Chirurgia (2024) 119: 515-532
No. 5, September - October
Copyright© Celsius
http://dx.doi.org/10.21614/chirurgia.3050

From Caustic Stenosis to Esophageal Cancer, a Challenging Evolution - Narrative Review

Dragos Predescu[1,2], Florin Achim[1,2]*, Silviu Constantinoiu[1,2], Alex-Claudiu Moraru[1,2], Alexandru Rotariu[1,2], Cristian Gelu Rosianu[3], Dragos-Viorel Scripcariu[4,5], Adrian Constantin[1,2]

[1]Faculty of Medicine, Carol Davila University of Medicine and Pharmacy Bucharest, Romania
[2]Department of Esophageal and General Surgery, Sf. Maria Clinical Hospital Bucharest, Bucharest, Romania
[3]Department of Gastroenterology, Sf. Maria Clinical Hospital, Bucharest, Romania
[4]Faculty of Medicine, Grigore T Popa University of Medicine and Pharmacy Iasi, Romania
[5]First Surgical Unit, Regional Institute of Oncology Iasi, Romania, ORCID ID: 0000-0002-9945-6328

***Corresponding author:**
Florin Achim, M.D.
Department of Esophageal and General Surgery
Sf. Maria Clinical Hospital Bucharest
011192 Bucharest, Romania
E-mail: achim.florin@yahoo.com

Received: 10.09.2024
Accepted: 22.10.2024

Rezumat

De la stenoza caustică la cancerul esofagian, o evoluție imprevizibilă – analiză narativă

Ingestia caustică rămâne o problemă complexă de sănătate publică la nivel mondial, atât la adulți cât şi la copii. Consecințele ingestiei caustice depind de severitatea leziunilor, starea generală a pacientului la prezentare şi promptitudinea managementului medical. Complicațiile pe termen lung includ stricturi sau stenoze, având drept consecință disfagia. În afara tulburărilor metabolice şi hidro-electrolitice, consecințe ale disfagiei, la distanță se raportează cazuri de cancer de esofag pe sediul stenozei esofagiene. Ingestia de produse caustice este un factor de risc pentru apariția cancerului esofagian, iar literatura de specialitate raportează apariția bolii, la aproximativ 30 până la 40 de ani după accident, cu determinarea în principal a carcinomului scuamos. Mecanismul fiziopatologic de apariție a cancerului esofagian legat de ingestia caustică nu este pe deplin înțeles. Diagnosticul cancerului esofagian pe cicatrice post-caustică se bazează pe doi piloni importanți: schimbarea clinicii prin apariția sau modificarea caracterelor disfagiei şi examinarea endoscopică a leziunii. Evident informațiile necesită a fi completate de explorări imagistice complexe, atât pentru certificarea diagnosticului, cât şi în scopul unui bilanț oncologic complet. Principiile şi modalitățile de tratament pentru „cancerul pe cicatrice esofagiană" sunt la fel cu cele al oricărui alt cancer esofagian: depistarea precoce, bilanțul oncologic complet şi

rezecția chirurgicală asociată unei terapii oncologice sunt pilonii principali pentru vindecare. Datorită complexității acestor cazuri, o serie de discuții şi recomandări apar ca necesare în managementul lor.

Cuvinte cheie: stenoză postcaustică, cancer esofagian, bypass esofagian

Abstract

Caustic ingestion remains a complex public health problem worldwide, both in adults and children. The consequences of caustic ingestion depend on the severity of the injuries, the general condition of the patient at presentation and the promptness of medical management. Long-term complications include strictures or stenoses, resulting in dysphagia. In addition to metabolic and hydroelectrolytic disorders, consequences of dysphagia, there are distant cases of esophageal cancer based on esophageal stenosis. The ingestion of caustic products is a risk factor for the occurrence of esophageal cancer, and the specialized literature reports the occurrence of the disease, approximately 30 to 40 years after the accident, with the determination mainly of squamous carcinoma. The pathophysiological mechanism of esophageal cancer related to caustic ingestion is not fully understood. The diagnosis of esophageal cancer on post caustic scar is based on two important pillars: the change of the clinic by the appearance or change of the characters of dysphagia and the endoscopic examination of the lesion. Obviously, the information needs to be completed by complex imaging explorations, both for the certification of the diagnosis and for the purpose of a complete oncological assessment. The principles and methods of treatment for "esophageal scar cancer" are the same as for any other esophageal cancer: early detection, complete oncological assessment and surgical resection associated with oncological therapy are the main pillars for cure. Due to the complexity of these cases, a series of discussions and recommendations appear as necessary in their management.

Key words: caustic stenosis, esophageal cancer, esophageal bypass

Introduction

Caustic ingestion remains a complex public health problem worldwide, in adults and children, the latter representing 80% of patients. The caustic agent (acid or alkaline) is a product that causes complex tissue damage in the mouth, pharynx, hypopharynx, esophagus, stomach, duodenum and can reach the jejunum, further customizing each case. Concomitant gastric and intestinal lesions may occur in 20% to 60% of cases (1-3).

Developing countries have a higher incidence of this type of accidents. In the United States, despite the decrease in ingestion incidents in children (5,000 to 15,000 per year), the current rate is 15.8 cases per 100,000 people (4). The American Association of Poison Control (AAPCC) has documented that approximately 200,000 people have been exposed to household cleaning agents, including caustic products, since 2000 (3).

The type of injury differs significantly (5). In children, ingestion is usually accidental and injuries tend to be milder due to the smaller volumes ingested. Adults usually ingest caustic substances as part of suicidal or homicidal acts either under the influence of alcohol or drugs, resulting in the ingestion of larger volumes of the substance and therefore the degree of impairment is often more severe (6).

Acidic products, most of the time, cause coagulation necrosis of the mucosa, a real protective eschar, which reduces the penetration of the active substance into the parietal depth and thus mitigating the tissue injury.

The most accessible acids are hydrochloric, sulfuric and oxalic acid, being widely used in civil construction and factories. Alkaline substances cause a liquefaction/saponification effect on the mucosa, affecting the entire wall of the affected viscera. Products containing alkaline substances are those used in cleaning, for household use, which contain sodium hydroxide, also known as caustic soda. Therefore, caustic stenosis of the esophagus depends on the ingested product, the amount that was ingested, its concentration and the patient's neuro-psychological state in direct connection with the progression and amount of the ingested substance (1,7-9).

