Surgical and multimodal approaches to cancer of the oesophagus : state of the art

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Abstract

This review article aims to discuss the modalities of oesophageal resection, to define the categories of patients who are most likely to benefit from oesophagectomy with extensive lymph node clearance, and to analyse the eventual contribution of nonsurgical neo-adjuvant or adjuvant therapies to improving long-term survival rates achieved by surgery alone.

Both the review of the literature devoted to potentially curative treatment of oesophageal cancer and the authors' own experience indicate that resection of the oesophageal tube en bloc with the locoregional lymph nodes provides patients with the best chance of long-term survival and cure. This is true, even though some of the resected lymph nodes are metastatic. Most phase III comparative studies fail to shown any overall survival improvement following multimodal therapy in comparison with surgery alone, so that there is now no scientific reason for systematic addition of radio- and/or chemotherapy to extensive surgery in potentially resectable neoplastic processes. However, neo-adjuvant radio- and/or chemotherapy is indicated in suspected non-resectable T4 tumors for downstaging and subsequent oesophageal resection in good responders. The benefit in terms of long-term survival and cure that can be expected from adjuvant chemo- and/or radiotherapy after radical resection of a neoplastic process having already spread into a large number of loco-regional lymph node requires objective evaluation by prospective, randomized studies. (Acta gastroenterol. belg., **1999**, 62, **272-282**).

Introduction

Oesophagectomy is the most common therapeutic modality for cancer of the oesophagus. The three aims of any oesophageal resection for cancer are to restore a free passage through the upper digestive tract, to provide patients with long-term survival and cure, and to provide survivors with a good quality of life.

Since the first successful oesophagectomy by Franz Torek (1) in 1913, numerous technical progresses were accomplished in both oesophageal resection and replacement through the impetus given by various surgeons, notably Kirschner (2), Ohsawa (3), Grey-Turner (4), Marshall (5), Adams (6), Lortat-Jacob (7), Sweet (8), Lewis (9), Gavriliu (10), Ong (11), Logan (12), Belsey (13), McKeown (14) and Akiyama (15). Parallel to these extraordinary technical advances, progresses in anesthesiology and intensive care made complex surgical operations possible and safe, as attested to by the dramatic decrease in postoperative mortality that was observed after oesophagectomy over the last 20 years (12,16-22). However, if most patients can be relieved from their obstructive symptoms after operation, meta-analysis of the surgical literature (18) indicates that the percentage of patients who can expect long-term survival and cure remains rather small, not exceeding 20% at 5 years in most series. Possible strategies for improving long-term survival include increasing the radicality of the resection by extensive lymphadenectomy, and the addition of a non-surgical therapy such as chemo- and/or radiotherapy to surgery.

Modalities and constraints of oesophagectomy for cancer

Tumor location

Tumors arising in the oesophageal tube are removed by subtotal oesophagectomy. Subtotal oesophagectomy usually consists of removal of the lower cervical, thoracic and abdominal segments of the oesophagus, so that the oesophageal substitute is anastomosed to the cervical oesophagus stump (14,15,23-26). Removal of the abdominal segment of the oesophagus with the nine-tenths of its thoracic segment is also called subtotal oesophagectomy (20,21,27-30). In this case, the oesophageal anastomosis is made at the apex of the chest. The use of the latter modality is restricted to lower two-third tumors. Subtotal oesophagectomy can be carried out by right thoracotomy, through the hiatus without thoracotomy (31-33), or by right thoracoscopy (34,35).

Tumors arising in the distal oesophagus and extending over the cardia are usually removed by distal oesophagectomy. Distal oesophagectomy (12,36-39) includes removal of the lower half or lower third of the thoracic segment of the oesophagus in continuity with its abdominal segment. It is combined with either proximal or total gastrectomy. The anastomosis is performed in the chest between the remaining half or two-thirds of the thoracic oesophagus and the oesophageal substitute. The procedure is usually carried out by left thoraco-phreno-laparotomy (39). According to some surgeons (24), however, oesophagectomy for cancer arising in the cardia should be extended up to the cervical esophagus.

