important. Although water-soluble contrast radiology should be used to establish that leakage has occurred, the technique is not completely accurate and may miss clinically significant leaks, as well as demonstrate radiological leakages of no clinical significance (31, 42). The majority of anastomotic leakages, whether in the neck or the chest, can be managed conservatively with nasogastric suction, appropriate local drainage, antibiotics and jejunal feeding. Dehiscence of the gastric resection line is usually due to ischaemia and is dramatic in its presentation. Early endoscopy should be considered if radiology is inconclusive. Re-exploration is essential (43). The placement of an anastomosis in the neck does not guarantee that leakage will not be into the thoracic cavity from dehiscence of the posterior anastomotic wall (16, 44).

Chylothorax. Chylothorax occurs in about 2-3% of transthoracic esophagectomies. It is easily recognised as the presence of milky fluid in the chest drain. The rate may be higher with transhiatal oesophagectomy, although this is not always the case (45-47). The condition has a high mortality if conservative treatment becomes prolonged due to hypoalbuminaemia and leucocyte depletion (48). The rate of chyle output on about the fifth post-operative day may predict the likelihood of spontaneous closure. Chyle production of greater than 10 ml per kg per day at that time is an indication for early reoperation and ligation of the thoracic duct (47). The operation can also be performed through a right toracoscopic approach (49).

Recurrent laryngeal nerve injuries. These injuries are more common during dissection of the upper third of the oesophagus. The majority of lesions are unilate-

ral and transient. The left recurrent laryngeal nerve is at risk during mediastinal lymphadenectomy; if a cervical anastomosis is used in association with such a dissection, it is wiser to place this on the left side, in order to minimise the risk of damage to both recurrent laryngeal nerves. Recurrent laryngeal nerve injury impairs the patient's ability to cough in the early postoperative period and adequately protect the airway during swallowing, thereby increasing the pulmonary morbidity rate. In most patients there is adequate compensation from the opposite cord. Tracheostomy should be considered in selected cases to protect the airway and improve pulmonary toilet. Thyroplasty or vocal cord injections are rarely required (50).

Benign anastomotic strictures. These can occur within the first few months after surgery, where they relate to postoperative edema/fibrosis or late, when they are due to gastroesophageal reflux. The incidence of early anastomotic stricture formation seems to be higher with cervical rather than intrathoracic anastomosis and in stapled procedures (51, 52). These early postoperative anastomotic strictures are easily dealt with by endoscopic dilatation, although multiple sessions may be necessary (53).

Hospital mortality. The review by Muller (1) confirmed that the average hospital mortality following resection in papers published between 1980 and 1988 was 13%. Many European centres have reported hospital mortalities well below this figure throughout the 1990's (54). Today, hospital mortality should not exceed 5% in high-volume referral centers.

The role of neoadjuvant therapy

There is no question that surgery remains the mainstay of treatment for patients with nonmetastatic esophageal carcinoma who are good operative candidates. However, the long term prognosis of these patients continues to be unsatisfactory even after a R0 resection. During the '80s and early '90s some randomised trials assessed preoperative radiotherapy compared with surgery alone, but none of these studies demonstrated a significant advantage for neoadjuvant radiation therapy (55). Preoperative treatment with chemotherapy or chemoradiotherapy has been proposed more recently with the aim to downstage the disease, treat micrometastases, and improve survival (56-57). As far as concerned preoperative chemotherapy, two recent randomised studies compared cisplatin and 5-fluorouracil with immediate surgery. In the RTOG (Radiation Therapy Oncology Study group) study, after a median follow-up time of 55 months, approximately 20% of patients in both arms remained alive (58). In contrast, in the MRC (Medical Research Council) study, a statistically significant survival advantage was seen for patients randomised to the preoperative chemotherapy arm (59). Interestingly, recent reports have suggested that changes in tumor metabolic activity as assessed by positron emission tomography and the glucose analog fluorodeoxyglucose allow reliable differentiation between responding and non-responding tumors already during the first cycle of preoperative chemotherapy (60). The combination of concurrent chemotherapy and radiotherapy followed by surgery has been studied in recent clinical trials. In these controlled trials, more than 20% of patients achieved a pathologic complete response, with 5-year survival in 25-35% of patients (61, 62). A distinct benefit of neoadjuvant therapy can be observed in patients with either locally advanced or resectable squamous-cell esophageal carcinoma who show a complete pathological response (63, 64). It is unknown at present whether conventional neoadjuvant therapy is able to eradicate foci of disseminated bone marrow tumor cells (65). The advent of promising antitumor drugs and targeted therapies is leading to a new generation of clinical trials combining these agents with conventional cytotoxic chemotherapy and radiation in an attempt to improve survival in esophageal cancer patients (66).