The consequences of caustic ingestion depend on the severity of the injuries, the general condition of the patient at presentation and the promptness of medical management. Mortality is significant, up to 20% in patients with severe damage. The immediate consequences are perforation with secondary sepsis, multiple organ dysfunctions, acid-base disorders. Complications such as tracheobronchial lesions and necrosis, tracheoesophageal fistulas, hemorrhage, perforation, aortoenteric fistula, or gastrocolic fistula may occur in patients who survive the initial event in the first two to three weeks after ingestion (10). Long-term complications include strictures (annular lesions with a maximum length of 1 cm, rarely unique, often tiered) or extensive stenoses involving a significant length of the esophagus, resulting in dysphagia. In addition to metabolic and hydroelectrolytic disorders, consequences of dysphagia (1,2,7,11), cases of esophageal cancer due to esophageal stenosis are reported at a distance (12,13).

The treatment of esophageal strictures secondary to the ingestion of caustic products will depend on the extent of the damage in the pharynx, esophagus, stomach and small bowel (4,11), the degree of dysphagia, and the systemic impact with its nutritional repercussions. The first treatment attempt to improve dysphagia, away from caustic ingestion, is endoscopic esophageal dilatation. If the patient is eligible, the maneuver can be performed repeatedly (2,4,14). If there is no improvement in dysphagia with weight gain, surgical treatment is indicated.

Sf. Maria Clinical Hospital is a tertiary center specialized in the pathology of the esophagus, including postcaustic esophageal stenoses and its reconstruction with visceral material. Over a period of 25 years between January 1, 2000, and August 31, 2024, 263 esophageal reconstructions were performed for this indication, in various reconstructive variants, 249 cases of esophageal bypass and 13 cases in which esophagectomy was performed. A number of 67 cases benefited from conservative, dilator-type endoscopic treatment. Interesting is the appearance of a neoplasm on the postcaustic scar in 10 patients, 9 with conservative treatment and only in 1 case with surgical bypass, all squamous cell type. The typical interval between caustic ingestion and cancer diagnosis was between 16 years and 34 years in our patients.

The aim of the article is to highlight the difficulties in managing these cases from the appearance of postcaustic stenosis to the malignant transformation. Although a strict management protocol cannot be developed, adaptation to each individual case being mandatory, understanding the mechanisms of the appearance of malignancy and its consequences is the basis of the therapeutic approach.

The article is based on the analysis of data considered relevant from studies and articles published in the last 25 years identified in Embase (Excerpta Medica Database), PubMed Central (PMC), Cochrane Library, MEDLINE Complete (EBSCO) corresponding to the period January 1, 2000, and August 31, 2024.

Inclusion Criteria:

- only literature in English such as book chapters, studies, study updates, case presentations, original articles or reviews related to esophageal cancer on post caustic scar.

Screening of Studies

The search strategy was based on keywords and phrases used in search engines, namely

the following terms: "caustic ingestion and esophageal cancer", "cancer on esophageal scar", "adenocarcinoma and esophageal squamous carcinoma".

Following the search, 143 book chapters, articles and studies on the issue were identified. For a selection based on the topic, we used "advanced option" and introduced additional criteria: "diagnostic of cancer in post-caustic stenosis ", "treatment of cancer in post-caustic scar ". This allows for display of the "search history" and for a ready combination of the individual searches using the boolean operators "AND" and "OR." Using this method, parentheses are automatically placed around each set of terms to maintain the logical structure of the search. Thus, 48 scientific materials were identified that strictly concern esophageal cancer on post caustic scar. We have associated with them a series of articles from the initial reference list for additional information considered relevant to the problem. Two authors (A.C. and D.P.) independently selected articles deemed relevant, preferring articles from high-ranking journals written in English. The decision to select an item was made by mutual agreement. The number of citations of the respective work was an important selection criterion. Differences were discussed and if consensus could not be reached between the two reviewers, we requested the consultation and recommendation of a third reviewer (F.A.). We excluded unpublished data from abstracts contained in volumes from various congresses or conferences as well as papers that were not in English.

The Risk of Malignancy

The incidence of esophageal cancer in patients with chronic esophageal stricture secondary to ingestion of corrosive agents is reported to be significantly higher than in the general population. The rate of progression to esophageal cancer ranges from 0.8% to 7.2% (13). Patients with corrosive ingestions are estimated to have a 1000-fold increased risk of developing esophageal cancer, which usually develops at 15-40 years after ingestion (13).

Approximately 1-4% of all esophageal cancer patients have a history of caustic ingestion (15-18). Estimates of the prevalence of esophageal cancer in patients with a history of corrosive ingestion managed with endoscopic dilatation have ranged from 2% to 16% (19,20).

Esophageal cancer is considered the seventh most common cancer, with the two histopathological forms (adenocarcinoma and esophageal squamous carcinoma), with over 570,000 new cases reported in 2018. Among the risk factors for esophageal squamous carcinoma are smoking, alcohol consumption, achalasia, hot drink consumption, zinc, vitamin C, E and folate deficiencies, red meat consumption, low socio-economic status and genetic factors. Esophageal adenocarcinoma is associated with reflux esophagitis, Barrett's esophagus, obesity, and alcoholism (21).

The ingestion of caustic products is a risk factor for the occurrence of esophageal cancer, and the specialized literature reports the occurrence of the disease, approximately 30 to 40 years after the accident, with the determination mainly of squamous carcinoma (22-26).

Jain et al. reported the case of a 14-year-old teenager, who developed esophageal squamous cell carcinoma with cervical lymph node metastases one year after ingesting a caustic substance (27). The first description in the specialized literature of the association of esophageal cancer – postcaustic ingestion was made in the literature by Teleky, in 1904 (14, 24,25,28).

Ruol et al. analyzed 25 patients with cancer on esophageal scar, with esophagus preserved in transit, as a late complication of caustic ingestion, after an average time interval of 48 years (with limits of 42-56 years after ingestion). Squamous cell carcinoma was diagnosed in 20 (80%) patients, adenocarcinoma in three (12%) and verrucous carcinoma in two patients. Esophagectomy was performed in 17 patients. The most common age range was between 40 and 70 years, with a mean of 59 years (29). A possible etiology for the process of carcinogenesis in the esophagus with caustic injury is the poor nutritional status of the scar

tissue (30).

Tustumi et al. performed a systematic review of the literature analyzing the risk of esophageal neoplasia in patients with esophagectomy or esophagoplasty. The authors concluded that the latency period for the appearance of cancer varied between 22 and 58 years, and the risk of malignancy in patients with postcaustic stenoses is 701.7-874.1 per 1 million people per year (14).

