Esophagus cancer

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Introduction

Esophagus cancer affects 5200 people in France each year and is the third most frequent digestive cancer, behind colorectal cancer and gastric cancer. It affects especially men (sex ratio = 12) for whom it is the fourth cause of mortality from cancer, after lung, colorectal, and prostate cancers.

The majority of esophagus cancers are epidermoid cancers (72%–96%), related to alcohol consumption and smoking. However, the incidence of adenocarcinomas is on the rise, first noted in the population registries in the United States, where this histology accounts for half of the cases, then in Europe and in France (one-quarter of cases in 2000) [1].

Prognosis for this cancer is poor because of the late diagnosis (most often with dysphagia) and poor patient condition (often elderly patients, poor general health; 12%–17% present associated ORL cancer). However, significant improvement has been noted in 5-year overall survival in European registries (Eurocare): 5% from 1978 to 1980 and 9% from 1987 to 1989 [2].

Since the appearance of concurrent radiochemotherapy, surgical excision is no longer the only curative treatment. This alternative, useable in patients who are less strictly selected, should provide improved results.

The recommendations of this national guideline stem from recommendations for clinical practice from the FFCD [3], the GERCOR [4], and the SOR of the FNCLCC [5, 6].

Pretherapy explorations

Diagnosis

Esophagogastric endoscopy with biopsies, (should be repeated if initially negative) and measurement of distances in relation to dental arcades. Staining (Lugol’s solution, Toluidine blue) is recommended to better evaluate tumor limits or to look for a second esophageal location.

Assessment of extension

The time lapse between tests to assess extension and the therapeutic decision should be as short as possible and should not go beyond 1 month.

References

First-line examinations:

• Complete clinical examination
• Thoracoabdominal CT scan: sensitive and specific for the diagnosis of visceral metastases (hepatic and pulmonary)
• Tracheobronchial fibroscopy: to eliminate tracheobronchial mucous extension or a second location; nonsystematic if adenocarcinoma of lower third in a nonsmoker
• ORL examination with indirect laryngoscopy to look for recurrent paralysis, synchronous ORL cancer

Second-line examination if no metastases on preceding examinations:

• Echoendoscopy: except in cases of locally evolved tumor (stenosis of upper third and tracheal invasion) or metastatic.
• It is completed by biopsy for histological confirmation of celiac adenopathy [7]
• Echoendoscopy with high-frequency (20–30 MHz) mini-probe is recommended to diagnose superficial cancer and indicate endoscopic treatment: of the nine individualized layers in the esophageal wall, the most important is the 4th hypoechogenic layer corresponding to the muscularis mucosa, which, when penetrated, indicates that the tumor is infiltrating the submucosa.
• Bone scintigraphy, brain CT only in case of warning signs.

Alternatives

• Chest x-ray,
• Abdominal ultrasound
• Supraclavicular ultrasound +/- ultrasound-guided brush cytology: to obtain cytological or histological confirmation of cervical adenopathy.
• PET has greater diagnostic precision than CT + echoendoscopy for detecting distant metastases [8]: theoretically, it can be used when CT and echoendoscopy conclude in a nonmetastatic tumor and resection is planned. The metastatic nature of the anomalies identified only by PET should be confirmed.
• Laparoscopy +/- laparoscopic echography: its utility has not been demonstrated for all cancers of the esophagus. This examination seems advantageous for adenocarcinomas of the cardia and the lower third of the esophagus.
• Esophageal transit study: locates the tumor, allows measurement of the size, notes any unhinging (negative sign), evaluates the dimensions of the stomach.

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Classifications

• There is no reference pretherapeutic classification: knowledge of the initial stage relies on the data from the clinical examination and paraclinical explorations. Several alternatives are possible (Annex I):
  — TNM UICC classification (1978)
  — CT classifications such as the Wurtz classification, modified by Bosset et al. [9]
  — Echosendoscopic classification, according to Tio et al. [10]

• In patients who have undergone surgery, the reference is the UICC pTNM classification, revised in 2002. Prognosis depends on the stage. The radicality of the section (R0, R1) is also a prognostic factor, whether it concerns the longitudinal or the circumferential margins.

TNM CLASSIFICATION TNM (UICC 2002)

T - Primary tumor
T0 No sign of primary tumor
Tis Carcinoma in situ
T1 Tumor invading the lamina propria or the submucosa
T2 Tumor invading the muscularis
T3 Tumor invading the tunica adventitia
T4 Tumor invading the adjacent structures

N - Regional adenopathy
Nx Lymph nodes not evaluated
N0 No sign of regional lymph node involvement
N1 Regional lymph node metastases

Cervical esophagus: cervical lymph nodes, internal jugular, periesophageal, and supraclavicular

Thoracic esophagus (upper, middle, and lower): periesophageal lymph nodes above or below the azygos, subcarinal, mediastinal and perigastric veins (except the celiac lymph nodes)

Celiac lymph nodes: always graded M
  — M1a for lower thoracic cancers,
  — M1b for others.