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Neoplastic spread

Intramural spread proceeds by either neoplastic emboli through the lymphatic vessels or submucosal extension of the neoplastic process in continuity with the mucosal lesion. Lymphatic vessels in the different layers of the oesophageal wall follow an ascending or a descending course, so as to drain into paraoesophageal lymph nodes located either more proximally or more distally than the primary (40-42). Potentially involved lymph nodes belong to one of 6 categories (15): cervical, superior mediastinal, middle mediastinal, lower mediastinal, superior gastric, and celiac axis lymph nodes. Data from both autopsy specimens (43) and resected squamous cell carcinomas (42-45) show that lymph nodes located far away from the primary tumor may be invaded by the neoplastic process while those located in its immediate vicinity are cancer-free (jumping metastases), so that any nodal group is liable to be involved by the neoplastic process, irrespective of the location of the primary tumor in the oesophageal tube. The risk of neoplastic invasion inversely correlates with the distance between the primary tumor and the nodal group concerned (19). Invasion rate of lymph nodes along the lesser curvature of the stomach (19) gradually drops from the uppermost (first) to the fourth branch of the left gastric artery, decreasing from 25.1% (first branch) to 14.1% (second branch), 8.5% (third branch), and 6% (fourth branch). Metastatic lymph nodes are never evidenced along the fifth branch. In practice, the portion of the lesser omentum including those four upper branches of the left gastric artery must be removed en-bloc with the oesophageal tube as far as radical upper abdominal lymph node dissection is concerned. This observation is of utmost importance with respect to modalities of gastric tailoring when digestive continuity after subtotal oesophagectomy is restored with the stomach. It directs, indeed, the length of the lesser curvature to be either denuded or resected (46-49).

Adenocarcinomas of the lower oesophagus and cardia spread downward into paragastric nodes as well as upward into paraoesophageal nodes and their subsequent connections, as was shown by both postmortem studies (50-51) and postoperative examinations of resected specimens (52-55). The potential for neoplastic recurrence in cervical nodes from an adenocarcinoma arising in Barrett's oesophagus has been emphasized by Altorki and Skinner (56). Adenocarcinomas of the cardia and lower oesophagus tend to spread upward through the submucosal layer of the oesophageal tube. Submucosal spread may be either continuous with the primary tumor or present as an isolated island located at a rather long distance from the cardia (57). In this respect, intraoperative frozen section of the surgical margin is far from fully reliable to direct the choice of the intrathoracic anastomosis level, owing to the risk of false negative pathologic examination (58).

Oesophagectomy according to lymph node dissection

Oesophagectomy is called standard when it consists of the removal of the oesophageal tube with some of the immediate adjacent lymph nodes for sampling. This is probably the most common type of oesophagectomy that is performed in the World.

The oesophageal tube can also be removed with the lymph nodes that are liable to be involved by the neoplastic process. Some surgeons remove each nodal group in an isolated fashion in view of mapping the dissected areas (19). For other surgeons, para-oesophageal dissection is carried out "en-bloc" as far from the oesophageal wall as possible (12,24,59-61), i.e. close to the vital structures in the posterior mediastinum. It results from such a dissection a real skeletonization of those vital structures, so that all the potentially involved lymph nodes as well as soft tissues in the vicinity of the oesophageal wall are removed en-bloc with the oesophageal tube. The basic principle of surgical technique is that mediastinal dissection is carried out through non-involved soft tissues in an attempt to surround those neoplastic processes that have spread at the most into but not beyond the resectable locoregional lymph nodes.

"En-bloc" esophagectomies can be classified into subcategories according to the number of anatomic fields cleared of lymph nodes (44,62-64). The term "two-field" dissection addresses subtotal esophagectomies with lymph node clearance throughout the abdominal and thoracic fields while the term "three-field" dissection addresses subtotal esophagectomies combined with lymph node clearance in the neck, chest, and upper abdomen.

The thoracic field varies according to the extent of the thoracic lymphadenectomy (62):

- standard lymphadenectomy: the sole paraoesophageal, paraaortic, subcarinal, and right and left parabronchial lymph nodes are removed.
- extended lymphadenectomy: it includes standard lymphadenectomy plus removal of the right apical, and right paratracheal nodes as well as those along the right recurrent laryngeal nerve.
- total lymphadenectomy: it includes the extended lymphadenectomy plus removal of the left paratracheal nodes as well as those along the left recurrent laryngeal nerve.

In any case, the existence of so many types of oesophageal resections obviously makes comparison of the results published in the surgical literature difficult.

Relevance of oesophagectomy for cancer

Setting

According to Logan (12), it is possible to take either of two views concerning cancer surgery: *"that cure is possible only when the tumor remains confined to the*

Table 1. — **Outcome of patients admitted for surgical treatment of an oesophageal cancer**