References

1. Müller JM, Erasmi H, Stelzner M, Zieren U, Pichlmaier H. Surgical therapy of oesophageal carcinoma. *Br J Surg* 1990; 77: 845-57.
2. Bonavina L. Early oesophageal cancer: results of a European multicentre survey. Group Europeen pour L'Etude des Maladies de L'Oesophage. *Br J Surg* 1995; 82: 98-101.
3. Hölscher AH, Bollschweiler E, Schneider PM, Siewert JR. Early adenocarcinoma in Barrett's oesophagus. *Br J Surg* 1997; 84: 1470-3.

4. Lerut T, DeLeyn P, Coosemans W, Van Raemdonck D, Scheys I, LeSaffre E. Surgical strategies in oesophageal carcinoma with emphasis on radical lymphadenectomy. *Ann Surg* 1994; 216: 583-90.
5. Bartels H, Stein HJ, Siewert JR. Preoperative risk analysis and postoperative mortality of oesophagectomy for resectable oesophageal cancer. *Br J Surg* 1998; 85: 840-4.
6. Bonavina L, Incarbone R, Saino G, Peracchia A. Esofagectomia per carcinoma:influenza dell'età sui risultati clinici e sulla sopravvivenza. *Chirurgia Italiana* 2002; 54: 587-90.
7. Begg C, Cramer L, Hoskins W, Brennan M. Impact of hospital volume on operative mortality for major cancer surgery. *JAMA* 1998; 280: 1747-51.
8. Patti M, Corvera C, Glasgow R, Way L. A hospital's annual rate of esophagectomy influences the operative mortality rate. *J Gastrointest Surg* 1998; 2: 186-92.
9. Ellis FH. Treatment of carcinoma of the esophagus or cardia. *Mayo Clin Proc* 1989; 64: 945-55.
10. Skinner DB, Little AG, Ferguson MK, Soriano A, Staszak VM. Selection of operation for esophageal cancer based on staging. *Ann Surg* 1986; 204: 391-401.
11. Sugimachi K, Watanabe M, Sadanaga N, et al. Recent advances in the diagnosis and surgical treatment of patients with carcinoma of the esophagus. *J Am Coll Surg* 1994; 178: 363-8.
12. Peracchia A, Bonavina L. Adenocarcinoma of the esophagogastric junction. Current concepts and management. EDRA, Milano, 2000
13. Clark G, Peters J, Ireland A, et al: Nodal metastasis and sites of recurrence after en bloc esophagectomy for adenocarcinoma. *Ann Thorac Surg* 1994; 58: 646-54.
14. Miller C.Carcinoma of the thoracic oesophagus and cardia; a review of 405 cases. *Br J Surg* 1962; 49: 507-10.
15. Giuli R, Sancho-Garnier H. Diagnostic, therapeutic and prognostic features of cancers of the esophagus: results of the international prospective study conducted by the OESO group. *Surgery* 1986; 5: 614-22.
16. Lam TC, Fok M, Cheng SW, Wong J. Anastomotic complications after esophagectomy for cancer. A comparison of neck and chest anastomoses. *J Thorac Cardiovasc Surg* 1992; 104: 395-400.
17. Sons HU, Borchard F. Cancer of the distal oesophagus and cardia. Incidence, tumourous infiltration and metastatic spread. *Ann Surg* 1986; 203: 188-95.
18. Alderson D, Courtney SP, Kennedy RH. Radical transhiatal oesophagectomy under direct vision. *Br J Surg* 1994; 81: 404-7.
19. Bonavina L, Ferrero S, Midolo V, Buffa R, Cesana B, Peracchia A. Lymph node micrometastases in patients with adenocarcinoma of the esophagogastric junction. *J Gastrointest Surg* 1999; 3: 468-76.
20. Skinner DB. En bloc resection for neoplasms of the esophagus and cardia. *J Thorac Cardiovasc Surg* 1983; 85: 59-71.
