Lecture No. 16

Esophageal Tumors

We could break down this chapter into distinct study parameters. Indeed, as the characteristics of neoplastic growth in the esophagus change, so do the clinical pictures, which differ in relation to anatomo-pathological structures, epidemiology and risk classes, nosological features and, above all, evolution of the lesion. We thus separate esophageal tumors into:

- Benign, the most frequently occurring and interesting of which is leiomyoma;
- Primary malignant, whose fundamental histotypes are squamous carcinoma and adenocarcinoma;
- Secondary malignant.

Although this chapter will take into account other less frequent forms, it's best to focus our attention on the these three.

Various benign tumoral forms have been described, but a great many of these are extremely rare, often small in size, not rarely asymptomatic, and noteworthy of mention only to distinguish them from malignant lesions. These forms account for only 0.5 to 2% of all esophageal tumors, and occur preferentially at a younger age compared to malignant forms. They may develop intramurally or extramurally, and structures vary: leiomyoma, 60%, cysts, 20% (*see Clinical Case no. 11 in this website*), polyps, 5%, fibroma, lipoma, schwannoma, adenoma, etc.

The most frequent benign esophageal tumor is thus leiomyoma, which, as we've said, appears in statistical findings in 60% of cases. It's wise to point out immediately that labeling leiomyoma as a benign tumor must be done with caution, since a significant share of cases reveal an origin that stems not so much from smooth muscle fiber as it does from c-kit positive (CD 117) mesenchymal elements. These are thus forms to be included in the category of gastrointestinal stromal tumors (GISTS), which are now well known to have malignant potential (*FP. Mattioli et al. Gastrointestinal tumors: clinical pathological review of a personal series. Chir. It. 2005, vol. 57; N. 5: 579-587*).

This tumor is usually localized in the submucosa, the mucosa lying above unharmed; it is encapsulated and easily enucleable; it most often arises in the distal two-thirds of the esophagus; it frequently displays an elongated, oval shape, and its dimensions seldom become conspicuous; it typically presents an intramural growth pattern.

Esophageal leiomyoma, if small, may be asymptomatic. Generally speaking, however, dysphagia is the sentinel symptom of the esophageal disorder. Esophagoscopy is the principal examination able to show a sharply-defined filling defect characterized by a round concave imprint on the esophageal wall, which, nevertheless, is normally mobile. Endoscopy confirms the integrity of the mucosa at the level of the imprint. Biopsy is to be avoided, since this would create adhesions between the mucosa and the neoplasm, which could in turn hamper surgical enucleation of the lesion. Indeed, this latter is easily resectable without interrupting the continuity of the mucosa. Surgical procedures, thoracotomic or preferably video- thoracoscopic, are sufficient to resolve the problem with relative ease.

Surgeons generally resort to endoscopic access, for purposes of both biopsy and resection, for other forms of benign endoluminal tumors.

Computerized tomography (CT) scan, magnetic resonance (MR) and endoscopic ultrasound- may be indicated in particular cases.

Malignant esophageal tumors constitute an important and troubling chapter, firstly because they represent a substantial percentage (roughly 7%) of all neoplasms of the digestive tract and, secondly, because - in spite of advances that have been made in the field - these lesions for their pathological features still have an unenviable reputation for the poor diagnosis that they harbor. It's estimated, in fact, that five-year survival for patients with advanced disease does not exceed 10%. We will see how this severity depends on a number of factors, which include specific features of neoplastic growth, anatomic characteristics of the organ, and some aspects of its clinical classification.

From a anatomic pathological standpoint there are a number of histological subtypes. It's nonetheless wiser to focus attention on the most frequent subtypes of disease, namely squamous cell carcinoma and adenocarcinoma.

We must point out from the start that over the past few decades an inversion of the roles in the frequency of these two diseases has become apparent. Once, when esophageal cancer was pronounced, the subtype most often implicated was squamous or spinocellular carcinoma. Today, however, that title belongs to adenocarcinoma, particularly when arising in the cardia or in the distal esophagus. This tumor has increased in frequency, and statistical outlooks point to a further rise. The disease arises most frequently in Western populations, where a parallel increase in the incidence of gastroesophageal reflux disease has been seen. Pathological and clinical findings have unequivocally linked the two pathologies.

As such, the complexity of the two lesions should be considered separately, as should the related clinical pictures.

Squamous cell carcinoma of the esophagus

Epidemiology. This tumor prevalently affects males (over 50 years of age), which, according to some statistical studies, represents the fifth leading cause of death from cancer. This figure must be taken with reserve, however, since the incidence rate of squamous cell carcinoma varies markedly according to the geographic area where it occurs. Indeed, while in Italy it affects only approximately 4/100,000, except in areas of the northwestern part of the country where incidence is higher, amounting to roughly 7-8/100,000, the disease in regions of East Asia occurs at a staggering rate of nearly 100 cases per 100,000 inhabitants/year.

Such markedly pronounced differences according to geographic area strongly implicate the role of environmental factors and correlated harmful agents. Prominent among these - as has been thoroughly demonstrated - is the abuse of alcohol and tobacco, above all if consumed together. As for the former, the quality (beyond the quantity alone) what is consumed would seem to be important: liquors distilled from pomace, such as grappa, may contain methanol (albeit at trace quantities) which could enhance the carcinogenic effect that ethanol has on the esophagus. The pathogenic action of tobacco is putatively magnified by the smoking of cigarettes with a high tar content. Some dietary habits are also considered to be risk factors, such as the consumption of excessively hot foods and beverages, or of products preserved poorly or with harmful substances (nitrosamine, various contaminating agents). Finally, some diseases are also implicated as risk factors, e.g., esophageal achalasia (megaesophagus), injury to the esophagus from caustic substances, and other rare pathologic conditions (Plummer-Vinson syndrome, esophageal diverticula, tylosis, etc.).

In recent years, still ongoing genetic investigations have revealed important molecular mechanisms that appear to be responsible for tumoral transformation, notably that of squamous cell

carcinoma, and in some way at least involved in the carcinogenic process (*Gochhait S. et al. Concomitant presence of mutations in mitochondrial genome and P53 in cancer development - a study in north Indian sporadic breast and esophageal cancer patients. Int. J. Cancer. 2008 Dec 1;123(11):2580-6*). Such studies also pave the way for possible molecular therapy approaches to the disease.

Anatomic Pathology - While all segments of the esophagus may be affected by squamous carcinoma, the middle third is the most frequent site of disease onset (approximately 60% of cases).

From a macroscopic standpoint (*see images in Synopsis no. 4 of this web site*) the tumor may present as fungating, ulcerating or infiltrating. The last of these involves the esophageal wall, sparing (at least apparently during early stages) the mucosa, whose surface may seem to be unimpaired. This may give rise to diagnostic problems, above all with endoscopy.