Author	Year	Patients admitted to the surgical unit	Patients not operated on	Patients explored	Patients operated on with a palliative intent	Patients operated on with a curative intent
Fok (66)	1994	n = 1,158	23.5 %	1.2 %	50 %	25.4 %
Aklyama (65)	1994	n = 1,298	11.2 %	2.8 %	30.8 %	55.2 %
Collard (59)	1995	n = 181	12.1 %	1.1 %	30.5 %	56.3 %

structure in which it takes origin or that cure may still be possible when the tumor has directly extended to the immediate adjacent tissues or has spread to closely related lymph glands". Advocates of the first option like M. Orringer (32) remove the oesophageal tube in order to restore a free passage for feeding and to reduce the tumor mass, the neoplastic disease being treated by adjuvant radio-chemotherapy. Proponents of the second option like D. Skinner (60) and H. Akiyama (65), in contrast, perform radical esophagectomies including extensive resection of the potentially involved loco-regional lymph nodes in view of curing patients with locally advanced neoplastic disease. We have to bear in mind, however, that such a radical operation addresses a selected group of patients only (24,63,65-68) (table 1). Comparison of the two attitudes is difficult owing to the lack of accurate staging of the neoplastic process after resection limited to the oesophageal tube. There is no study having compared survival rates achieved by resection of the oesophagus "en-bloc" with all the lymph nodes from the apex of the chest down to the hiatus to those obtained by simple removal of the oesophageal tube. Studies comparing transthoracic oesophagectomy with limited lymph node dissection to transhiatal oesophagectomy without lymph node dissection fail to demonstrate any significant difference in terms of survival (69-72) (table 2).

Table 2. — **Prospective studies comparing survival after transhiatal oesophagectomy without lymph node dissection (TH) to that after transthoracic oesophagectomy with standard lymph node clearance in the chest and upper abdomen (TT)**

Author	Approach (n)	Survival rate (follow-up)
Goldfaden (69)	TH (n = 29)	13 % (5 years)
	TT (n = 43)	10 %
Goldminc (70)	TH (n = 32)	30 % (3 years)
	TT (n = 35)	18 %
Hankins (71)	TH (n = 26)	9 % (4 years)
	TT (n = 52)	8 %
Putnam (72)	TH (n = 42)	16 % (5 years)
	TT (n = 134)	18 %

Radical two-field dissection

Several surgical teams have reported substantial 5-year survival rates after radical two-held dissection in patients having some of the loco-regional lymph nodes involved (table 3).

The recent study of 213 consecutive esophagectomies including extended two-field lymphadenectomy performed at the University of Louvain Academic Hospital (80) indicates that meticulous resection of the paraoesophageal soft tissues en — bloc with the oesophageal tube (Ro resection) can provide 48% of the patients with 5-year survival. The survival rate is 70% when the tumor is still confined to the oesophageal tube (Tis, T_1, T_2, T_3 N_0) versus 31% when some of the loco-regional lymph nodes are involved by the neoplastic process (fig. 1). In contrast, none of the 93 patients who underwent incomplete resection of the neoplastic process (R_1, R_2 resection) during the same period was cured in spite of the fact that adjuvant radio- and/or chemotherapy was given to some of them (overall 5-year survival of the 306 patients including hospital mortality : 34%). Interestingly, survival curve after Ro resection of a neoplastic proces still confined to the oesophageal wall takes a linear shape, so that the death rate (percentage of patients who die per month) is 0.5% on average. In contrast, the survival curve of the neoplastic processes that are resectable in totality, although having already spread beyond the oesophageal wall, exhibits a bi-phasic pattern ; i.e. a rapid initial

Table 3. — **5-year survival rate after more or less extensive thoraco-abdominal (two-field) lymph node dissection : data from specialized centres**

Author	Year	Number of patients	Overall survival rate	Survival rate of No patients	Survival rate of N+ patients
Akiyama (19)	1981	52	34.6%	53.8%	15.3%
Isono (73)	1991	2,799	26.7%	45%	29%
Kato (74)	1991	73	33.7%	—	—
Akiyama (65)	1994	393	38.3%	55%	27.9%
Peracchia (67)	1990	240	20.8%	35%	7%
Watson (75)	1994	156	23%	47.4%	10.5%
Huang (75)	1990	349	30.6%	44.9%	12.8%
Altorki (77)	1990	111	—	T_1, T_2N_0 55% T_3 N_0 15%	T_1, T_2, ≤ 4 nodes : 29% any T, > 4 nodes : 8%
Roder (73)	1994	116	31%	—	—
Isono (79)	1990	333	17.2%	—	—

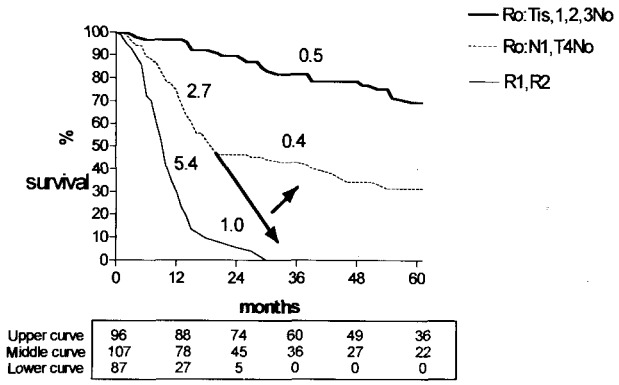

Fig. 1. — KAPLAN-MEIER's survival curves and death rates in neoplastic processes remaining confined to the oesophageal wall (upper curve), those which are resectable in totality although having already breached the oesophageal wall (middle curve), and those which are not resectable in totality (lower curve). The long arrow figurates the drop in survival that would be expected if positive loco-regional lymph nodes would have been left in place. The short arrow indicates the gain in survival that can reasonably be ascribed to resection the potentially invaded loco-regional lymph nodes. The numbers of subjects at risk at each interval are shown in the bottom box.