Lesional Morphopathology and Histopathology Data

A significant proportion (4-33%) of patients who have ingested a corrosive agent develop severe, often multiple, layered lesions (especially in the case of strictures). These injuries involve the narrowing in varying degrees of severity of the esophageal lumen (13). Moreover, an important particularity, in direct connection with the prognosis of the dilatation treatment, is the consistency of the stenotic changes. The appearance is directly proportional to the quality (hardness) of the fibrotic tissue subsequent to the caustic injury and not least to the fibrosis additionally induced by each dilatory session suffered. In this sense, although the (theoretical) beneficial effect of some complementary anti-inflammatory treatments is invoked to improve the fibrous remodeling, the result ultimately depends on the healing characteristics of each individual case (difficult to quantify). At the opposite pole, separated from the "quality" (consistency) of the fibrotic tissue, we find the length of the stenotic affected esophageal segment. Stenoses longer than 3 cm are highly likely to be unresponsive to dilator treatment (31). These aspects, although insufficiently documented in the literature, highlighted the direct connection with the aggression of the dilator treatment, which thus induces different degrees of postprocedural inflammation, inflammation documented to be directly related to the risk of malignancy.

A thorough review of cases with esophageal stenosis after lye ingestion, with a total of 63 cases of post caustic scar carcinomas (32), concluded that the majority of corrosion carcinomas occur corresponding to the tracheal bifurcation (53 cases). This aspect is speculated to be due to the physiological narrowing of the esophageal lumen at this level, through the relationships of the esophagus with the bifurcation of the trachea. For this reason, the aggression of the caustic substance seems to be maximum at this level (through physiological stasis), as well as the trauma of the dilator treatment, secondary to this anatomical peculiarity.

The pathophysiological mechanism of esophageal cancer related to caustic ingestion is not fully understood. Studies have shown that the epithelium overlying a damaged area is vulnerable to neoplastic transformation, especially if it is subjected to chemical, physical or thermal aggression for prolonged periods. Malignant transformation is a complex process, resulting from a differentiation process in several stages, from native esophageal mucosa to cancer (33,34). In the post-aggression esophageal epithelium, a change in cellular pattern occurs. Cell turnover changes, with the induction of histopathological adaptations such as epithelial hyperplasia, focal hyper-keratosis and subepithelial mixed inflammatory exudate (35). The effect is that of a chronic esophagitis, on the one hand as a cicatricial or post-traumatic alimentary and/or dilatory response. A series of aggression mechanisms with chronic or acute action, physical (thermal or traumatic) and/or chemical (various chemical compounds, caustic or non-caustic) are supposed triggers for the conversion of the esophageal epithelium to carcinoma. This phenomenon may justify the higher incidence of esophageal carcinoma in patients with preserved esophagus in alimentary transit.

Eskander et al. analyzing the endoscopic biopsies of 100 children with caustic strictures undergoing endoscopic dilatation, of both sexes, with an average age of 5.9 years, documented in 85% of cases chronic esophagitis and muco-submucosal inflammation in the form of basal cell hyperplasia, intraepithelial vascular spaces, hyperkeratosis and parakeratosis, hydropic changes, and sub-

epithelial fibrosis. In 13% of cases, they identified the presence of reactive atypia in the form of severe neutrophilic inflammatory atypia. Moderate squamous dysplasia was diagnosed in two cases (36). Similarly, Nagaich et al. (35) reported that the predominant histological changes in endoscopic esophageal biopsies, in patients with post caustic esophageal strictures, were epithelial hyperplasia, focal hyperkeratosis, and mixed inflammatory exudate at the subepithelial level.

Attila et al. (37) state that the presence of the intraepithelial inflammatory infiltrate additionally complicates the pathologist's task, making it difficult to recognize dysplastic lesions, because inflammation causes cellular changes that can be very similar to those in dysplasia.

Controversially, somewhat opposed to all studies in the literature, is the work of Nagaich et al. (35) who did not reveal a single case of dysplasia on histological examinations of endoscopic biopsy specimens in patients older than 3 years, including those with post caustic esophageal stenosis who underwent endoscopic dilator treatment for more than 10 years (35). Nagaich follows the histological changes and the risks of dilatory treatment (over an average period of 10 years), regarding the occurrence of dysplasia and concludes that there are no risks of chronic dilatory treatment. This result, apparently singular in the literature, can be explained by the study of Allam et al. (38) which concludes that in children there is not a long enough period of chronic esophagitis to allow the onset of dysplasia during childhood. Dysplasia (possibly conversion to esophageal cancer) will be evident in the adult period of these patients, after many years of chronic inflammation, initiated since childhood. Kavin et al. (39), based on initial biopsies, before the first session of dilation treatment in patients with post caustic esophageal stenosis, reported minimal histopathological changes, suggesting that the repeated trauma of dilation treatment with plugs could induce/activate a series of histopathological mechanisms of mucosal conversion to dysplasia. This conclusion can also be drawn from the study conducted by Nagaich (35). This theory is not without controversy, however.

Regarding the increase in the incidence of esophageal adenocarcinoma in patients with post caustic stenosis, an aspect mentioned in the literature but at the same time as squamous carcinoma, the details regarding the direct relationship of the post caustic lesion and the changes preceding the appearance of this form of neoplasia (somewhat inappropriate for the esophagus) are several times omitted. It can be assumed, of course, in principle, that the histological changes described in the evolution from esophageal squamous epithelium to squamous cell carcinoma (to which the data in the literature actually refer) are largely identical (at least up to a point). However, the absence in the literature of the identification of the histological sequence to intestinal metaplasia in direct connection with the caustic injury and supporting the subsequent development of an adenocarcinoma with esophageal topography is noted. We can assume, of course, that post caustic esophageal aggression is in a complex relationship with the increase in the incidence of esophageal adenocarcinoma through two mechanisms, both through direct and indirect aggression. The indirect mechanism refers to the increase in the incidence of gastroesophageal reflux in the context of an esophagus with caustic aggression, whose clearance is greatly affected. The link between reflux disease, intestinal metaplasia and the occurrence of esophageal adenocarcinoma has long been known and thoroughly documented. The increased incidence of reflux disease in patients with a history of caustic ingestion is otherwise reported and well documented in the literature. A study of 100 children with post caustic esophageal stricture managed by repeated dilation therapy reported 14 cases of reflux disease. In 4 of these cases, dilator treatment for esophagoplasty was abandoned precisely for this reason (31). The direct link between the ingestion episode and GERD is

difficult to document. This can be pre-existing and/or accentuated by the anatomical-physiological changes secondary to caustic ingestion. The concern still exists in the literature, although the approach to the subject is sporadic due to the small number of cases.