Cervical lymph nodes:
  — N for cervical esophagus cancers,
  — M1a for cancers of the upper part of the thoracic esophagus (from the entrance to the thorax to the tracheal bifurcation, approximately 24 cm from the dental arcades),
  — M1b for the subjacent locations.

M - Distant metastases
M0 No distant metastasis
M1 Presence of distant metastasis
For the tumors of the lower part of the thoracic esophagus
M1a Metastases in celiac lymph nodes
M1b Other metastases

For tumors of the upper part of the thoracic esophagus
M1a Metastases in the cervical lymph nodes
M1b Other metastases
For tumors of the middle part of the thoracic esophagus
M1a Not applicable
M1b Metastases in the nonregional lymph nodes or other distant metastases

Examination of at least six mediastinal lymph nodes is necessary for proper evaluation of the lymph node status.

<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
<th>5-year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Tis</td>
<td>N0</td>
<td>M0</td>
<td>&gt;95%</td>
</tr>
<tr>
<td>I</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
<td>50%-80%</td>
</tr>
<tr>
<td>IIa</td>
<td>T2-3</td>
<td>N0</td>
<td>M0</td>
<td>30%-40%</td>
</tr>
<tr>
<td>IIb</td>
<td>T1-2</td>
<td>N1</td>
<td>M0</td>
<td>10%-30%</td>
</tr>
<tr>
<td>III</td>
<td>T3</td>
<td>N1</td>
<td>M0</td>
<td>10%-15%</td>
</tr>
<tr>
<td>IV</td>
<td>T4</td>
<td>NO-1</td>
<td>M</td>
<td>5%</td>
</tr>
<tr>
<td></td>
<td>M1a</td>
<td></td>
<td></td>
<td>&lt;5%</td>
</tr>
<tr>
<td></td>
<td>M1b</td>
<td></td>
<td></td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>

Classification of superficial cancers (in situ or T1)

1. The Japanese classification
   In superficial cancers, this classification distinguishes:
   a) T1 mucosa cancers (m1 = in situ or severe dysplasia in Europe; m2 = microinvasive, i.e., invading lamina propria; m3 = cancers invading the muscularis mucosae)
   b) T1 submucosa cancers (sm1: superficial part of the submucosa, sm2: middle part, sm3: deep part)

2. Other classification:
   a) T1a with no invasion of the muscularis mucosae: <4% of misjudged adenopathies and possibility of endoscopic treatment,
   b) T1b with invasion of the muscularis mucosae: lymph nodes invaded in 30%-60% of cases.

Epidemiologically associated cancers

• ORL cancer: ORL examination, ORL panendoscopy with general anesthesia
• Lung cancer: tracheobronchial fibroscopy
The search for ORL or tracheobronchial cancer, indispensable in cases of epidermoid carcinoma, is advised in patients who are smokers presenting an adenocarcinoma of the esophagus.

Operability tests

Preanesthesia tests (ASA classification) systematically including:
• Nutritional status (percentage of weight loss, protidemia, albuminemia)
• Respiratory test (lung function, gasometry)
• Cardiovascular examination (pulse and search for heart murmurs, ECG, echocardiography)
• Liver tests
• General health (WHO classification)
• Preoperative consultation to help stop tobacco and alcohol consumption.

Complementary tests if chemotherapy is planned

• ECG and consultation in cardiology for 5FU and cisplatin (hydroniation)
• Neurological examination (peripheral neuropathy?), creatininemia and clearance calculation for cisplatin
**Nonoperability and nonresectability criteria**

**Nonoperability criteria**

Relative contraindications
- Age ≥75 years
- WHO ≥2
- Weight loss >10% of base weight
- Severe arteriopathy

Absolute contraindications
- Respiratory impairment (PaO2 ≤60 mmHg, PaCO2 >45 mmHg, VEMS ≤1000 ml/sec)
- Decompensated cirrhosis (ascites, jaundice, presence of esophageal varices)
- Renal failure (creatinemia >1.25 x N)
- Myocardial infarct dating from less than 6 months or unstable heart disease.

**Nonresectability criteria**

- Tumor invading the mediastinal structures (T4): tracheobronchial tree, recurrences, aorta
- Distant visceral or lymph node metastases classed M1 (M1a, M1b)

**Methods**

**Surgery**

**TECHNIQUE**

**Reference**

Transsthoracic subtotal esophagectomy with lymph node removal (mediastinal and left gastric arteries), and gastric restitution. The usefulness of cervical lymph node removal has not been demonstrated. Examination of at least six mediastinal lymph nodes is required for proper evaluation of the lymph node status (UICC recommendations). During the Munich Consensus Conference (1994), examination of at least 15 lymph nodes was considered optimal [11] (expert agreement).