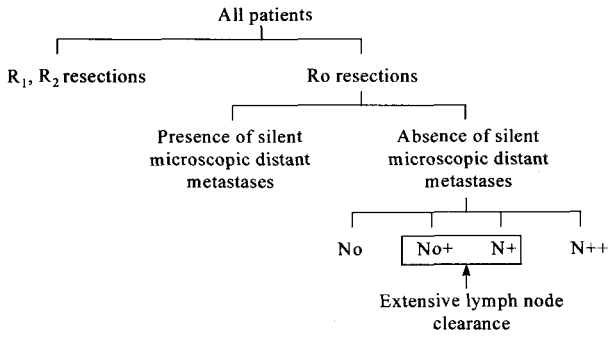

Fig. 2. — Diagram showing subgroups of patients who are liable to benefit from oesophagectomy with extensive lymph node dissection,i.e. those having no silent distant micrometastases and a few of the loco-regional lymph nodes involved (No : really cancer-free lymph nodes ; No^+ : false - negative pathologic examination ; N^+ : small number of metastatic lymph nodes ; N^{++} : large number of metastatic lymph nodes) (Ro resection : micro- and macroscopically complete resection ; R1 resection : microscopically incomplete resection ; R2 resection : macroscopically incomplete resection).

drop at the rate of 2.7% deaths per month until 20 months postoperatively and a smoother descent at the rate of 0.4% deaths per month, afterwards. The brake in the death rate of patients operated on for a neoplastic process which, although resectable, has already spread into loco-regional lymph nodes illustrates the actual benefit one can draw from performing en-bloc oesophagectomy with extensive lymph node dissection in comparison with non-radical surgery which leaves invaded loco-regional lymph nodes in place. In the latter situation, indeed, local recurrence or dissemination of the neoplastic disease from the residual metastatic lymph nodes is unavoidable. It thus appears that the first merit of extensive surgery is to classify patients into two distinct categories, i.e. those who have a chance of cure (complete resection) and those who have not (incomplete resection). The second merit is to provide some of those patients operated on for a locally advanced neoplastic process with long-term survival and cure. As a consequence, both completeness of the resection and lymph node involvement are key-parameters allowing the surgeon to give the patient and his relatives objective information on the long-term outcome of the neoplastic disease just after operation. However, there are only two categories of patients who are liable to benefit from extensive lymph node clearance (fig. 2), i.e. those having a small number of lymph nodes involved (N^+) and those with so-called normal lymph nodes at routine (single section) histologic examination but having some neoplastic cells in some of them that can only be disclosed by thorough (serial sections) examination (N_o^+) On the contrary, those patients having concomitant microscopic metastases into distant organs, a large number of lymph nodes involved (N^{++}) or, rather, really cancer-free lymph nodes (N_o) are good candidates for a more limited surgical procedure like conventional transhiatal oesophagectomy without any lymph node dissection (32). This viewpoint is supported by recent data from a series of 42 Barrett's adenocarcinomas that were resected with a curative intent by one of the authors over an 11-year period (81). Five-year survival rate reached 59.3% for the whole series, 73.1% for patients classified No, and 42.1% for those having positive lymph nodes. In the latter group, five-year survival rate closely depended on the number of positive lymph nodes found in the resected specimen, being 61.5% when there were at the most 5 lymph nodes involved whereas all patients with > 5 positive nodes died within the 20-month period that followed radical surgery. The fact that 5-year survival rate in those patients classified No was not significantly different from that of those having ≤ 5 lymph nodes involved undoubtedly proves that loco-regional extraoesophageal neoplastic spread does not preclude long-term survival and cure after radical surgery. Different authors have reported similar data that attest to the influence of the number of metastatic lymph nodes on survival. For instance, 5-year survival rate in IDE's series (82) was 60.3% in the presence of a single metastatic node, 32.3% in the presence of 2 to 5 positive nodes, and 8.8% only when ≥ 6 lymph nodes were invaded. For Akiyama (65), 5-year survival rate decreased from 51.6% to 9.6% depending on whether fewer or more than 8 lymph nodes were involved. The discriminant number of positive lymph nodes in the resected specimen is one for Bardini (83) and Abe (84) while it is four for Demeester (24), Skinner (61) and Huang (76). After Siewert (85), involvement of > 7 lymph nodes means that death will