Caustic ingestion produces major damage to the esophageal mucosa, affecting especially the narrowest segment, the middle esophagus, in the region of the aortic arch. The presence of an area of columnar epithelium with this topography has been reported only sporadically in association with re-epithelialization of a caustic injury (40).

The case of a patient with postcaustic stenosis is reported in the literature, in which the middle esophageal columnar epithelium area is identified, with cardiac and not fundic characters, suggesting a metaplastic and not heterotopic origin. The immune profile of the columnar cells supports the gastric phenotype (SOX2 [+], MUC5AC [+], and MUC6 [+]) and suggests intestinal cryptic differentiation (CDX2 [focal] [+]), despite the absence of the intestinal morphological phenotype, assessed by the presence of goblet cells (41).

Re-epithelialization of the lesion induced by caustic ingestion in an acidic environment may be the bio pathogenic mechanism of the metaplastic process. This hypothesis is supported by the presence of morphological features of peptic esophagitis below the metaplasia zone (42). The presence of a well-circumscribed island of columnar epithelium in the mid-esophagus favors the theory of the esophageal origin of the metaplastic lineage from stem cells located either in the native squamous mucosa or in the submucosal glands. These data support re-epithelialization in the mid-esophageal segment after caustic injury, likely modulated by the presence of gastroesophageal reflux, leading to phenotypic reprogramming of the regenerative epithelium, mimicking the Barrett's esophagus model. Columnar metaplasia is also suggested to originate in stem cells of the esophageal epithelium (41).

Beyond speculation, it is certain that the histological details of the transition sequence from normal epithelium to neoplasm are insufficiently documented. In fact, there are many variables both from the point of view of the complexity of the caustic substances incriminated on the one hand, and on the other hand of the different forms of neoplasia reported or suspected to be directly related to caustic ingestion.

Moreover, a case of pseudo-epitheliomatous hyperplasia (a benign condition caused by prolonged inflammation) mimicking an esophageal squamous carcinoma in a patient with esophageal stenosis after caustic soda ingestion is reported in the literature (43).

On the other hand, the adenocarcinoma developed on the colonic graft following its use for esophageal substitution is described. Malignant degeneration in these situations can be attributed to the aggression of the colonic mucosa by bile or gastric secretions and is described at an interval of 5-47 years after the surgical intervention (44). The alarm signal can be clinical, through the appearance of symptoms such as dysphagia, reflux or even respiratory manifestations. Gastric graft adenocarcinoma is traditionally considered extremely rare. However, if we follow the dynamics of the reports, we note that in 2019 there were estimated to be less than 10 cases documented in the literature, currently a few dozens are known (45). The etiology is supposed to be due to repeated mechanical aggression, reflux of bile-pancreatic digestive juices, local ischemia as well as other factors, requiring more than 10 years of evolution for the development of such a neoplasia (46).

Genetic and Immunological Aspects

Genetic factors have been found to play a minor role in the pathogenesis of esophageal cancer (47,48). The overlap of such determinism with the ingestion incident, however, leads to a different approach. Epithelial dysplasia is thought to be a precancerous lesion for the esophagus, which is usually preceded by chronic esophagitis (49,50). de Oliveira Junior et al. recorded the differential expression of miRNAs (miR-374 and miR-574) on biopsies

of the esophageal mucosa of children with caustic strictures less than 5 years after the accident. The authors conclude that the identification of this biomarker is a promising strategy for improving the early diagnosis of esophageal cancer in caustic lesions with a high risk of progression (51).

Changes in miRNA expression are known to contribute to cancer development and progression, with different miRNA expression profiles associated with distinct biological tumor behavior (52). Studies have documented that pathways of axon guidance, vesicle-mediated transport, membrane trafficking, EGFR signaling, and pathways in cancer were commonly enriched with a large number of miRNA-regulated genes in lesions with less and more than 5 years of caustic exposure (51). An adaptive immune system regulation has been identified as an enriched pathway in lesions with less than 5 years of caustic ingestion, and signaling by interleukins in lesions after 5 years of caustic ingestion. Deregulated pathways of immune response may occur in lesions after a short time of caustic exposure, and over time being observed in lesions after 5 years of exposure; the latter being more often associated with tumor development and progression (53).

Diagnosis

The diagnosis of esophageal cancer on post caustic scar is based on two important pillars: the change of the clinical elements by the appearance or modification of the characters of dysphagia (or the appearance of new clinical elements during the monitoring) and the endoscopic examination of the lesion. Obviously, the information needs to be completed by complex imaging explorations, both for the certification of the diagnosis and for the purpose of a complete oncological assessment. In these cases, as rare as they are difficult to manage, the information provided following clinical and paraclinical exploration needs to be constantly interpreted dynamically, always in comparison with the results of previous investigations. This desire is possible through the monitoring protocol in which these patients with the status of "chronic patients" are included. An additional recommendation, for more objectivity, would be, as far as possible, to monitor these patients in the same medical service (ideally by the same medical team).

From a certain point of view, the diagnosis of corrosive esophageal cancer is more difficult than the diagnosis of de novo esophageal cancer because of the preexisting symptoms of dysphagia and difficult endoscopic access for evaluation and biopsy.

A particular situation from a diagnostic point of view is represented by the esophagus with remaining caustic lesion after an esophageal bypass procedure in order to control dysphagia. It is estimated that between 13-31.3% of the remaining esophagus, with bypass, a form of carcinoma develops (14). These situations are all the more serious as endoscopic monitoring (the most objective) of the esophagus excluded from digestive transit is almost impossible. Thus, the early diagnosis of an esophageal cancer becomes improbable, which is essential in the curative treatment of this neoplasia. Moreover, the exclusion from the digestive transit of the esophagus through the bypass, deprives the diagnostic protocol of the suggestive elements of malignancy provided by the occurrence (or worsening) of dysphagia, within the clinical monitoring.

Clinically, the diagnosis of post caustic esophageal cancer should be suspected in patients with corrosive ingestion if, after a latent, oligosymptomatic period, dysphagia appears or worsens, or the response to endoscopic dilator treatment loses its effectiveness, requiring either more laborious or more aggressive maneuvers, or the interval between endoscopic dilations is shortened, in order to control dysphagia. The appearance of respiratory symptoms or non-specific symptoms such as unsystematized, capricious chest pain, dysphonia secondary to vocal cord paresis (left recurrent involvement), weight loss without changes in nutritional intake in a patient known to have post caustic esophageal stenosis, which has been stable for a long time,

requires a paraclinical reevaluation due to the suspicion of malignancy (54).