21. Akiyama H, Tsurumaru M, Udagawa H, Kajiyama Y. Radical lymph node dissection for cancer of the thoracic oesophagus. *Ann Surg* 1994; 220: 364-73.
22. Roder JD, Busch R, Stein JH, Fink Y, Siewert JR. Ratio of invaded to removed lymph nodes as a predictor of survival in squamous cell carcinoma of the oesophagus. *Br J Surg* 1994; 81: 410-3.
23. Siewert JR, Roder JD. Lymphadenectomy in oesophageal cancer surgery. *Dis Esoph* 1992; 2: 91-7.
24. Peracchia A, Bonavina L, Via A, Incarbone R. Current trends in the surgical treatment of esophageal and cardia adenocarcinoma. *J Exp Clin Cancer Res* 1999, 18: 289-94.
25. Kato H, Tachimori Y, Mizobuchi S, Igaki H, Ochiai A. Cervical, mediastinal and abdominal lymph node dissection for superficial carcinoma of the thoracic esophagus. *Cancer* 1993; 72: 2879-82.
26. Hölscher AH, Voite H, Buttermann G, Siewert JR. Function of the intrathoracic stomach as esophageal replacement. *World J Surg* 1988; 12: 835-44.
27. Bonavina L, Anselmino M, Ruol A, Bardini R, Borsato N, Peracchia A. Functional evaluation of the intrathoracic stomach as an oesophageal substitute. *Br J Surg* 1992; 79: 529-32.
28. Cheung HC, Cusiu KF, Wong J. Is pyloroplasty necessary in oesophageal replacement by stomach? A prospective randomised controlled trial. *Surgery* 1997; 102: 19-24.
29. DeMeester TR, Johansson KE, Franze I, et al. Indications, surgical technique and long-term functional results of colon interposition or bypass. *Ann Surg* 1988; 208: 460-74.
30. Bartels H, Thorban S, Siewert JR. Anterior versus posterior reconstruction after transhiatal oesophagectomy: a randomised controlled trial. *Br J Surg* 1993; 80: 1141-4.
31. Van Lanschott JJB, van Blankenstein M, Oeiss HY, Tilanus HW. Randomised comparison of prevertebral and retrosternal gastric tube reconstruction after resection of oesophageal carcinoma. *Br J Surg* 1999; 86: 102-8.
32. Fok M, Ah-Chong AK, Cheng SW, Wong J. Comparison of a single layer continuous hand-sewn method and circular stapling in 580 oesophageal anastomoses. *Br J Surg* 1991; 78: 342-5.
33. Valverde A, Hay JM, Fingerhut A, Elhadad A. Manual versus mechanical esophagogastric anastomosis after resection for carcinoma: a controlled trial. *Surgery* 1996; 120: 476-83.
34. Zieren HU, Müller JM, Pichlmaier H. Prospective randomized study of one- or two-layer anastomosis following oesophageal resection and cervical oesophagogastrostomy. *Br J Surg* 1993; 80: 608-11.
35. Orringer M, Marshall B, Iannettoni M. Eliminating the cervical esophagogastric anastomotic leak with a side-to-side stapled anastomosis. *J Thorac Cardiovasc Surg* 2000; 119: 277-88.
36. Kawahara K, Maekawa T, Okabayashi K, et al. Video-assisted thoracoscopic esophagectomy for esophageal cancer. *Surg Endosc* 1999; 13: 218-23.
37. Wakefield SE, Mansell NJ, Baigrie RJ, Dowling BL. Use of a feeding jejunostomy after oesophagogastric surgery. *Br J Surg* 1995; 82: 811-3.
38. Fan ST, Lau WY, Yip WC, Poon JP. Prediction of postoperative pulmonary complications in oesophagogastric cancer surgery. *Br J Surg* 1987; 74: 408-10.