Only in a very limited percentage of cases (5%) is it possible to identify the cancer in the so-called forms of "*in situ* carcinoma", "superficial carcinoma" or "intramucosal carcinoma" all falling under the heading of "*early esophageal cancer*". These early stage forms are generally asymptomatic and take time (3-4 years) to progress to the point that they can be diagnosed. In those areas where esophageal carcinoma is endemic (China, Japan, the Far East) and where, therefore, widespread screening is justified, such forms can be identified by means of cytologic brushings.

From a histological point of view the tumor is characterized by polygonal cells with eosinophilic cytoplasm, with intercellular bridges or thorns, and production of keratin: in essence, the classical picture of spinocellular carcinoma. These features are all the more pronounced in well-differentiated forms, while they are sparse and focal in poorly-differentiated lesions. At times, a poorly differentiated squamous cell carcinoma may resemble other neoplastic forms, e.g., adenocarcinoma, when scattered necrotic cells take on an almost glandular appearance.

This neoplasm has the sad reputation of being extremely invasive, infiltrating all layers of the esophageal wall, which, because it lacks a serous lining, expedites extra-esophageal mediastinal development.

Squamous cell carcinoma spreads primarily via the lymphatic system.

Here, a few words about the esophageal lymphatic system are warranted: it is characterized by a fine mucosal network that extends longitudinally along the organ and into the submucosa. We thus have two parallel systems, which are themselves connected one to the other and with the lymphatic network of the pharynx above and with that of the stomach below. From these two superficial systems channels sink into the muscular layers, where in turn they form a dense network. At this point the lymphatic system extends to the tunica adventitia and connects to epiesophageal lymph centers, from which the connection with the paraesophageal lymph nodes begins and then integrates with the general lymphatic system of the mediastinum.

At one time it was thought that esophageal carcinoma was multicentric, given the observation of synchronous and metachronous tumor foci arising also distantly to the primary lesion, which were even interpreted as being autonomous carcinogenic phenomena. Taking into account the notions described above about the anatomy of the esophageal lymphatic system, it becomes clear that these neoplastic manifestations are the result of the prevalently longitudinal directional flow of the mucosal and submucosal lymphatic network, along which tumor cells spread - precisely - longitudinally, migrating considerably (as far as 10 cm) from the primary lesion. This observation necessarily warrants the extensive demolition (total or near-total esophagectomy) for the treatment of squamous cell carcinoma.

The above-mentioned reasons make it clear that the lymphatic system is the main cause for the distant dissemination of this tumor, and that lymph node metastasis can be relatively far-reaching, originating from any tumoral site on the esophagus.

Distant sites, particularly in the liver, bone, lung or brain, can be reached by bloodstream metastasis.

Symptomatology

Esophageal cancer strikes - treacherously - without signs and without symptoms; when these do appear, dysphagia will be the most evident. But at this point it will be too late, since dysphagia arises when the tumor has brought about the stenosis of the esophageal lumen by at least 50% and involved no less than two-thirds of the esophageal wall. It is therefore clear that the disease will by no means be diagnosed early.

We have already said that progression from the early stage of disease to that in which dysphagia sets in comes about over many months. Over this time lapse of time (no shorter than 6 months or more) other symptoms may appear that are not exactly pathognomonic: burning and pain in the throat that are generally interpreted as pharyngitis, but that no common remedy improves; excessive salivation - sialorrhea; a repulsion for some foods, which patients (often elderly) find difficult to swallow (*"it gets stuck in my throat"*, *"it goes down the wrong way"*, *"it makes me cough"*, and so on). These disturbances remain so at length or are disregarded by the patient, who attempts by him/herself to treat them, or seeks out the assistance of a physician, who often underestimates the symptoms or at any rate does not link them to a possible esophageal pathology.
Asthenia, weight loss and anemia may, with time, set in, but these symptoms are still not always correctly assessable. However, if the patient has the above symptoms, even if mild, and belongs to a risk class - older than 60, a heavy smoker, heavy drinker, from (or lives in) a region with a high incidence of esophageal cancer, or has a current or past history of conditions known to be in some way linked to the pathogenesis of an esophageal tumor, the physician must bear this diagnosis in mind and begin an appropriate diagnostic workup.

Unfortunately, when dysphagia is full-fledged and persistent, the disorder's diagnosis becomes dramatic: this is the stage when the lesion often infiltrates the esophagus extensively, and may already affect the nearest adjacent structures. The patient no longer receives sufficient nourishment and if the obstruction is closed, not only will the passage of solid foods be blocked, but so will that of liquids. These conditions will also be conducive to episodes of regurgitation.

Signs of advanced disease are odynopahgia, hoarseness, dysphonia (involvement of the recurrent laryngeal nerves), and respiratory symptoms (cough).

From a clinical standpoint, this advanced stage of disease may also entail weight loss, anemia, and signs of metastatic spread, such as palpable supraclavicular and/or laterocervical lymph nodes.

Diagnosis

It is wise to state immediately that those patients belonging to a risk group should be assigned to a monitoring program.

Esophagoscopy provides a relatively easy and valuable tool to detect neoplastic lesions even at an early stage. Early stage forms of disease can be revealed and biopsied by means of chromo-endoscopy (Lugol, toluidine blue), which can detect initial, microscopic lesions - in short, early cancers - and from the stained areas specific biopsy specimens can be taken.

In endemic regions, where the implementation of screening programs is advisable, brush cytology allows the detection of lesions still at an entirely early stage, whereby a small brush in a capsule attached to a long wire is swallowed by the patient, and on reaching the stomach, the brush released from the dissolved capsule expands and is withdrawn by means of the wire, thereby allowing brushing of the esophageal mucosa and collection of cells. The diagnostic accuracy of brush cytology ranges from around 85 - 95%, while that of biopsy is from 83 -90%; combination of

the two methods reaches and exceeds 97%. Double-contrast barium study may also prove useful for the identification of early stage lesions.

In advanced disease, barium swallow allows detection of minor or severe modifications of the esophageal lumen due to neoplastic growth, with different pictures emerging according to the tumor's macroscopic features. Esophagoscopy again becomes fundamental to demonstrate variations occurring in the esophageal lumen, and endoscopic biopsy will permit diagnostic confirmation of the lesion and specification of histological and cytological details. In the event impassable stenosis, endoscopic brushing of the narrowed tract is helpful. The degree of extraluminal growth is reliably measured by means of endoscopic ultrasound (EUS). These examinations specify the degree of T in the TNM classification.

The other staging elements (N and M) are obtained through CT scan, MRI, ultrasonography (liver, cervical and supraclavicular lymph node involvement), and PET (CT-PET). Above all in advanced stages of disease, a tracheobronchoscopy is advisable in order to rule out possible damage to the tracheobronchial tree.

TNM assessment (JSED, AJCC, UICC - see the acronyms page in this website) is furthermore of utmost importance in establishing prognosis and in comparing results achieved using other methods and in other patient series.