occur at the latest 16 months after operation. The latter author emphasizes the importance of the ratio of the number of lymph nodes resected to the number of those which are invaded, according to whether it is superior or inferior to 20%. Likewise, in Huang's series (76), 5-year survival rate drops from 19.8% to 4.3% according to whether this ratio is lower or higher than 50%. In Demeester's series (24), which is exclusively composed of adenocarcinomas, patients without any evidence of neoplastic recurrence beyond 3 years of follow-up have less than 5% of the lymph nodes invaded by the neoplastic process whereas this percentage is 16.5% in those having experienced neoplastic recurrence in the mean time. In Lerut's series (86), 5-year survival rate is 90% for stage I tumors, 56% for those in stage II, and 16% for those in stage III.

Radical three-field dissection

Systematic addition of a radical lymph node clearance in the neck to extended dissection in the posterior mediastinum and upper abdomen lies on 3 kinds of arguments :

1. Pathologic data from Akiyama's team (65) have clearly demonstrated the potential for squamous cell carcinomas of the thoracic oesophagus to spread into cervical lymph nodes irrespective of the location of the primary in the oesophageal tube.
2. Several Japanese authors (45,65,82) reported a relatively high recurrence rate in the neck after 2-field dissection ranging from 23% to 46%.
3. Data from several Japanese surgical teams have suggested some survival improvement after 3-field dissection in comparison with lymph node dissection limited to the chest and upper abdomen (table 4). So, in the nationwide study conducted by Isono (73) including 4,590 patients, overall 5-year survival rate increased from 26.7% after thoraco-abdominal lymph node clearance to 34.3% after 3-field dissection. Those respective percentages are 37.5% vs 53.3% for Akiyama (65), 17.2% v.s. 29.4% in Isono's own series (79), 33.7% v.s. 48.7% for Kato (74), and they are 58% v.s. 65% at 4 years for Ide (82). The benefit from the addition of cervical lymph node clearance is significant not only for those patients having positive lymph nodes in the resected specimen but also for those with negative nodes. After Akiyama (65) for instance, five-year survival rate increases from 55% to 83.9% in No patients and from 27.9% to 43.1% in N+ patients. This is due to the fact that patients classified No after 2-field dissection but having in fact, metastatic lymph nodes in the neck, move from one category to the other after 3-field dissection. Another point is that 3-field dissection in those series comprised not only bilateral cervical dissection but also more extensive dissection at the apex of the chest than that usually performed with the 2-field dissection technique.

In spite of this, most Western oesophageal surgeons are still reluctant to consider esophagectomy with 3-field dissection as a routine surgical technique. Main reasons for this are :

1. The access to the thoracic inlet and upper mediastinum is more difficult in Caucasian than in Asian patients for anatomic reasons (88).
2. The longer duration of the operative procedure and the need for two concomittant working teams.
3. The discrepancy between different Japanese series concerning the real benefit in terms of survival one can expect from adding cervical dissection, once positive lymph nodes are present in each of the 3 fields. So, even though 5-year survival rate is still 20.8% in such a situation for Ide (83), none of the patients from Isono's own series (79) lived more than 5-years after removal of positive lymph nodes in the 3 fields.
4. The higher risk of postoperative death which was reported after 3-field dissection by some authors such as Akiyama (65) and Ide (82). Actually, the risk ranges from 2.3% to 10.4% (65,73,82,89), and it is even lower than after 2-field dissection for Isono (73) and Kato (74).
5. The postoperative morbidity related to sharp dissection of both inferior laryngeal nerves enhances the need for temporary tracheostomy (73,82).

Nevertheless, three-field dissection has been introduced in Western Countries (56,89,90). According to Siewert (85), such an operative procedure should be applied at least, to carcinomas located in the upper half of the oesophageal tube which drain preferably

Table 4. — **5-year survival rate after colo-thoraco-abdominal (three-field) lymphadenectomy : data from specialized centres**

Author	Year	Number of patients	Overall survival rate	Survival rate of N⁻ patients	Survival rate of N+ patients
Isono (73)	(1991)	1,791	34.3%	57%	33%
Aklyama (55)	(1994)	324	55%	83.9%	43.1%
Kato (74)	(1991)	77	48.7%	—	—
Peracchia (89)	(1994)	54	42% (3 years)	57% (3 years)	23% (3 years)
Ide (82)	(1990)	54	65% (4 years)	—	—
Isono (79)	(1992)	146	31.4%	48.9%	23%
Baba (87)	(1994)	106	30.8%	56%	1 node : 54.5% 2 → 5 nodes : 17.3% ≥ 6 nodes : 7.2%

into lymphatics running in the upper mediastinum towards the neck. In any case, assessment of the potential superiority of the 3-field over the 2-field dissection technique requires a prospective randomized study conducted by experienced Western oesophageal surgeons.