**Alternatives**

- Esophagectomy with no thoracotomy [12]: in case of contraindication (respiratory) to thoracotomy (level of evidence B)
- Esophagectomy with thoracotomy with extensive lymph node removal, either celiac or mediastinal (two fields), or celiac, mediastinal, and cervical (three fields) (level of evidence C)
- Total esophagectomy with pharyngolaryngectomy for lesions reaching the esophageal mouth, when radiochemotherapy cannot be proposed, or in a salvage situation after radiochemotherapy failure (expert agreement).

**MORTALITY, MORBIDITY**

- Hospital mortality: 5%–10% currently in the registries, ≤5% in specialized departments, in selected patients;
- Morbidity: dominated by pulmonary and infectious complications (25%–30% of cases).

**RESULTS**

Five-year survival varies from 5% to 25% in population registries and multicenter series, reaching 30%–40% in specialized units [13]. It depends on stage and resection (R0), which depends on patient selection and the team’s expertise [14, 15]. When the surgical technique is standardized, adenocarcinomas, whose threshold is almost exclusively subcardinal, have a better long-term prognosis than epidermoid cancers [60].

**Radiotherapy and chemoradiotherapy**

**SOLE TREATMENT**

**Reference**

Exclusive medical treatment of the local-regional forms is concurrent chemoradiotherapy (Table II and Table III): indeed, the combination of fractionated radiotherapy and chemotherapy is superior to radiotherapy alone in patients who have not undergone surgery [16, 17]. Except in cases of contraindication, nonoperable cancer patients should receive a combination of concurrent radiotherapy and chemotherapy (level of evidence B).

When chemoradiotherapy is carried out with curative intent, fractionated radiotherapy, more effective, should be preferred to split-course radiotherapy (FNCLCC-FFCD 9305 trial) (level of evidence B) [18]. In cases of concurrent chemoradiotherapy, the radiotherapy dose should be limited to 50 Gy. A higher dose, combined with chemotherapy, does not seem superior in terms of local control or survival (level of evidence B) [19]. Radiotherapy should be delivered with a linear accelerator, following a conformal technique based on a dosimetric CT study, every field treated each day.

Inoperable patients who are carriers of a locally progressing tumor (resectable T3, T4, N0, or N1), two randomized trials have studied the question of the advantage of surgery. The FFCD 9102 trial comparing surgery preceded by chemoradiotherapy and exclusive chemoradiotherapy did not show a difference in overall survival between the two approaches for T3 tumors in patients who were responders to chemoradiotherapy [20]. Surgical patients had higher early mortality, longer hospitalization but fewer local-regional recurrences. In the Stahl et al. trial, patients were randomized before the beginning of treatment: this study confirmed the equivalence of strategies with or without surgery on overall survival, with local control improved by surgery and higher mortality related to treatment in this case [21] (level of evidence B).

**Alternatives**

- Exclusive radiotherapy is an alternative to chemoradiotherapy only when concurrent chemotherapy is contraindicated.
Chemoradiotherapy with split-course irradiation (type 2 series of 20 Gy in five fractions or three series of 15 Gy in five fractions) [18, 22] can only be used in palliative situations (level of evidence B), notably in patients with metastases (expert agreement).

High-dose-rate curietherapy can be used with a palliative disobstruction aim [23] (level of evidence B). It remains infrequently used because of the technical restrictions.

**Radiosurgery Associations**

Adjuvant treatments to surgery

- **Adjuvant radiotherapy, pre- or postoperative, is no longer indicated** (level of evidence A)
- The utility of adjuvant or neoadjuvant chemoradiotherapy has not been proven (level of evidence C): criticizable positive trials, contradictory meta-analyses (Table IV) [9, 24-31]. Prescribing them is useful only within prospective trials.

Rescue surgery after **chemoradiotherapy** in locally advanced forms

- Rescue surgery after chemoradiotherapy in locally advanced forms chemoradiotherapy provides results that are equivalent to those of surgery alone in responders [20, 21]. In cases of nonresponse, resection, the alternative treatment, must be quickly planned. In the trial conducted by Stahel et al., nonresponders had longer survival after resection compared to those who continued chemoradiotherapy [21].

**Chemotherapy**

Palliative chemotherapy of metastatic cancers

Many phase II trials have shown the effectiveness of chemotherapy, but few randomized studies are available. None have sought to establish that it is more effective than symptomatic treatment. In addition, the older studies only included epidermoid carcinomas, contrary to the more recent studies that were most often reserved for cardia or even gastric adenocarcinomas; however, to date no significant difference in chemosensitivity between the two histological types has been recognized.