The standard radiological examination is performed routinely in any surgical service, having no direct diagnostic role but being essential for the identification of concomitant or related pleuro-pulmonary pathologies induced by caustic ingestion (e.g. aspiration broncho-pneumonia by altering the swallowing mechanism secondary to the involvement of the pharynx, lung abscesses) or, why not, of pathologies with primary etiology at this level. Any questionable lesion requires additional investigations, the exclusion or discovery of any pathologies at this level modulating the operative strategy. The existence of signs of local emphysema or emphysema that grows rapidly (Minni Gerode sign) even reaching the level of the pharynx, can be suggestive of esophageal perforation. The incident is possible especially in the context of the unnoticed malignancy of the esophageal scar, which frequently induces more aggressive dilation maneuvers to control dysphagia. In these cases, the radiological examination of the mediastinum shows its widening, highlighted on the radiology of the face but especially on the plain tomography. Sometimes the trachea and esophagus appear dislocated, in both cases but especially in profile, and at other times the diaphragm is immobilized in a high position, obviously due to phrenic paralysis.

Barium swallow is an accessible exploration that can provide important information regarding topography, patency of the stenosed area and, performed with air contrast, provides details on mucosal morphology. Any suspicion of a possible esophageal fistula contraindicates the use of barium as a contrast agent due to the granulomatous and fibro parous reaction secondary to its penetration into the mediastinum or lung. In these conditions, the use of water-soluble contrast agents is recommended, although the accuracy of the obtained image decreases.

Marchand (55) insisted on a very fine radiological examination combined with appropriate exposure techniques (patient position, mode of administration of contrast material, etc.) and suggested a radiological classification of strictures that can be used as a management therapeutic guide (*Table 1*).

The radiological semiology and the quantification of the lesions becomes useful by comparison with the examinations performed in dynamics (within the monitoring of the patient with post caustic esophageal stenosis). The change in the morphological character of the esophageal stenosis (loss of the safety line, deviation of the axis of the stenotic filament, additional "tightening" of the stenotic lesion, etc.) raises the suspicion of malignancy of the monitored caustic lesion (*Fig. 1*).

Upper Endoscopy (EDS)

Endoscopic monitoring is essential in the chronic phase of the disease. There is no consensus in the literature, nevertheless, some authors recommend starting a regular follow-up approximately 10-20 years after the caustic accident. They suggest that endoscopy needs to be performed every 2–3 years, but the exact intervals are not consensually established (56-59). The limits of the method are obvious. The morphological characteristics of the stenotic area are directly related to the ability to carry out the investigation and the accuracy of the information obtained in this way (*Fig. 2*). Exploration needs to be performed by an experienced team in the operating room under general anesthesia with IOT, following Jackson's aphorism “look for the lumen and follow it” to decrease the risk of perforation (60). A guidewire passed through the stenosis followed by dilatation with balloon or plugs may facilitate endoscopic exploration. EGD when combined with magni-

Table 1. Radiological classification of post caustic esophageal strictures (according to Marchand)

Grade	Characteristic appearance
1	short, incomplete, non-circumferential fibrosis
2	annular fibrous cord, elastic stricture
3	short tight stricture
4	extended stricture > 1cm (stenosis) a) only superficial fibrosis, easily dilatable b) extensive, tubular, progressive fibrosis

fication and chromo-endoscopy techniques may be the key to improved diagnosis, with direct consequences on prognosis.

There are studies that described the use of optical chromoendoscopy with NBI in the detection of esophageal carcinoma, concluding that the method can improve the identification of planar lesions that were not observed with conventional endoscopy (61). A comparative study between NBI technique and Lugol's chromoendoscopy in the diagnosis of esophageal carcinoma highlighted that NBI and Lugol's chromoendoscopy had the same sensitivity, both being easy to perform techniques (62).

The accuracy of NBI endoscopy in esophageal cancer screening is similar to Lugol chromoendoscopy. In particular, the specificity of NBI endoscopy with or without magnification was higher than Lugol chromoendoscopy. Although Lugol chromoendoscopy is currently the gold standard for esophageal cancer monitoring, NBI endoscopy could be the endoscopic investigation of first choice for screening in the future (63).

Pennachi et al. used a group of 38 patients with caustic stenosis for the early detection of esophageal carcinomas. Fourteen lesions were detected by Lugol's solution chromoendoscopy and 9 by Narrow Band Imaging. All suspicious

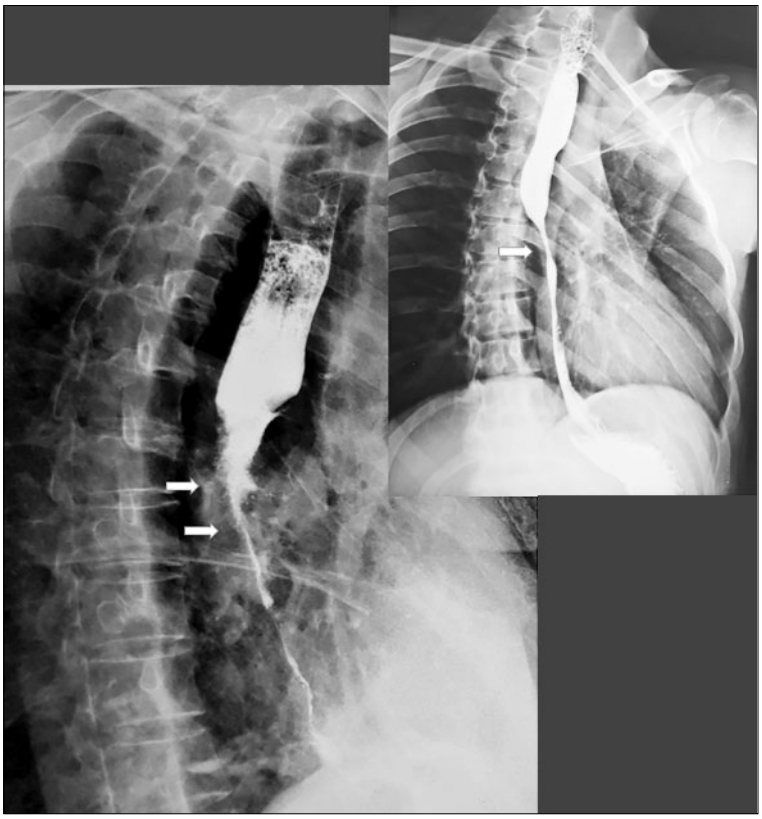


Figure 1. Radiological appearance of a barium swallow, esophageal time. An appearance of stenosis with neoplastic characters is noted at the junction of the upper 1/3 with the middle 1/3 of the thoracic esophagus. In the cartridge, the contrast radiology image performed 12 years ago, with the appearance of a chronic stenotic lesion after caustic soda ingestion (Collection of St. Mary's Clinic).