Causes of death

To be alive 5 years after radical oesophageal resection for cancer does not preclude neoplastic recurrence in the very long term. Indeed, survival rate in Huang's series (76) dropped from 29.6% at 5 years to 22.5% at 10 years, to 19.7% at 15 years, and to 11% at 20 years. The cause of death was a neoplastic recurrence in 40% of the patients who died beyond 5 years and 24.2% in those beyond 10 years. Similar data were reported by other authors (91,92). Detection of recurrent neoplastic disease is usually based on CT-scan made at regular intervals. It has been shown recently (93,94) that regular measurement of the carcinoembryonic antigen blood level may detect subclinical recurrence, so as to make salvage therapy more efffficient. On the other hand, other conditions than neoplastic recurrence may account for the death of some patients prior to the classic term of 5 years. For instance, 13.6% of one of the authors own patients (59) who did not live 5 years following radical surgery died of unrelated conditions such as myocardial infarction, liver cirrhosis, pulmonary embolism, breast cancer, mesenteric infarction, or endoscopy-related aspiration. None of them presented with any sign of neoplastic recurrence at the time of their death. Likewise, 10% of the patients operated on by Baba (87) died of extra-oesophageal cancers, among which three arose in the gastric transplant used for oesophageal replacement.

Neo-adjuvant and adjuvant therapies

Numerous prospective, randomized studies (95-112) have been conducted regarding the potential benefits of neo-adjuvant or adjuvant chemo- and/or radiotherapy in an attempt to increase both the resectability rate of oesophageal cancer and the long-term survival after oesophagectomy (table 5).

Correct interpretation of those studies requires however, the following considerations :

1. The relatively high postoperative mortality rate in some studies, especially those conducted in the late seventies and the early eighties (95,96) biases the results in terms of survival.
2. While some studies compare histologically homogeneous groups, other studies contain both squamous cell and adenocarcinoma patients.
3. Randomization concerns either all the patients whose oesophagus can be resected (i.e. with a curative or a palliative intent) or only patients who undergo oesophageal resection with a curative intent.
4. Oesophagectomy in most comparative studies consists of a resection of the oesophageal tube either with a standard lymphadenectomy or without any lymph node clearance, which are both palliative surgical procedures unless the neoplastic process is still confined to the oesophageal wall or has exclusively spread into the few nodal groups that are taken with the specimen. This is probably the reason why survival rate is astonishingly low in some studies (97,103,106).

Resectability

According to data from the prospective, randomized studies taken as a whole, i.e. combining all tumor stages, neo-adjuvant radioand/or chemotherapy fail to increase significantly the resectability rate of oesophageal cancers (table 5). This is true despite the usually high rate of tumor shrinkage (i.e. from 25% to 61%) and the homogeneity of the randomized groups with respect to pretherapeutic clinical stage distribution. Nevertheless, a higher rate of curative resection after preoperative radiochemotherapy is reported by some authors among whom Bosset (107) and Nygaard (97). Moreover, non-randomized studies conducted on patients having a huge oesophageal tumor considered unresectable at preoperative CT-scan show that preoperative chemo- or radiochemotherapy can reduce the tumor mass, so as to bring responders to resective surgery and to provide some of them with a good quality long-term survival (113-115). Preoperative administration of radiotherapy (100) or radiochemotherapy (106,107) can also reduce the percentage of patients with metastatic lymph nodes in the resected specimen.

Survival

Phase 3 studies show that addition of radio- and/or chemotherapy to surgery does not significantly improve survival rates achieved by surgery alone. This is indeed the case in 17 comparative studies. However, two other studies by Walsh (106) (surgery v.s. radiochemotherapy + surgery) and by Huang (100) (surgery v.s. radiotherapy + surgery) show a higher survival rate in the group of patients treated by combined therapy. In Fok's study (110), in contrast, postoperative radiotherapy significantly impairs long-term survival due to severe irradiation-related complications and earlier appearance of metastatic disease than after surgery alone. In Nygaard's study (97) comparing three therapeutic regimens to surgery alone, 3-year survival rate is significantly better in a group combining patients receiving neo-adjuvant radiotherapy and chemotherapy and patients treated by preoperative radiotherapy without chemotherapy, while there is no significant difference between the randomized groups taken two by two.