The conventional drugs whose activity is the most solidly established are cisplatin and 5FU. The 5FU–cisplatin combination provides 30%–40% of objective responses, with a median duration of 8 months. Median survival is 8–12 months. In a phase II randomized trial in 93 patients [32], combining 5FU and cisplatin significantly improved the objective response rate compared to cisplatin alone (35% versus 19%), but increased toxicity. Combining LV5FU2 and cisplatin [33, 34]. New drugs, vinorelbine and paclitaxel, must be added. Combining irinotecan and cisplatin, gemcitabine and cisplatin, vinorelbine and cisplatin, paclitaxel, and cisplatin (+/- 5FU) give response rates between 30% and 60% [35-41] (Table V); associating LV5FU2 and CPT11 was evaluated as second-line treatment with satisfactory results [42].

All in all, palliative chemotherapy is a recommended treatment for patients in good general health.

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**Table II.** – Phase III trials comparing 5FU continuous chemoradiotherapy and exclusive radiotherapy exclusive in esophageal cancers, according to Seitz [59]

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>No. of patients (Histology)</th>
<th>Stage</th>
<th>Treatment</th>
<th>Local control (% of patients)</th>
<th>Median survival (months)</th>
<th>2-year survival (%)</th>
<th>5-year survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brésil, 1991</td>
<td>Araujo in '99</td>
<td>59</td>
<td>II</td>
<td>RT (50 Gy/5 weeks) + 5FU–MMC–BLEO</td>
<td>58%</td>
<td>22%</td>
<td>6%</td>
<td></td>
</tr>
<tr>
<td>USA, Intergroup 1992-1997, 1999</td>
<td>Herskovic et al. [16, 17]</td>
<td>121 (106 E + 15A)</td>
<td>12T1, 95T2, 14T3</td>
<td>RT (64 Gy/6.5 weeks) + 5FU–CDDP**</td>
<td>38%</td>
<td>9.3</td>
<td>10%</td>
<td>0%</td>
</tr>
<tr>
<td>ECOG, 1990-98</td>
<td>Smith in '99</td>
<td>118</td>
<td>NA</td>
<td>RT (40 Gy/4 weeks) + 5FU–MMC</td>
<td>56% (p=0.01)</td>
<td>14.1</td>
<td>38% (p=0.005)</td>
<td>26%</td>
</tr>
<tr>
<td>South Africa, 1998</td>
<td>Slobber et al. in '99</td>
<td>70 (70 E)</td>
<td>T3</td>
<td>RT (40 Gy/10 fr/5 weeks) + 5FU–MMC</td>
<td>-</td>
<td>4.8</td>
<td>3%</td>
<td>-</td>
</tr>
</tbody>
</table>

*Local control: at end of treatment for Araujo, at 1 year for Herskovic.

**5FU–CDDP: continuous 5FU (1g/m2/24 h from D1 to D4) + cisplatin (75 mg/m2 D1): 4 cycles weeks 1, 5, 8, and 11.

E, epidermoid cancer; A, adenocarcinoma; NA = data not available

**Table III.** – Phase III trials comparing different exclusive chemoradiotherapy modalities

<table>
<thead>
<tr>
<th>Authors, ref.</th>
<th>No. of patients (Histology)</th>
<th>Treatment</th>
<th>Local control (% of patients)</th>
<th>Median survival (months)</th>
<th>2-year survival (%)</th>
<th>5-year survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>France</td>
<td>FNCLCC-FFCD</td>
<td>RT(50 Gy/5 sem)+FUP</td>
<td>58%</td>
<td>13.6 months</td>
<td>36%</td>
<td>21%</td>
</tr>
<tr>
<td>Jacob 1999</td>
<td>[18]</td>
<td>RT(20 Gy/5 FX2)+FUP</td>
<td>29%</td>
<td>11.9 months</td>
<td>25%</td>
<td>10%</td>
</tr>
<tr>
<td>USA INT 0123</td>
<td>[19]</td>
<td>RT(50 Gy/5 sem)+FUP</td>
<td>NA</td>
<td>17.5 months</td>
<td>33%</td>
<td>-</td>
</tr>
<tr>
<td>Minsky, 2002</td>
<td>[19]</td>
<td>RT(65 Gy/5 sem)+FUP</td>
<td>NA</td>
<td>12.9 months</td>
<td>24% NS</td>
<td>-</td>
</tr>
</tbody>
</table>

E = epidermoid cancer, A = adenocarcinoma, NA = data not available

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**Reference**

- Continuous 5FU–cisplatin [32]

Continuous 5FU: 800–1000 mg/m²/24 h D1–D4 or D5
Cisplatin: 75–100 mg/m² D1 or D2 (or fractionated over 5 days).
Cycles every 21–28 days.