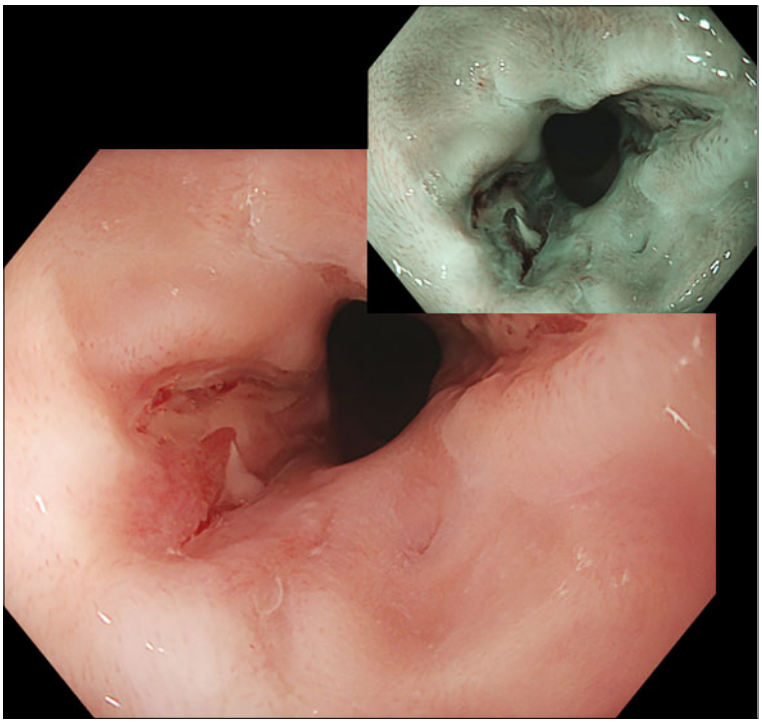


Figure 2. Endoscopic appearance of postcaustic stenosis, post-dilation with a balloon with biopsy confirmation of a squamous cell cancer. Post caustic esophageal stricture lesions, approximately 10 mm ulcer, with surrounding edema and hyperemia. In the NBI image - disorganized mucosa.
(Collection of St. Mary's Clinic)

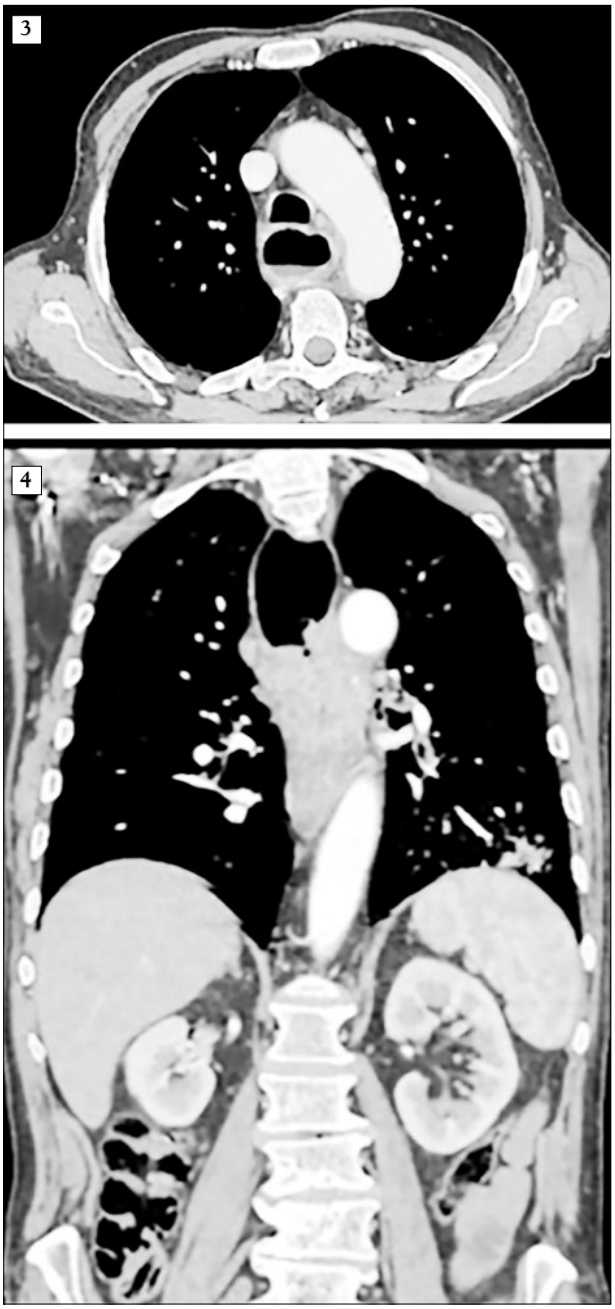
lesions were adjacent to esophageal stenosis. The sensitivity and specificity for Lugol's chromoendoscopy was 100% and 66.67%, respectively. The sensitivity was higher because all carcinoma cases were diagnosed this way. The explanation for the low specificity, at least as far as Lugol's iodine is concerned, may be due to the healing process subsequent to the caustic injury, the areas of vascular neoformation and fibrosis, with low glucose content and therefore negative for iodine staining. The positive predictive value was low, 14.29%, being directly related to specificity; the negative predictive value was high, 100%, because all cancers were diagnosed. The authors concluded that the general accuracy for this investigation was 73% (32,64).

Ultrasound Endoscopy

Ultrasound endoscopy is usually attached to EDS evaluation, being the main method in tumor evaluation in terms of parietal extension, with an accuracy of 60-97% for esophageal cancer. In contrast, in cases with neoplasm on post caustic scar, the performance of the investigation decreases dramatically for obvious technical reasons, through the difficulty/impossibility of the transesophageal progression of the transducer (65). The use of small diameter devices can be considered. There is already experience with high-frequency mini-probe endoscopic ultrasonography in the evaluation of patients with post caustic esophageal stenosis (66,67). It is documented that the thickness of the esophageal wall, the length of the stenosis and the involvement of the deeper layers of the esophageal wall are important prognostic elements for the efficiency of endoscopic dilatation to control dysphagia (66). Moreover, an esophageal wall thickness at the level of the stenosis greater than 9 mm is considered highly suggestive of malignancy (68).