Treatment

We have already said that squamous cell carcinoma of the esophagus is often first seen by the physician at a late stage, and the treatment that could be elective and "curative", i.e., surgery, is frequently unsuccessful and does not achieve the hoped for results. These, as in other fields of surgical oncology, depend on disease stage and on the possibility of obtaining radical intervention. As a result, while the 5-year survival after surgery for early stage disease without lymphoadenopathy reaches nearly 95%, in T1N0M0 tumors, in which the microscopic absence of residual disease (R0) can be achieved to a high degree, 5-year survival ranges from 60 - 80%. But if regional lymph node involvement is present - even with a relatively limited tumor (T1N1M0) - survival diminishes drastically. It becomes clear that the lack of radical intervention with the persistence of disease (R1) and in spite of the resective treatment of the most advanced tumors will have tragic long-term results.

It is therefore understandable why in a large number of cases, perhaps more than 50%, surgery is neither feasible nor does it resolve the problem. This is the reason for which palliative approaches, and more recently alternative therapies, have been sought for some time. In any case, surgery remains the most important treatment, be it for curative purposes or as a useful palliative means in many cases.

Above and beyond technical variations advocated by different authors and the personal preferences of every surgeon, surgical intervention for the treatment of squamous cell carcinoma of the esophagus follows these operative steps: demolition of the esophagus - lymphadenectomy - reconstruction of alimentary tract.

Demolition of the esophagus. For some authors, its extent varies according to the site of the tumor: as such, if the lesion is located on the lower third of the organ, a distal partial esophagectomy with intrathoracic anastomosis between the esophageal stump and the stomach (or colon or jejunum). Two objections to the procedure can be raised. The first is that, as was said above, squamous cell carcinoma of the esophagus tends to spread longitudinally, with foci even at a considerable distance from the primary tumor; thus, partial resection of the esophagus would not protect against possible unrecognized residual disease and related consequences. The second objection is that the possible anastomotic dehiscence, if occurring in the thorax, entails an extremely high risk for the patient, even *quoad vitam*.

Consequently, for many surgeons, including this author, the safest procedure is a total or near-total esophagectomy (short proximal stump). Safe, because beyond maximizing oncological

radicality, an anastomotic dehiscence arising in the neck is more manageable and less dangerous. This procedure obviously becomes compulsory if the primary tumor lies in the middle-upper third, or even in the cervical segment, of the esophagus. Should this second case arise, removal en bloc of the esophagus, hypopharynx and larynx is necessary.

Lymphadenectomy. The procedure defined as "standard" includes the mediastinal lymph centers - field 2 - (paraesophageal, right parabronchial subcarinal). Depending on the surgeon's preference, and above all on the diagnostic findings, this field may be enlarged to encompass a total mediastinal lymphadenectomy. If the lesion is distal, the lymphadenectomy must include the abdominal stations - field 1 - (paracardial, lesser gastric curve, celiac tripod). If the tumor is located in the cervical segment, the latero-cervical and supraclavicular stations - field 3 - must be removed. Since excessively extensive lymphadenectomies raise operative morbidity considerably, many surgeons, especially in Western countries, tend to limit their proportions as much as possible.

The reconstructive phase. The esophagus may be substituted by the stomach (esophagogastroplasty), the colon (esophagocoloplasty), or the jejunum (esophagojejunoplasty). The stomach lends itself very well for the purpose, since it is rich in vasculature (thereby assuring anastomotic hold), it may be pulled up to the neck if appropriately tubulized, and generally yields good functional results. When the stomach cannot be used (e.g., due to previous gastric resection), a colic loop interposed isoperistaltically, pedunculated on its vascular axis. Use of the jejunum is indicated in cases of distal resection of the esophagus.

Nabeya's operation is preferred by many surgeons, including this author. It entails a total esophagectomy by right transthoracic access, lymphadenectomy, laparotomic tubulization of the stomach, anastomosis between the short esophageal stump or the hypopharynx and the gastric tube by cervicotomy. Passage of the gastric tube from the abdomen to the neck may be performed by means of a posterior transpleural mediastinal or an anterior extrapleural retrosternal mediastinal approach (following Lortat Jacob's teachings). Since learning and mastering video-assisted thoracoscopic esophagectomy, the anterior extrapleural mediastinal approach has become our preferred method. Furthermore, this procedure is shorter than the posterior approach, and the length of the tube is always sufficient.

Description of total esophagectomy with esophagogastroplasty by means of cervical transposition of the gastric apparatus via anterior retrosternal mediastinal approach.

Thoracic procedure

Placement of five thoracic trocars - 11.5 mm in diameter: 1) posterior axillary line in the fifth intercostal space; 2) midaxillary line in the sixth intercostal space; 3) posterior midaxillary line in the fourth intercostal space; 4) anterior axillary line in the fourth intercostal space; 5) scapular angle in the fourth intercostal space.
Opening of the mediastinal pleura.
Interruption of the arch of the azygos vein (EndoGIA 30 white).
Isolation of the esophagus.
The neoplastic lesion produces an egg-shaped deformation in the distal third of the esophagus, without apparently passing through the wall.
Satellite lymph nodes are increased in volume.
Lymphadenectomy.
Once dissection on the pleural cupola is completed, and in proximity of the diaphragmatic hiatus, the esophagus is interrupted at the junction of the middle and upper third segments (EndoGIA 30 blue).
Control of hemostasis.
Drainage via a Bülau drain and suture of port sites.

This procedure is illustrated in the attached videos:
Video-assisted thoracoscopic esophagectomy for squamous cell carcinoma - Parts 1 and 2

Abdominal procedure

Xipho-umbilical midline laparotomy.

The distal esophageal stump is pulled under the diaphragm.
Preparation of the gastric apparatus: Kocher's maneuver; digitoclasia of the pylorus; liberation of the greater curvature with conservation of the gastro-epiploic arch; section of the left gastric vein and artery **(Fig. 1)**.
Celiac tripod lymphadenectomy.
Preparation of the gastric tube (Multifire GIA 80) with oversew of the mechanical stapling on the tube **(Fig. 2 - 6)**.