The O.E.S.O. study (99) emphasizes the role played by the dose of radiations and chemical agents administered on survival. Indeed, while no patient receiving

Table 5. — **Prospective, randomized trials comparing surgery alone to (from top to bottom) surgery + preoperative radiotherapy, surgery + pre- or perioperative chemotherapy, surgery + preoperative radio-chemotherapy, surgery + postoperative radiotherapy, and surgery + postoperative chemotherapy. Data from literature**

Author	Neoadjuvant or adjuvant therapy	Median survival in months		Survival in % (follow-up in years)		Survival p	Resectability rate in %		Postop. mortality in %		Postop. morbidity in %		response rate in %
		S	CT	S	CT		S	CT	S	CT	S	CT	
Gignoux (95)	preop. 33 GY	—	—	10	9 (5 y.)	> 0.05	82	74	20	25	—	—	—
Launois (96)	preop. 39-45 GY	—	—	11	9 (5 y.)	> 0.05	67	75	21	27	equal		—
Nygaard (97)	preop. 35 GY	8	11	9	21 (3 y.)	0.08	69	54	13	11	34	33	—
Wang (98)	preop. 40 GY	—	—	37	33 (5 y.)	> 0.05	83	90	4	3	—	—	—
Huang (100)	preop. 40 GY	—	—	25	45 (5 y.)	—	90	92	4	4	—	—	—
Schlag (101)	preop. 5-FU, C.P.	10	10	—	—	> 0.05	79	70	10	19	26	40	50
Fok (102)	preop. 5-FU, C.P.	12	14	—	—	0.4	92	82	4	4	—	—	43 (7*)
Nygaard (97)	preop. C.P., Bleo	8	8	9	3 (3 y.)	> 0.05	69	58	13	15	34	34	—
Giuli (99)	preop. + postop. ; C.P., Bleo., Vind.	—	—	16	27 (4 y.)	0.15	—	—	7	12	—	—	61 (28*)
Roth (103)	preop. + postop., C.P., Vind., Bleo.	9	9	5	25 (3 y.)	0.34	equal		—	—	47	29	47
Kok (104)	preop. C.P., Etop.	12	15	—	—	> 0.05	—	—	—	—	—	—	30
Kelsen (105)	preop. 5 FU, C.P. □	16	15	26	23 (3 y.)	0.74	89	76	6	6	—	—	19 (2*)
Walsh (106)	preop. C.P., 5 FU + 40 GY	11	16	6	32 (3 y.)	0.01	—	—	1.5	7	equal		25*
Bosset (107)	preop. C.P. + 37 GY	18	18	—	—	0.78	—	—	4	12	26	32	44 (26*)
Urba (108)	preop. C.P., 5 FU, Vinbl. + 45 GY	18	17	36	41 (2 y.)	0.37	—	—	—	—	—	—	28*
Leprise (109)	preop. C.P., 5FU + 20 GY	—	—	14	19 (3 y.)	> 0.05	—	—	7	8.5	44	48	58 (10*)
Nygaard (97)	preop. C.P., Bleo + 35 GY	8	9	9	17 (3 y.)	0.3	69	66	13	23	34	47	—
Fok (110)	postop. 49-52 GY	15	9	—	—	0.02	—	—	—	—	—	—	—
Teniere (111)	postop. 45-55 GY	18	18	—	—	> 0.05	—	—	—	—	—	—	—
Giuli (99)	postop. 45 GY	—	—	16	0[Δ] (4 y.)	0.14	—	—	—	—	—	—	—
Ando (112)	postop. C.P., Vind.	—	—	42	45 (5 y.)	0.52	—	—	—	—	—	—	—

S = surgery ; CT = combined therapy ; 5-FU = 5-Fluorouracil ; CP = Cisplatin ; Bleo. = Bleomycin ; Vind. = Vindesine ; ETOP = Etoposide ; Vinbl. = Vinblastine ; * = complete histologic response rate ; [Δ] = 27% if higher dosages. □ : postop. 5 FU ; C.P. in preop. responders.

the proposed radiotherapy regimen of 45 Gy was living at 4 years postoperatively, 4-year survival rate was 27% in the group of patients who received higher doses and a greater number of sessions. Likewise, 4-year survival rate was 40% in the group of patients who could receive full dosage chemotherapy and curative surgery whereas all the patients in whom chemotherapy was discontinued did not live more than 4 years postoperatively.

As shown by three studies (101-103), preoperative chemo- or radio-chemotherapy significantly increase survival rate of patients whose primary tumor is responsive to neo-adjuvant therapy. As a consequence, administration of chemo- or radiochemotherapy prior to surgery allows selection of the patients who have a good chance of long-term survival after oesophageal resection. However, complete histologic response to neo-adjuvant chemo and/or radiotherapy (from 7% to 28% of the cases) does not equate with cure. Sooner or later, indeed, a substantial percentage of these excellent responders will experience either local recurrence or dissemination of the neoplastic disease into distant organs (99,109). The rate of complete histologic response at final examination of the resected specimen correlates with the dose of chemical agents administered. In the O.E.S.O. study (99) for instance, a complete histologic response was recorded in 38% of the patients receiving full dosage chemotherapy while this was the case in only 14% of those who did not receive the full dose. On the other hand, the fact that neoplastic cells can still be found at final histologic examination of resected specimens (108) from patients in whom complete endoscopic response has been documented legitimates subsequent oesophageal resection.