**Alternatives**

- LV5FU2–cisplatin [33,34]
- Navelbine +/- cisplatin [35], in epidermoid carcinomas
- LV5FU2-CPT11, in second-line therapy after 5FU–cisplatin failure, in patients in good general health, who make the request and are informed, notably in cases of adenocarcinomas [42].

**Neoadjuvant or adjuvant chemotherapy**

- Neoadjuvant chemotherapy (Table VI): the MRC’s OE 02 study included the greatest number of patients. In 802 randomized patients, it showed a significant survival benefit (+3.5 months median survival and +9% 2-year survival) in the arm where surgery was preceded by two courses of continuous 5FU and cisplatin [43]. This treatment, which did not increase postoperative mortality, is an alternative for adenocarcinomas and epidermoid cancers of the esophagus. However, it is not a reference because most of the other trials and the meta-analysis of 11 published trials were negative [44] (level of evidence debated, B or C).

- Postoperative chemotherapy (Table VII) was studied in the Ando et al. trial and in 242 patients [45]: with two postoperative courses of 5FU-cisplatin, 5-year survival with no recurrence (main objective of the trial) was significantly improved; this benefit was observed in the subgroup of patients with lymph node involvement. The improvement in overall survival, however, was not significant. The other trials found no benefit (Table VII). Postoperative chemotherapy (two courses of 5FU-cisplatin) can be discussed (alternative) in patients who first underwent surgery and have lymph node involvement on the excised specimen, in good general health, who make the request and are informed (level of evidence C).

---

**Table IV. – Phase III trials comparing preoperative radiochemotherapy and surgery alone in esophageal cancers**

<table>
<thead>
<tr>
<th>Authors, year, Center</th>
<th>No. patients (No. adenocarc)</th>
<th>Protocol</th>
<th>Medial survival</th>
<th>3-year survival</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Le Prisé, 1994* Rennes [26]</td>
<td>86 (0)</td>
<td>Surgery alone FU then 20 Gy then FU-P</td>
<td>11 months</td>
<td>11 months</td>
<td>Sequential treatment</td>
</tr>
<tr>
<td>Apinop, 1994 Songkla [27]</td>
<td>69 (0)</td>
<td>Surgery alone 40 Gy/4wks+5FU-P</td>
<td>7.4 months</td>
<td>9.7 months</td>
<td>Small sample size</td>
</tr>
<tr>
<td>Walsh, 1996 Dublin [24]</td>
<td>113 (113)</td>
<td>Surgery alone 40 Gy/4wks +5FU-P</td>
<td>11 months</td>
<td>16 months</td>
<td>Adenocarcinomas</td>
</tr>
<tr>
<td>FFCD-EORTC*, 1997 Bosset [9]</td>
<td>297 (0)</td>
<td>Surgery alone 2x18.5Gy+P</td>
<td>18.6 months</td>
<td>18.6 months</td>
<td>Split-course RT</td>
</tr>
<tr>
<td>Urba, 2001 Michigan [25]</td>
<td>100 (75)</td>
<td>Surgery alone 45 Gy/30 fractions/3 wks +5FU-P-V</td>
<td>17.5 months</td>
<td>17 months</td>
<td>Operative excess mortality</td>
</tr>
<tr>
<td>Burmeister, 2005 [30]</td>
<td>256 (156)</td>
<td>Surgery alone 35 Gy + 5FU-P</td>
<td>18.5 months</td>
<td>21.7 months</td>
<td>RFS improved in epidermoid cancers (0.04)</td>
</tr>
<tr>
<td>Lee, 2004 [31]</td>
<td>101 (0)</td>
<td>Surgery alone 45 Gy + 5FU-P</td>
<td>27.3 months</td>
<td>28.2 months</td>
<td></td>
</tr>
</tbody>
</table>

* Sequential (and nonconcurrent) radiochemotherapy protocol

RFS: Recurrence-free survival

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**Table V. – Main phase II trials combining new chemotherapy drugs and cisplatin (C) in esophageal cancer**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Reference</th>
<th>N</th>
<th>Histology</th>
<th>Response rate (%)</th>
<th>SSP (months)</th>
<th>SG (months)</th>
<th>Toxic death (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C + CPT 11</td>
<td>Ilson [37]</td>
<td>35</td>
<td>Combined*</td>
<td>57</td>
<td>4.2</td>
<td>14.6</td>
<td>0</td>
</tr>
<tr>
<td>C + CPT 11</td>
<td>Ajani [38]</td>
<td>38</td>
<td>Adenocarcinoma</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(stomach included)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C + Gemcitabine</td>
<td>Kroep [36]</td>
<td>36</td>
<td>Combined*</td>
<td>41</td>
<td>–</td>
<td>9.8</td>
<td>0</td>
</tr>
<tr>
<td>C + Vinorelbine</td>
<td>Conroy [35]</td>
<td>71</td>
<td>CE</td>
<td>34</td>
<td>3.6</td>
<td>6.8</td>
<td>1</td>
</tr>
<tr>
<td>C + Paclitaxel</td>
<td>Ilson [39]</td>
<td>38</td>
<td>Combined*</td>
<td>44</td>
<td>3.9</td>
<td>6.9</td>
<td>4 (11%)</td>
</tr>
<tr>
<td>C+ 5FU +Paclitaxel</td>
<td>Ilson [40]</td>
<td>61</td>
<td>Combined*</td>
<td>48</td>
<td>5.7</td>
<td>10.8</td>
<td>0</td>
</tr>
<tr>
<td>C + VP16+Paclitaxel</td>
<td>Lokich [41]</td>
<td>25</td>
<td>Adenocarcinoma (stomach included)</td>
<td>100</td>
<td>–</td>
<td>12.5</td>
<td>0</td>
</tr>
</tbody>
</table>