Computed Tomography (CT)

Imaging diagnosis has an important role in the stage evaluation of esophageal cancer secondary to caustic ingestion. In principle, the appearance of contrast uptake in areas of chronic fibrosis (monitored by imaging in the history), the change in the appearance of the scar (which from retractile can become infiltrative) or the appearance of loco-regional lymph nodes, are important alarm signals in



Figures 3, 4. Computed tomography image, in transversal incidence (3) and frontal (4). An important tumor process is found located on the mid-thoracic esophagus, starting at the level of an old postcaustic scar. An important dilatation of the upper esophagus is noted. (Collection of the St. Mary's Clinic)

the direction of a possible malignancy of the area post caustic scars (*Figs. 3, 4*).

Noh et al. analyzed chest CT scans in 14 patients with caustic strictures associated with esophageal neoplasms that occurred at an average of 42 years after the caustic accident. The most frequent changes were eccentric wall thickening (71.4%), homogeneous esophageal wall enhancement (69.2%), periesophageal infiltration (78.5%), and enlarged mediastinal or hilar lymph nodes (14.3%) (36). Regarding the tumor dimensions, the relationship with neighboring structures, possible distant metastases, tomography becomes essential for the diagnosis.

Magnetic Resonance Imaging (MRI)

MRI is not routinely included in T-staging protocols of esophageal carcinoma, but several studies have highlighted its high accuracy and sensitivity for initial staging (69-72). The role is particularly noteworthy in differentiating early stages (T1-T2) from advanced ones (T3-T4) but also in differentiating fibrosis and inflammatory remodeling from malignant lesions. However, the experience of using MRI, particularly in cases with esophageal neoplasm on post caustic scar, is not reported in the literature (65).

The detection of malignancy of an esophageal fibrotic scar is based on the appearance of restriction on diffusion sequences associated with hypo signal on the ADC map (focal restricted diffusion on diffusion-weighted imaging (DW) sequence). Also, an important sign is the appearance of contrast uptake in areas of chronic fibrosis. These semiotic elements need to be evaluated comparatively, within the imaging monitoring of the patient with post caustic stenosis. Certain aspects can be misinterpreted, leading to serious diagnostic errors, if we take into account that in the early stages post-endoscopic dilatation, the recent fibrosis subsequent to the maneuver, can register a certain degree of contrast uptake. In the chronic phase of the evolution of fibrosis, these fibrotic foci no longer gain contrast, (except for a malignancy focus). At the same time, the change in the appearance of the scar, which from retractile can become infiltrative, as well as the appearance of loco-regional lymph nodes must represent a strong alarm signal.

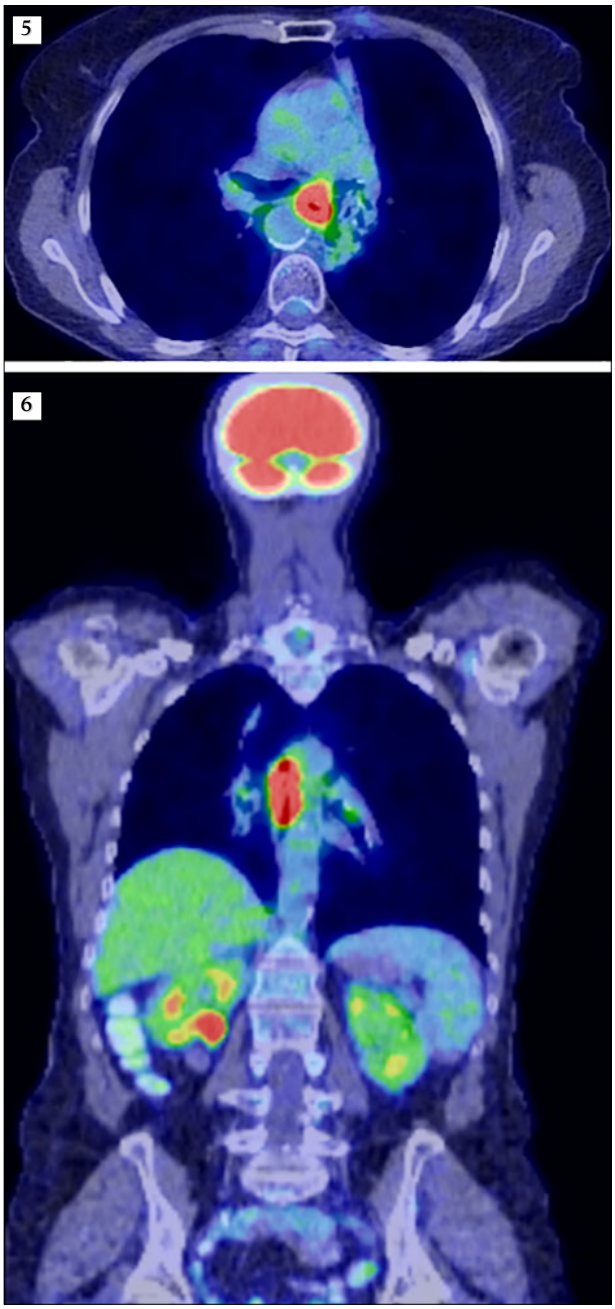
Bronchoscopy is indicated to evaluate possible invasion of the trachea and/or bronchi. Being known to be the preferred location of the caustic lesion in the mid-thoracic esophagus, as well as the subsequent perilesional fibrosis that topographically corresponds to the distal trachea or the tracheal carina, the involvement of the respiratory tree by the malignant post caustic scar radically changes the treatment tactics and obviously the patient's prognosis (14,25,36,73-75).

PET CT Scan

Interference with carbohydrate metabolism by administration of 2-fluoro-2 deoxy-D-glucose with its accumulation predominantly in neoplastic tissue, which has a high rate of glucose utilization compared to fibrous tissue, could logically be useful in detecting malignancy post caustic esophageal scar. The investigation is demanding and is not used in the detection of malignancy of a post caustic stenosis, but it remains in the standard protocol of the oncological balance, in a patient diagnosed with cancer, being necessary especially in the evaluation of distant metastases. In conclusion, the PET CT method can represent a solution to doubtful cases, in which the other diagnostic methods did not bring a clarification of the situation (*Fig. 5, 6*).

Treatment

The principles and methods of treatment for "esophageal scar cancer" are the same as for any other esophageal cancer: early detection, complete oncological assessment and surgical resection associated with oncological therapy are the main pillars for cure. Treatment of esophageal cancer is usually accompanied by a significant decrease in quality of life (76,77). Treatment options, seemingly numerous for patients with esophageal squamous cell carcinoma, are a mix of chemotherapy, radiation therapy, combined chemoradiotherapy,



Figures 5, 6. PET-CT image. Transversal and frontal sections showing tracer uptake at the level of an esophageal, mid-thoracic tumor process. A few metabolically active periesophageal and subcarinal adenopathies are also detectable. (Collection of St. Mary's Clinic)

immunotherapy, various targeted therapies, endoscopic resection for early lesions and, of course, surgical treatment.