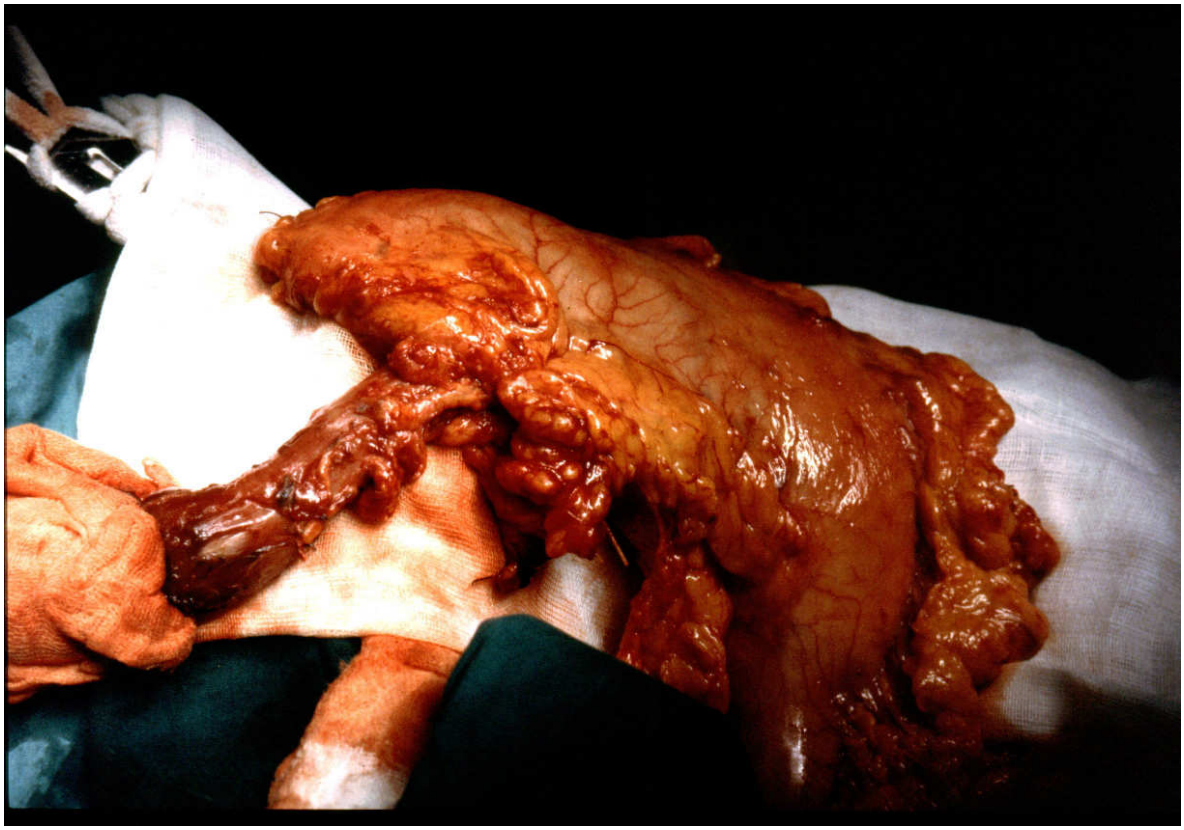

Fig. 1 - Esophageal-gastric mobilization with preservation of the gastro-epiploic arch

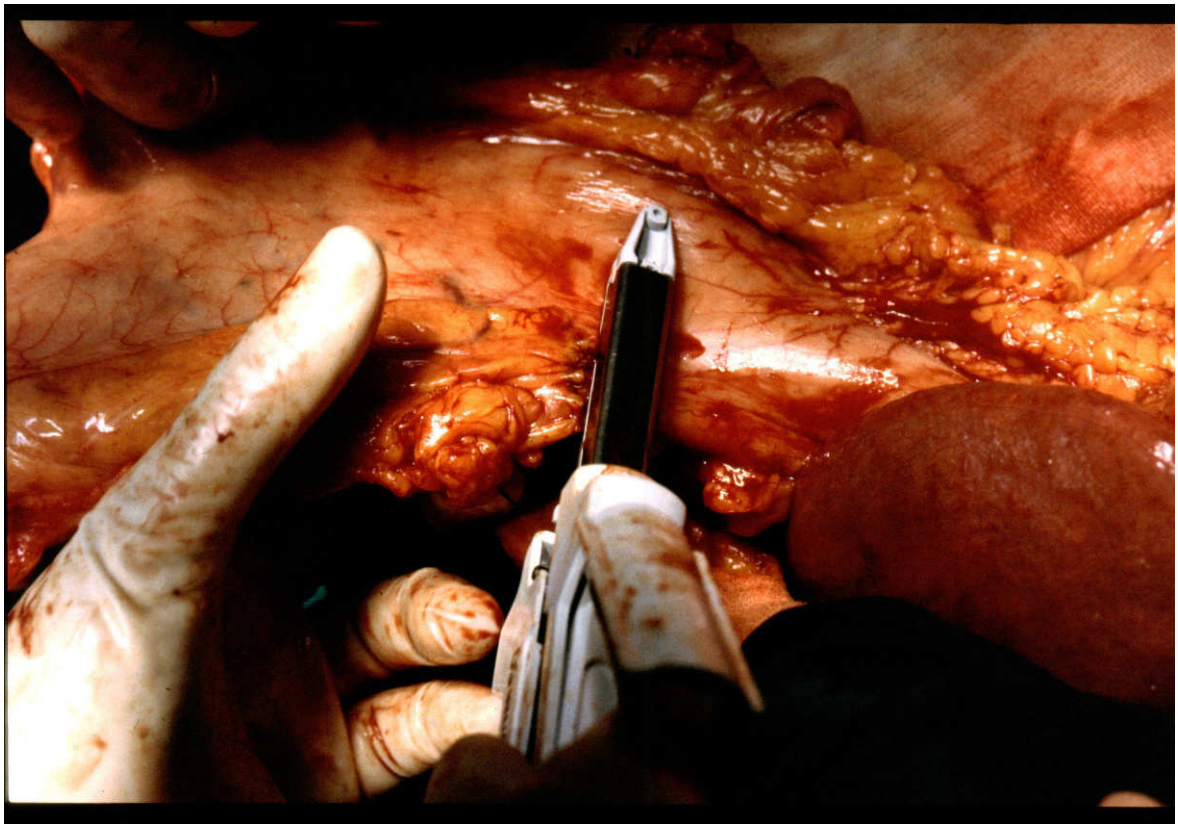

Fig. 2 - Preparation of the gastric tube with a “cut and sew” machine, beginning from the angulus - lesser curvature.