*No difference in response between the histological types

---

Table VI. — Preoperative chemotherapy: recent phase III trials, according to Seitz (59)

<table>
<thead>
<tr>
<th>References</th>
<th>No. of patients</th>
<th>Protocol</th>
<th>Response rate</th>
<th>Resectability</th>
<th>Survival (median)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Law 1997 (in 59)</td>
<td>147</td>
<td>Two courses of 5FU-CDDP</td>
<td>67% (p=0.0003)</td>
<td>16.8 months (NS)</td>
<td></td>
</tr>
<tr>
<td>Kok 1997 (in 59)</td>
<td>160 (148 evaluable)</td>
<td>Two courses of etoposide-CDDP</td>
<td>36%</td>
<td>85%</td>
<td>18.5 months (p=0.002)</td>
</tr>
<tr>
<td>Kelsen 1997 (in 59)</td>
<td>467 (423 evaluable)</td>
<td>Three courses of 5FUc-CDDP</td>
<td>65%</td>
<td>14.9 months</td>
<td></td>
</tr>
<tr>
<td>MRC 2002 (43)</td>
<td>802</td>
<td>Two courses of 5FU-CDDP</td>
<td>84% 71%</td>
<td>16.8 months (p=0.00213.3 months)</td>
<td></td>
</tr>
</tbody>
</table>

Table VII. — Cancers of the esophagus: postoperative chemotherapy; phase III trials

<table>
<thead>
<tr>
<th>Author, year, reference</th>
<th>No. of patients</th>
<th>Protocol</th>
<th>Median survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>AURC Pouliquen,1996 (in 59)</td>
<td>120*</td>
<td>5FU-CDDP (6-8 cycles) vs surgery alone</td>
<td>14 months vs 14 months</td>
</tr>
<tr>
<td>Ando 1997 (in 59)</td>
<td>205</td>
<td>CDDP-VDS vs surgery alone</td>
<td>48 vs 45% at 5 years (NS)</td>
</tr>
<tr>
<td>Ando 2003(45)</td>
<td>242</td>
<td>5FU-CDDP (2 cycles) vs surgery alone</td>
<td>Survival with no recurrence: 55% vs 45% at 5 years (p=0.037) Overall survival: 61% vs 52% at 5 years (p=0.13)</td>
</tr>
</tbody>
</table>

*stratum I (62 patients): N+, complete resection, stratum II (58 patients): incomplete resection

**ENDOSCOPIC TREATMENTS**

- With curative intent: reserved for superficial cancers classified m1 or m2, after echoendoscopy with a high-frequency miniprobe (20–30 MHz). Involvement of the muscularis mucosae (m3) or a depressed or ulcerated aspect are contraindications to endoscopic treatment alone. Mucosa resection is the treatment of choice [46] if the lesion’s diameter is not over 2 cm, because it allows the resected specimen to be histologically examined, contrary to other endoscopic destructive methods (laser, dynamic phototherapy [47]) and high-dose-rate curie-therapy [48].

- With palliative intent:
  - There are numerous techniques: esophageal dilatations, endoprotheses, tumor destruction techniques (photodestruction laser, monopolar or bipolar electrocoagulation, high-dose-rate curie-therapy, intratumor injections, etc.). The objective is to improve dysphagia, contrary to placing an endoscopic (or radiologic) percutaneous gastrostomy, which ensures food intake without modifying the possibilities of swallowing. These techniques are indicating while waiting for other treatments to start or after their failure.