39. Nagawa H, Kobori O, Muto T. Prediction of pulmonary complications after transthoracic oesophagectomy. *Br J Surg* 1994; 81: 860-2.
40. Watson A. Operable esophageal cancer: current results from the West. *World J Surg* 1994; 18: 361-7.
41. Vigneswaran WT, Trastek VF, Pairolero PC, et al. Transhiatal esophagectomy for carcinoma of the esophagus. *Ann Thorac Surg* 1993; 56: 838-46.
42. Sauvanet A, Baltar J, Le Mee J, Belghiti J. Diagnosis and conservative management of intrathoracic leakage after oesophagectomy. *Br J Surg* 1998; 85: 1446-9.
43. Paterson IM, Wong J. Anastomotic leakage: an avoidable complication of Lewis-Tanner oesophagectomy. *Br J Surg* 1989; 76: 127-9.
44. Bonavina L, Van Lanschot J. Complications in oesophageal and gastric surgery. *Dig Surg* 2002; 19: 86-7.
45. Dougenis D, Walker WS, Cameron EW, Walbaum PR. Management of chylothorax complicating extensive esophageal resection. *Surg Gynecol Obstet* 1992; 174: 501-6.
46. Orringer MB, Bluett M, Deeb GM. Aggressive treatment of chylothorax complicating transhiatal esophagectomy without thoracotomy. *Surgery* 1988; 104: 720-6.
47. Dugue L, Sauvanet A, Farges O, et al. Output of chyle as an indicator of treatment for chylothorax complicating oesophagectomy. *Br J Surg* 1998; 85: 1147-9.
48. Bolger C, Walsh TN, Tanner WA, Keeling P, Hennessy TP. Chylothorax after oesophagectomy. *Br J Surg* 1991; 78: 587-8.
49. Bonavina L, Saino G, Bona D, Abraham M, Peracchia A. Thoracoscopic management of chylothorax complicating esophagectomy. *J Laparoendosc Adv Surg Techn* 2001; 11: 367-9.
50. Griffin SM, Chung SC, Van Hasselt CA, Li AK. Late swallowing problems after oesophagectomy for cancer. Malignant infiltration of the recurrent laryngeal nerves and its management. *Surgery* 1992; 112: 533-5.
51. Orringer MB. Transhiatal oesophagectomy without thoracotomy for carcinoma of the thoracic esophagus. *Ann Surg* 1984; 200: 282-8.
52. Finley RJ, Inculet RI. The results of esophagogastrectomy without thoracotomy for adenocarcinoma of the esophagogastric junction. *Ann Surg* 1989; 210: 535-43.
53. Pierie JP, de Graaf PW, Poen H, van der Tweel I, Obertop H. Incidence and management of benign anastomotic stricture after cervical oesophagogastrostomy. *Br J Surg* 1993; 80: 471-4.
54. Peracchia A, Bonavina L, Ruol A, Stein H. Esophageal cancer: a European perspective. In: Esophageal carcinoma: state of the art. J Lange, J Siewert (Eds), Berlin, Springer Verlag, 2000; 119-22.
55. Arnott S, Duncan W, Gignoux M, et al. Preoperative radiotherapy in esophageal carcinoma: a meta-analysis using individual patient data. *Int J Radiat Oncol Biol Phys*, 1998.
56. Kelsen D. Multimodality therapy for adenocarcinoma of the esophagus. *Gastroenterol Clin North Am* 1997; 26: 635-45.
57. Ajani JA. Current status of new drugs and multidisciplinary approaches in patients with carcinoma of the esophagus. *Chest* 1998; 113: 112-9.
58. Kelsen D, Ginsberg R, Pajak T, et al. Chemotherapy followed by surgery compared with surgery alone for localized esophageal cancer. *N Engl J Med* 1998; 11: 1118-23.
59. Clark P. Surgical resection with or without preoperative chemotherapy on oesophageal cancer: an update by the UK Medical Research Council Upper GI tract cancer group. Proceedings ASCO 2001, 20: 126.
60. Weber W, Ott K, Becker K, et al. Prediction of response to preoperative chemotherapy in adenocarcinomas of the esophagogastric junction by metabolic imaging. *J Clin Oncol* 2001; 19: 3058-65.
61. Bosset J, Gignoux M, Triboulet J, et al. Chemoradiation thaerapy followed by surgery compared with surgery alone in squamous-cell cancer of the esophagus. *N Engl J Med* 1997; 337: 161-8.
62. Urba S, Orringer M, 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.
63. 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. *Ann Surg* 1997; 226: 714-24.
64. Ancona E, Ruol A, Santi S, et al. Only pathological complete response to neoadjuvant chemotherapy improves significantly the long term survival of patients with resectable esophageal squamous cell carcinoma. *Cancer* 2001; 91: 2165-74.
65. Bonavina L, Soligo D, Quirici N, et al. Bone marrow disseminated tumor cells in patients with carcinoma of the esophagus or cardia. *Surgery* 2001; 129: 15-22.
66. Geh J. The use of chemoradiotherapy in oesophageal cancer. *Eur J Cancer* 2002; 129: 15-22.

Correspondence: Prof. Luigi Bonavina
Istituto Policlinico San Donato
Via Morandi, 30
20097 San Donato Milanese (Milano)
Tel: +39-02-52774621
Fax: +39-02-52774622
E-mail: luigi.bonavina@unimi.it