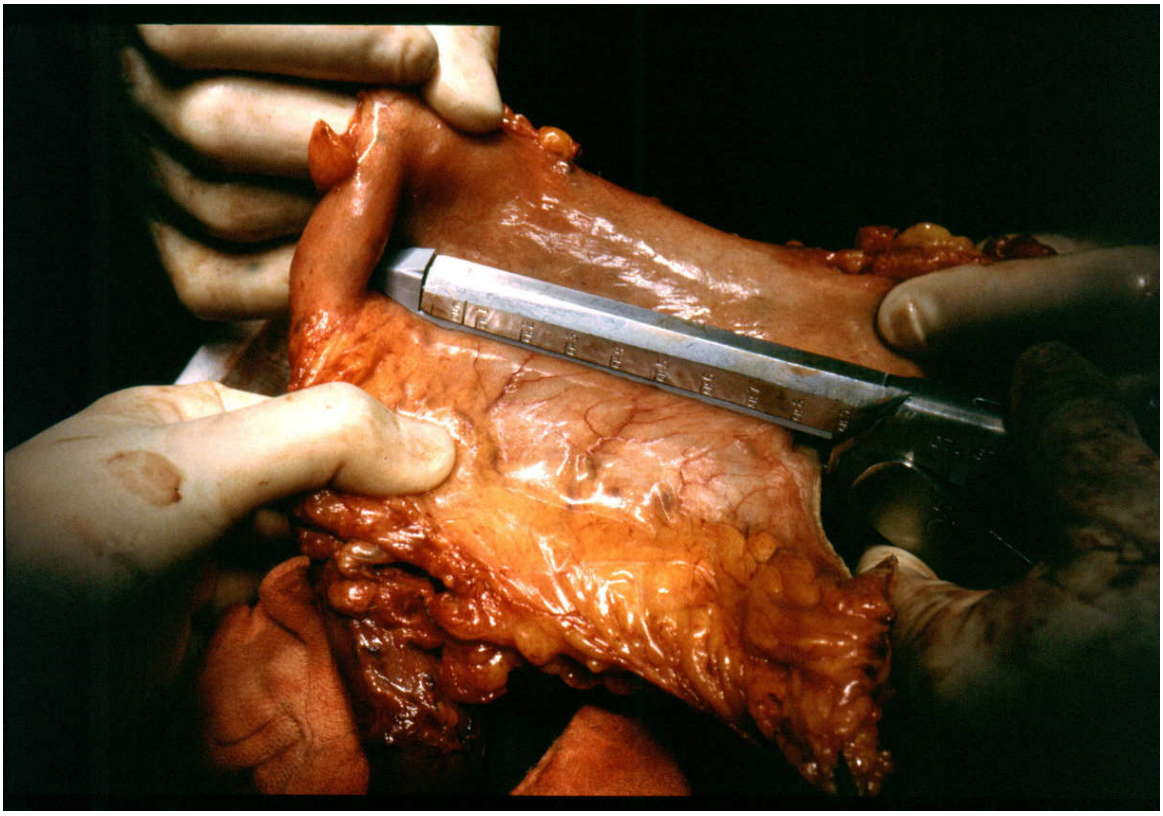

Fig. 3 - Continued preparation of the gastric tube up to the fundus

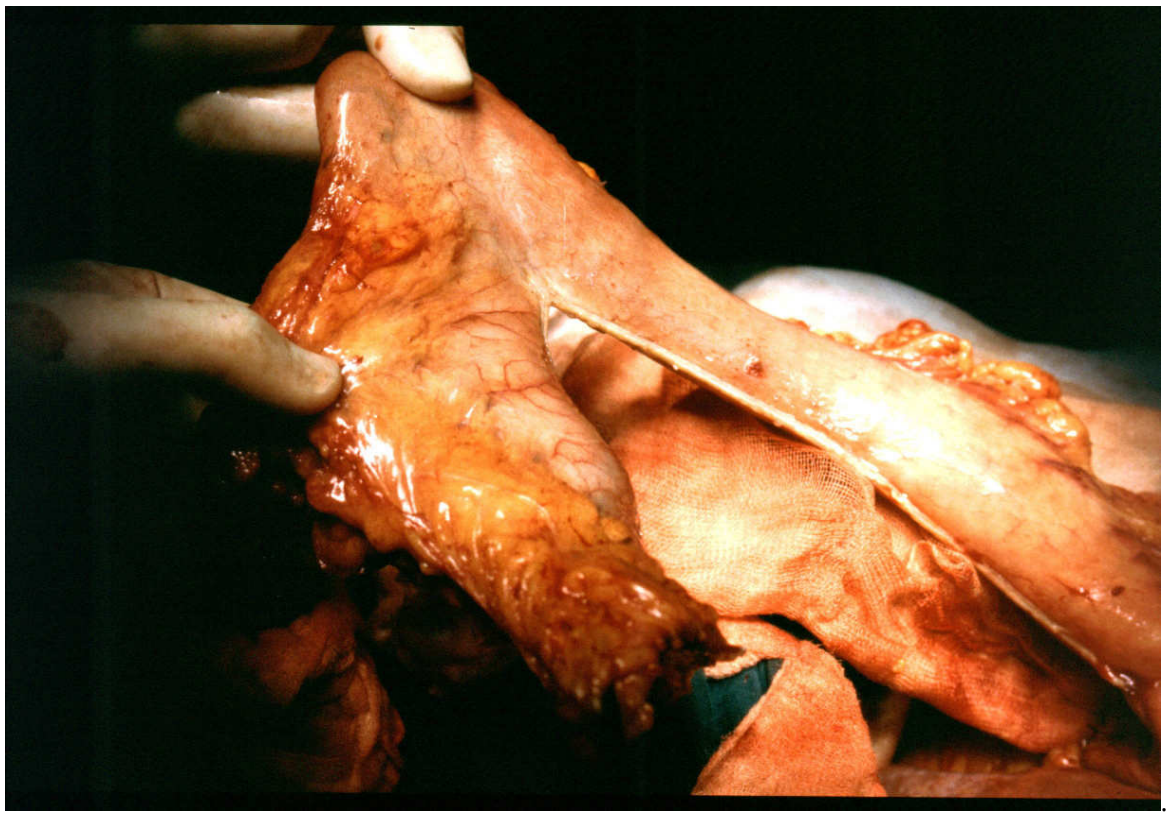

Fig. 4 - The tube remains well vascularized.