  The endoscopic method is chosen depending on the tumor’s characteristics (location, endoscopic aspect), the center’s technical facilities, and the patient’s general condition [49]. There are indisputable indications or contraindications: a) covered stent in cases of esophagorespiratory fistula; b) no stent if the upper pole of the tumor is located less than 2 cm from the cricopharyngeal muscle; c) no laser in cases of infiltrating tumor. Stents are currently the most frequently used endoscopic treatment for palliation of neoplastic stenoses of the esophagus [50]. Self-expanding metal stents have replaced plastic stents because they are easier to deploy, with a significantly lower risk of initial complications found in three out of four studies and significantly reduced mortality in one study (level of evidence A). As with plastic stents, positioning them does not require substantial dilatation. Metallic stents provide sustainable and significant improvement of dysphagia, as good as plastic stents in three studies and better in one study [51-54]. The disadvantage of uncovered stents is the risk of tumor spread within the prosthesis; the disadvantage of covered stents is the risk of migration, even if it remains low, varying between 0% and 15% of cases. The risk of major complications seems to be increased in patients who have had radiochemotherapy before or after placement of the stent, according to two retrospective studies [55, 56].

  Of the other endoscopic techniques, the most often used is dilatation, often before other endoscopic treatments or in addition to medical treatment of dysphagia such as radiochemotherapy. The other treatments are less often available and less used: bipolar probe electrocoagulation (Bicap) is useful in circumferential tumors, notably of the cervical esophagus where stents are contraindicated; endocavitary irradiation is as effective as stents [23], but few centers are equipped in France; the same holds true for dynamic phototherapy; laser phototherapy is much less used because it requires repeated sessions.

**Therapeutic indications**

The therapeutic indications are the same for epidermoid and glandular cancers despite their pathological and physiopathological differences.

**Superficial cancers (in situ or T1–m1 or m2)**

Reference

Endoscopic treatment by mucosectomy, if the diameter of the
lesion is <2 cm (after staining), it is not ulcerated, and if its superficial aspect (m1 or m2) can be confirmed by echoendoscopy using a high-frequency miniprobe.

This is the reference technique because it allows histological examination of the resected specimen so as to confirm that the lesion is indeed superficial and that the margins are healthy.

When the mucosectomy shows that the lesion is invasive (m3 or sm1, 2, 3), the risk of lymph node extension is evaluated between 10% (m3) and 30%–40% (sm).

- Esophagectomy in operable patients
- Chemoradiotherapy whenever possible in inoperable patients.

Alternatives
If mucosectomy is impossible, the discussion will be based on the patient’s condition:
- esophagectomy
- radiochemotherapy
- radiotherapy
- high-dose-flow curietherapy [48]
- other local destruction techniques (phototherapy, laser, etc.).

Trials
none

Operable invasive cancers

STAGES I AND II (T1–T2 N0–N1 OR T3 N0)
- Cancers of the thoracic esophagus

Reference
Esophagectomy

Alternatives
- Exclusive chemoradiotherapy
- Neoadjuvant chemotherapy (two courses of SFU–cisplatin) before esophagectomy
- Adjuvant postoperative chemotherapy (two courses of SFU–cisplatin), only if N+ and patient is in good general health, makes the request and is informed.

Trial
- Cancers of the cervical esophagus

No Reference

Concurrent chemoradiotherapy is generally proposed in first-line treatment when pharyngolaryngectomy is necessary. Resection is proposed when there is no complete response, if R0 resection is possible (expert agreement).

Trial

WITH TRACHEOBRONCHIAL MUCOSAL INVASION, NO FISTULA

Reference
Exclusive chemoradiotherapy, type RTOG - 85 - 01 (Herskovic)

Alternatives
- Complementary esophagectomy after re-evaluation, in operable subjects with proven tumor persistence
- Primary esophagectomy in cases of contraindication to radiochemotherapy
- Esophagectomy preceded by neoadjuvant chemotherapy (two courses of SFU–cisplatin), notably in subcarinal adenocarcinomas.

Trial

NB: this trial is not studying operable cancers, but some now consider that stage III cancers are contraindicated for surgery.

Inoperable nonmetastatic cancers

NO TRACHEOBRONCHIAL MUCOSAL INVASION

Reference
Exclusive chemoradiotherapy, type RTOG - 85 - 01 (Herskovic) (level of evidence A):
- RTOG, called Herskovic
  RT 50 Gy in 5 weeks (2 Gy/fractionated, 25 fractions). SFU 1000 mg/m²/day in continuous perfusion from D1 to D4 and CDDP 75 mg/m² at D1 or D2. Four courses (weeks 1, 5, 8, 11).
  Herskovic et al. (16).

Alternative
Radiotherapy alone (if chemotherapy contraindicated)

Essai

WITH TRACHEOBRONCHIAL MUCOSAL INVASION, NO FISTULA

Reference
No reference

Alternatives
- Primary chemotherapy, followed by chemoradiotherapy especially when tracheobronchial invasion disappears (expert agreement)
- Continuous primary radiotherapy at a low dose per fraction (1.5 Gy/fraction, 15 fractions), then evaluation and chemoradiotherapy to be discussed if the tracheobronchial invasion disappears [61], exclusive endoscopic treatment (of the esophageal or tracheobronchial obstruction).