Neoplastic recurrence

The trial by Bosset (107) (i.e. surgery v.s. preoperative radiochemotherapy + surgery) indicates that neo-adjuvant radiochemotherapy results in a longer disease-free survival, a longer interval free of local disease, and a lower rate of cancer-related deaths, all this, however, at the expence of a significantly higher postoperative mortality rate. In Leprise's study (109) (i.e. surgery v.s. preoperative radiochemotherapy + surgery), in contrast, the disease-free interval was not statistically different between the two groups, which could be ascribed to low-dosage preoperative irradiation (i.e. 20 GY). Likewise, the time to recurrence in Urba's study (108) (i.e. neo-adjuvant radiochemotherapy + surgery v.s. surgery) is similar in both arms. Some studies (95,110) also indicate that local neoplastic recurrence occurs less often after combined therapy than after surgery alone whereas distant metastases are more common with the former than with the latter therapeutic modality.

Toxicity

The main drawback of most neo-adjuvant chemo- or radiochemotherapy regimens is the fact that they carry a rather high risk of toxic complications (113) which may lead to reduction of either the dose of medications or the number of therapeutic courses (105) (e.g. 30% of the patients included in the O.E.S.O. study (99)). In the same way, although the difference is not always statistically significant, postoperative in-hospital mortality in the combined therapy group is most of the time (9 studies among 14) superior to that recorded after surgery alone (table 5). In addition, histologic changes in the posterior mediastinum secondary to neo-adjuvant therapy can modify surgical landmarks and make intraoperative dissection difficult and hazardous.

We have also to bear in mind that neo-adjuvant therapy is liable to impair both the quality and duration of palliation in non-responders. The reasons for this are the adverse effects of the preoperative treatment and the persistence of obstructive oesophageal symptoms for the numerous weeks that preceed surgery. In addition, some patients may experience progression of their neoplastic disease in the mean time, so as to get more disabling complaints or even to be excluded from resective surgery (e.g. up to 20% of patients not operated on in Nygaard's study (97) and 24% in Kelsen's study (105)). Such a poor outcome obviously counter-balances the positive effects of neo-adjuvant therapy in good responders in such a way that the overall benefit that can be drawn by all oesophageal cancer patients included in a given clinical trial is far from evident. This is all the more so since the magnitude of response to neo-adjuvant therapy in a given subject cannot at present, be predicted before treatment. In this respect however, in vitro chemosensitivity testing (117) and examination of the expression of BCL-2 protein and metallothionein (118) from pretreatment endoscopic biopsy specimens are promising.

Conclusions and perspectives

The review of the literature devoted to the surgical management of oesophageal cancers indicates that :

1. Extensive oesophageal resection en-bloc with all the potentially invaded locoregional lymph nodes performed by experienced surgeons can provide a substantial percentage of patients with long-term survival and cure, provided fewer than 5 lymph nodes are metastatic.
2. There is no scientific reason for systematic addition of radio- and/or chemotherapy to surgery in patients having a potentially resectable cancer of the oesophagus.
3. Neo-adjuvant radio- and/or chemotherapy is indicated in huge upper-third tumors that are suspected to invade immediate adjacent mediastinal structures.
4. The potential benefit that can be expected from adjuvant radio- and/or chemotherapy after radical resection of a neoplastic process that has already spread into a large number of loco-regional lymph

nodes requires objective evaluation by prospective, randomized studies.

All this is confirmed by the conclusions of the consensus conference organized by the International Society for Diseases of the Esophagus (I.S.D.E.) in 1995 (119). It appears, indeed, that :

1. *"Resective surgery remains the mainstay of treatment".*
2. *"In patients with a potentially resectable tumor, all forms of combined modality therapy have to be compared to surgical resection alone".*
3. *"In patients with a locally advanced tumor, surgical resection alone gives dismal results ; therefore, first line chemoradiotherapy is suggested in dedicated centres* (120)*".*
4. *"It is generally admitted that, when irradiation is given with a curative intent, it should be combined with chemotherapy* (121a,121b). *The best regimen remains controversial".*

In any case, the inability of radio- and/or chemotherapy to significantly improve long-term survival after radical oesophageal resection for cancer underlines the need for new therapeutic modalities. In this respect, postoperative vaccination based on the MAGE-system is currently experimented in specialized centres (122, 123). On the other hand, the use of the Positron Emission Tomography scan (P.E.T.-scan) in routine clinical practice (124,125) should allow more accurate preoperative staging and better patients' selection for esophagectomy with radical lymph node dissection.

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