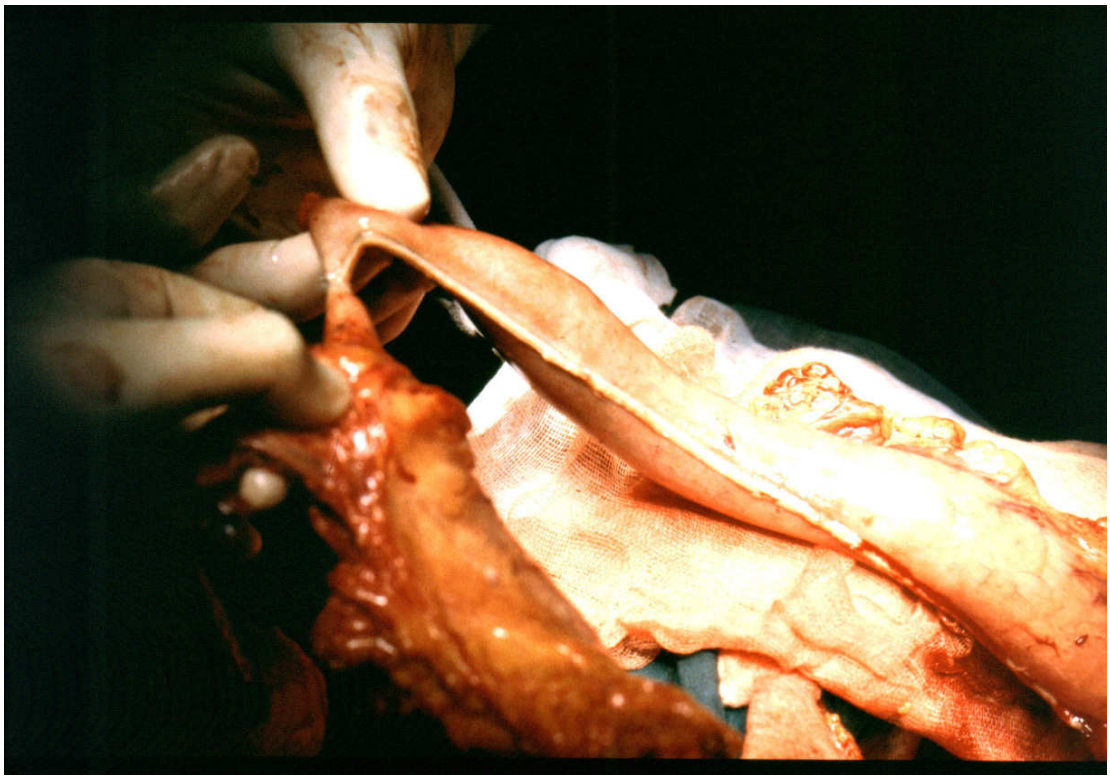

Fig. 5 - Completion of the tube.

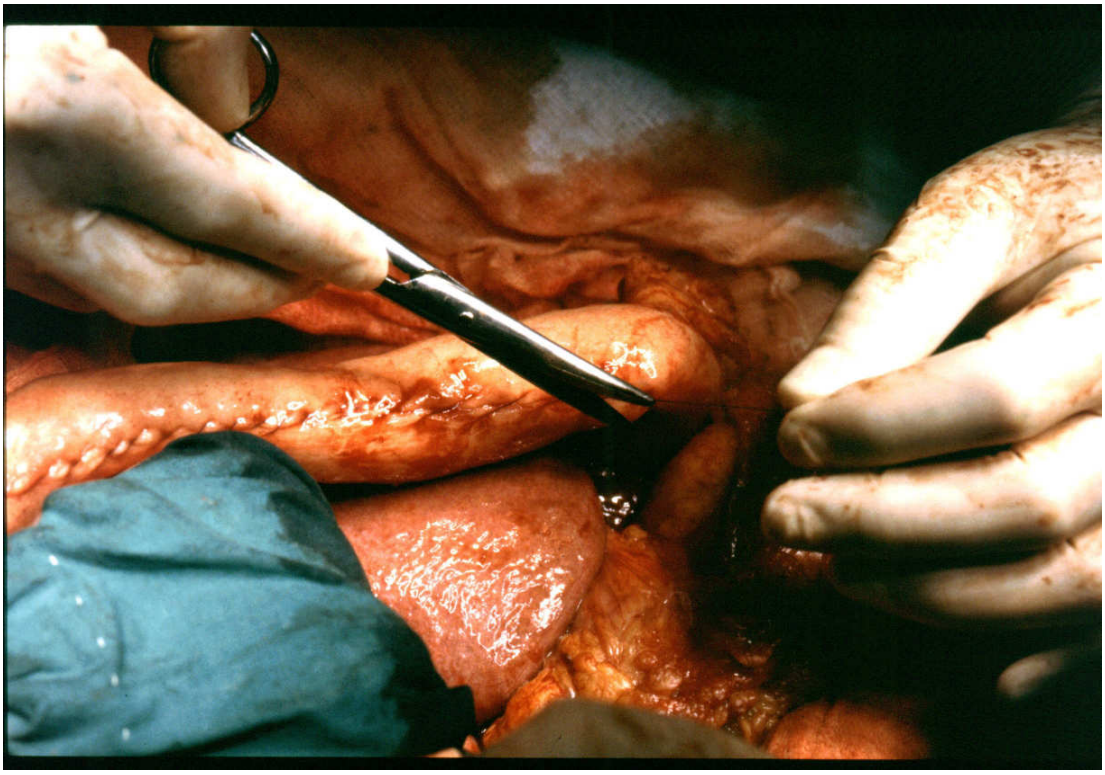

Fig. 6 - Oversewing of the mechanical stapling on the tube, now ready for translocation into the thorax up to the neck via a retrosternal mediastinal route

Removal of the surgical specimen **(Fig. 7)**: esophagus with tumor and gastric stump (fundus and lesser curvature). Preparation of access to the anterior retrosternal mediastinal space.

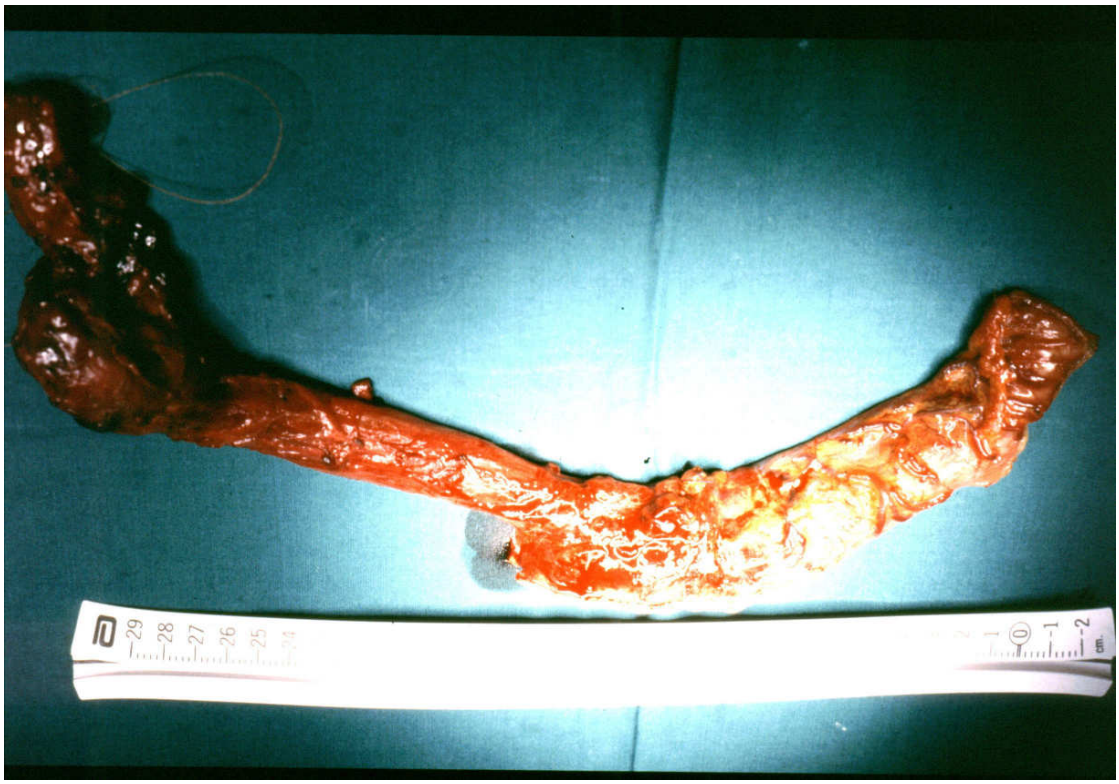

Fig. 7 - The surgical specimen.