WITH FISTULA

Reference
Covered expanding esophageal stent plus or minus tracheobronchial stent if tracheal invasion is highly obstructive.
Alternative

Jejunostomy, preferred over gastrostomy (because of the risk of reflux) or parenteral feeding (more as a solution while waiting) if a stent cannot be deployed or it is ineffective.

Metastatic cancers

The main objective is to favor quality of life.

GENERAL GOOD HEALTH PRESERVED (WHO 0.1 OR 2)

No reference

Alternatives (expert agreement)

a) Significant dysphagia:
   — concurrent chemoradiotherapy (classic continuous radiotherapy, or concentrated split-course), then possible continuation of chemoradiotherapy alone when there is objective response on metastases and the esophageal tumor.
   — chemotherapy and endoscopic treatment of dysphagia
   — endoscopic treatment of dysphagia.

b) Dysphagia absent or insubstantial:
   — chemotherapy, combined with radiotherapy if dysphagia worsens,
   — symptomatic treatment.

The effectiveness of chemotherapy has not been validated in randomized trials. However, its use is recommended in subjects in good general health, informed, provided that tolerance and efficacy are evaluated regularly (expert agreement). The protocols currently used are 5FU-cisplatin or LV5FU2-cisplatin. If this treatment fails (progression or toxicity) no other plan is recognized. First-line phase II trials have tested: FOLFOX 4, FUFl–gemcitabine, mitomycin-C-CPT11, Navelbine, and second-line: LV5FU2-CPT11.

Trial

FFCD project (phase II): LV5FU2–CPT11 +/- anti-EGFR in first-line treatment or after recurrence following treatment based on cisplatin. Coordinator: L Dahan

GENERAL HEALTH ALTERED (WHO 3 OR 4)

Reference

Endoscopic treatment of dysphagia.

Monitoring

After curative treatment

• Clinical examination every 3–6 months for 3 years
• Paraclinical examinations: depending on symptoms (esophageal transit, fibroscopy of the upper digestive tract, chest x-ray, sonography and/or CT) or according to the protocols in therapeutic trials. Fibroscopy monitoring of the esophagus every 1–2 years seems warranted in case of persistent endobrachyesophagus or conservative treatment to look for foci of in situ cancer.
• For early diagnosis of new ORL or bronchial locations:
• Annual ORL examination looking for metachronous cancer, in cases of epidermoid cancer [57]
• bronchial fibroscopy: not systematic
• Assistance in smoking and alcohol cessation should be proposed.

After palliative treatment

Clinical examination and complementary examinations oriented by symptoms.

Treatment of recurrences

Local or regional recurrence

Alternatives

Depending on the extension and the general health of the patient (expert agreements):

a) after esophagectomy:
   • radiochemotherapy,
   • radiotherapy (if chemotherapy contraindicated)

b) after exclusive radiochemotherapy:
   • esophagectomy,
   • chemotherapy,
   • endoscopic treatment of the dysphagia, endocurietherapy.

Metastatic recurrence

GENERAL HEALTH ALTERED (WHO 3 OR 4)

Reference

Endoscopic treatment of dysphagia.
Annex

Annex 1a: CT classification

Classification ctTNM for thoracic esophageal cancers [according to WURTZ et al., modified by BOSSET et al. [9]

Primary tumor (T)
- ctT1: nonvisibility or mass <10 mm in diameter
- ctT2: mass 10–30 mm in diameter
- ctT3: mass >30 mm in diameter with no sign of invasion to mediastinal structures
- ctT4: idem + sign of spread to mediastinal structures

Lymph nodes (N)*
- ctN0: no detectable adenopathy
- ctN1: regional adenopathy (mediastinal and/or perigastric)

Distant metastases (M)
- ctM0: No distant metastasis
- ctM1: presence of distant metastases (including celiac and cervical adenopathies)

Definition of stages

<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IIa</td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IIb</td>
<td>T1 T2</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td>III</td>
<td>T3 N1</td>
<td>M0</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>T4 all</td>
<td>N all</td>
<td>M0</td>
</tr>
</tbody>
</table>

* Considered pathologies of the lymph nodes from 10 mm.

Annex 1b: Echoendoscopic classification

T N M ultrasound classification for esophageal cancers, after Tio et al. [10]

- uT1: tumor invading the mucosa and the submucosa
- uT2: tumor invading the mucosa without going beyond
- uT3: tumor invading the tunica adventitia (or the serous membrane)
- uT4: tumor invading the adjacent structures
- uN0: no lymph node invasion
- uN1: lymph nodes invaded around tumor: round, same echogenicity as the tumor
- uN2: lymph nodes invaded distant from the tumor (5 cm above or below the upper or lower pole of the tumor).

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