Cervical procedure
Cervicotomy
The proximal esophageal stump is drawn up to the neck (Fig. 8).

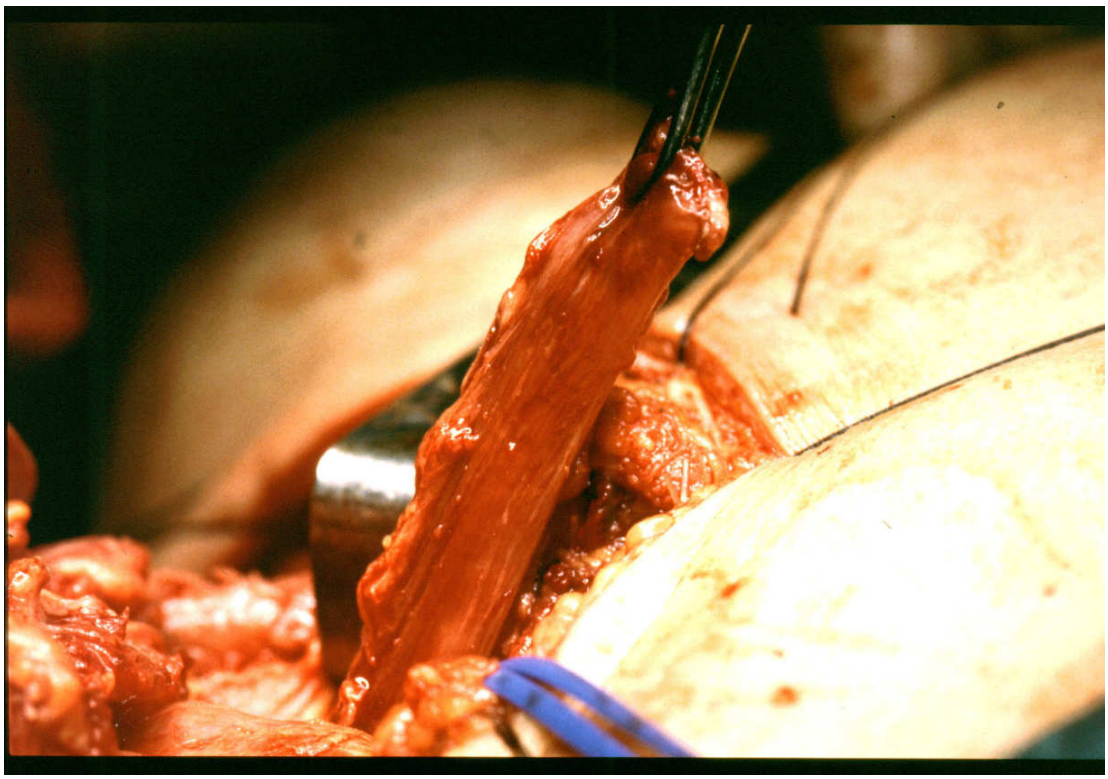

Fig. 8 - Extrinsecation of the proximal esophageal stump

Blunt completion of the retrosternal tunnel up to the suprajugular region.
Positioning of the gastric tube.
Resection of the proximal esophageal stump.
Suture between the hypopharynx-esophagus and the gastric tube **(Fig. 9)**: monolayer (Vicryl 3/0), manual, terminolateral ("end-to-side") anastomosis

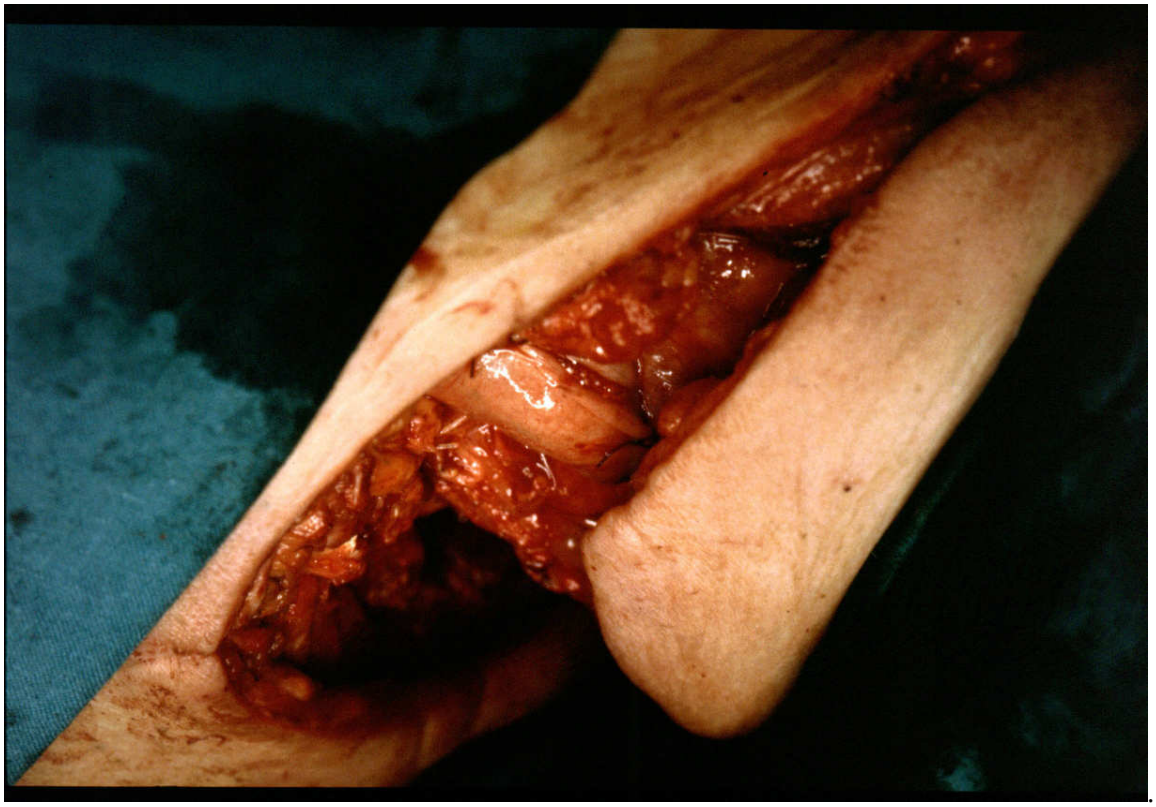

Fig. 9

Positioning of the transanastomotic probe.
Aspirated tube drainage.
Suture of the cervicotomy.

Final abdominal procedure
Toilet of the abdominal cavity; suture of the abdominal wall without drainage.

Surgery of the esophagus was once burdened by a high mortality rate due to anesthesiologic and cardio-respiratory problems, and to a high number of episodes of post-anastomotic dehiscence. Improvements in recent years, however, in anesthesiologic techniques and in nutritional support systems (TPN), the increased strength of mechanical staplers, and the advent of video-assisted thoracoscopic access have all contributed to lowering mortality to acceptable rates, which in specialized centers have dropped to 3%. For the same reasons the incidence of morbidity has also diminished.

As we have seen, the highly aggressive nature of this tumor often prevents the eradication of disease by surgical therapy. It has been known for some time that squamous cell carcinoma is sensitive to radiotherapy; anticancer chemotherapy has revealed itself to be an effective weapon, as well. It has since been demonstrated that radio- and chemotherapy combined yields statistically significant advantages over the two single treatment modalities alone or administered sequentially. These treatment approaches find applications not only in cases in which, for varied reasons, surgery is not feasible, or as postoperative adjuvant, but for some years now also in a neo-adjuvant setting. This last protocol has enjoyed increasingly widespread use, since it appears to improved surgical outcomes. The rationale underlying the use of chemoradiotherapy is that esophageal carcinoma must be viewed as a systemic disease from its onset: the proven activity of radiation on the tumor is enhanced by that - which is, in fact, systemic - of chemotherapy. Results reported in the literature

are exciting: quite often the complete disappearance of the esophageal lesion is achieved, and destaging on histopathological analysis even reaches pT0N0! This outcome seems to hold true in 24 - 32% of cases and, as a result, a significant improvement in survival is also registered.

Palliative therapies essentially tend to restore in some way the passage of food. This purpose may be achieved using somewhat dated and now rarely implemented surgical means, such as gastrostomy and bypass. More advanced techniques aim to open the obstructed esophageal lumen: dilatations, endoprostheses, endoscopic techniques (YAG laser, photodynamic therapies, BICAP, etc.). These procedures are reliably effective, but short-lived and not free from contraindications and complications.

Adenocarcinoma of the esophagus

This tumor was once held to be unusual in the esophagus compared to squamous cell carcinoma, which was considered characteristic of the organ. In recent years, however, its incidence has risen sharply and now accounts for approximately 30% of esophageal cancers, and this trend is destined to progressively increase. Adenocarcinoma almost always arises in the terminal esophagus or, to be more precise, in the gastroesophageal junction (GEJ), such that many authors now prefer to define the disease as adenocarcinoma of the cardia. Neoplastic proliferation may be localized on the esophageal side of the cardia, between 1 and 5 cm above it (type 1), and generally develop on Barrett's esophagus (*see Lecture no. 15 in this web site*). Otherwise, they may straddle the anatomic cardia, 1 cm above and 2 cm below (type 2). Finally, type 3 tumors are defined as those localized from 2 to five cm below the cardia. While the macroscopic appearance is similar to that described for squamous cell carcinoma, histologically the tumor bears a resemblance to the structure of gastric adenocarcinoma: papillary formations, intestinal-type glandular acini, with broad invasive edges occasionally with signet-ring cell infiltrates.

The difficulties in interpretation that characterize the study of all pathological situations involving two different but contiguous systems are implicit with this neoplastic localization, as well. On the one hand, we have a structure made up of compound basement epithelium, which progresses into the epithelium of the cardial transition, and, finally, to the simple, cylindrical, mucous secreting epithelium of the stomach. We have different structures and lymphatic drainage on both sides, i.e., mediastinal and abdominal. This anatomic complexity has spawned noteworthy uncertainty in the definition of this neoplasm (esophageal?, gastric?), which is often the focus of significant debate over classification raised at conferences. Consequently, varied and serious issues arise involving above all staging criteria, which obviously generate uncertainties and a lack of therapeutic guidelines. The literature reflects the scarce chance for comparison of results from different patient series.

From an etiopathogenic standpoint, perhaps the most important of the already-mentioned risk factors for squamous cell carcinoma are the syndromes of gastroesophageal reflux and the Barrett's esophagus that, as has been repeatedly stated, it can lead to (*see again Lecture no. 15*). In fact, it now seems indisputable that the percentage increase of this tumor parallels the rise in the number of cases of reflux disease, above all in populations of the western world.

As such, prior to the onset of dysphagia, i.e., the expression of the tumor's advanced stage, often the patient has had the disturbances of reflux disease (GERD) for some time; these may have been treated or not, have frequently been present for a long time, and have not been subject to control by endoscopic monitoring. If the reflux is not acidic (DGERD), and the symptomatology is deficient and deceptive, the risk increases dramatically and unfortunately the first symptom could well be dysphagia.

The diagnostic workup firstly entails endoscopy with biopsy; radiology will record the features of modifications, especially on the esophagus, and endoscopic ultrasonography (EUS) will reveal the tumor's extrinsic extension. The pathological increase of the tumor markers CEA, CA 19.9, CA 72.4 will be detected on laboratory examinations. For the reasons mentioned above, fundamental for treatment purposes more so than for other oncological conditions, will be the examinations aimed at establishing the correct and precise staging of disease (CT, PET, CT-PET, MRI, etc.). Obviously, these examinations must include many regions, particularly the thorax and the abdomen.

Based on what has been discussed above, the problems involving the localization of this tumor impact significantly on the surgical options and strategies. The crucial question is whether the disease must be affronted as esophageal or gastric, bearing in mind the frequent concomitance of both entities. Diagnostic tests can define and label the type (1 - 2 - 3) of disease extension in both organs. Staging tools will guide the extent of demolition and lymphadenectomy. Without neglecting that this latter procedure must comprise stations in both the mediastinum (mid- and paraesophageal, subcarinal and paratracheal) and the abdomen (bilateral paracardial, celiac tripod), the extent of organ resection is still an issue. Is a with resection of the gastric fundus appropriate for type 1 disease? Distal esophagectomy and total gastrectomy for types 2 and 3? Or, here likely falling into the category of "*overtreatment*", a total esophago-gastrectomy? For the moment, the strategy to undertake is entrusted to the skills and experience of the single surgeon. However, it's hoped that investigative protocols emerging from the comparison of important patient series will help to answer the questions provocatively posed above.

An adenocarcinoma is less radiosensitive than a squamous cell tumor. An approach incorporating neoadjuvant radiotherapy and chemotherapy nonetheless is advisable, above all for the anticancer action that chemotherapeutic agents have at the systemic level.

These treatments, however, including those implemented in an neoadjuvant setting, all suffer from the same dearth of investigations on disease response and long-term survival. Prospective trials on these issues are warranted and, indeed, to be solicited.