Multidisciplinary or multimodal treatment is the most indicated, associating surgery with chemotherapy and possibly radiotherapy and immunotherapy, in the neoadjuvant or adjuvant variants (21,78). The oncological option remains the only weapon in advanced cases with one essential condition – an efficient feeding route.

Overall, despite technical advances and therapeutic strategies, with an obvious improvement in survival over the last two decades, the prognosis remains poor, with an overall 5-year survival of less than 20% (79, 80). Although squamous cell carcinoma and adenocarcinoma are biologically different and have different molecular profiles, there is still considerable overlap in treatment strategies for these two subtypes of esophageal neoplasia.

Endoscopic resection of early lesions is considered the optimal option for early lesions (81) but, on the other hand, the fibrous changes that do not allow the preservation of the esophageal parietal stratigraphy make unlikely the effectiveness of a technique that requires the exact individualization of the layers of the esophageal wall in order to dissect the lesion. There is no reported experience in the literature for endoscopically resected cases of early post caustic stenosis carcinoma. The therapeutic protocol for advanced cases basically includes a sequential approach, chemotherapy or radio-chemotherapy followed by resection surgery. Surgery is the main and only possible curative treatment, although non-surgical alternatives (without esophagectomy) are being reported with promising results (wait & see RCT protocol). This approach is based on the different responsiveness to oncological therapy of the two HP forms of esophageal cancer, squamous carcinoma being more responsive to RCT than adenocarcinoma. A recent review of the literature concluded that the addition of esophagectomy to chemoradiotherapy in locally advanced squamous cell carcinoma provides a nonsignificant benefit or no difference in overall survival and may be associated with a greater increase in treatment-related mortality (82,83).

For cases in which esophagectomy is indicated, the technical options are varied, depending on the particularities of each

individual case, the available equipment and, very importantly, the experience and preference of each individual team, adapted to the case. It is documented that minimally invasive technique (MIE) and robotically assisted minimally invasive esophagectomy (RAMIE) can be performed safely with improved or at least similar postoperative results from an oncological point of view compared to open esophagectomy (84,85) but with an excellent peri- and postoperative quality of life for the patient.

An aspect that needs to be taken into account, formally or informally, at the stage of preoperative tactical preparation is a possible additional technical difficulty arising from the periesophageal fibrotic process, subsequent to caustic ingestion and/or the dilation sessions recorded in these cases over the evolution of the years. This aspect, difficult to quantify, can vary widely, from minimal difficulty to laborious dissections performed in important fibrous tissue. This variable is also found in cases with neoadjuvant radiotherapy and/or intra-esophageal stenting.

The literature records a low percentage of esophagectomies, for the esophagus with malignant post caustic scar, due to advanced disease at the time of diagnosis. In most series, patients underwent radiotherapy, with or without associated chemotherapy, and gastrostomies or jejunostomies for nutritional support. A1 reports 9 cases and only one survived beyond 5 years. The number of esophagectomies performed being small, it is not possible to evaluate the authors' preference for a certain access route (transhiatal, transthoracic or video thoracoscopy), nor the most used way of reconstructing the digestive tube (8,14,24,74,75,86,87).

Immunotherapy has shown many benefits in some cancer patients. The main immunotherapy options for patients with squamous cell carcinoma are anti-programmed cell death 1 ligand 1 (anti-PD-L1)/anti-programmed cell death 1 (anti-PD-1) and anti-cytotoxic T-lymphocyte-associated antigen-4 (anti-CTLA-4) therapy (21). Targeted therapy options are few, mainly using targeting epidermal growth factor receptor (EGFR), human epidermal growth factor receptor 2 (HER2), or phosphoinositide 3-kinase/ mammalian target of rapamycin (PI3K/mTOR) (21).

Discussions

Ingestion of a caustic substance is a severe event, with serious consequences, both immediate and in the medium and long term in a particular population group for medical purposes - patients in childhood (accidental ingestion) or in adults, in whom the ingestion episode is due to related psychiatric conditions (suicide attempts and/or chronic alcohol users).

A number of discussions and recommendations appear as necessary. These patients should be closely monitored indefinitely and this may contribute to a cancer diagnosis at an early stage, despite the fact that information from clinical and paraclinical investigations is difficult to interpret. Anyway, the need for dilatative endoscopic assistance creates the prerequisites for an early diagnosis. In particular, esophageal carcinoma that develops after caustic ingestion can be diagnosed earlier because the tumor tends to develop only intramurally, limited by the perilesional fibrous scar. Thus, although the lesion is small, being developed on a post caustic stenotic esophagus, it will cause an early change in the semiology of dysphagia or an obvious and rapid worsening of a pre-existing dysphagia.

In the face of a post caustic esophageal stenosis, there is a consensus in the literature regarding the primary treatment of dysphagia by endoscopic dilation techniques. The risk of malignant degeneration seems to occupy a secondary place, without being lost sight of in the remote monitoring protocol (clinical and paraclinical). The appearance of an esophageal cancer on a post caustic scar is a consequence of the evolutionary phenomena of the scar tissue, which is subsumed by the repeated aggression of the dilatory and possible treatment and nutrition in the case of the esophagus preserved in the digestive transit. The risk of esophageal perforation

should not be minimized in the context of endoscopic dilation treatment to control dysphagia, which may require a long period (decades) in these patients. The benefits per case after the medical costs, the risk and the complications of an operative act as well as a modest risk of malignancy mean that, currently, the dilatory treatment is still the first therapeutic option chosen in most cases, complemented by a complex monitoring plan, sustainable on long term, which also includes the early identification of a possible malignancy.

Based on these considerations, perhaps the most controversial problem in patients with post caustic esophageal stricture for which there is no endoscopic solution - resection or conservative attitude regarding the esophagus (bypass), both from the perspective of dysphagia management, but especially in the direction of reducing the risk of malignancy.

Excluding the esophagus from transit through a bypass technique would be beneficial by reducing the risk of neoplastic degeneration because it decreases the aggression with mechanical inflammatory effect produced by the alimentary or dilatory bolus on the scar tissue. At the same time, the reflux in the esophageal "butt" creates the conditions for other neoplasia induction mechanisms. In conclusion, the exclusion of the esophagus from the digestive transit by esophageal bypass does not significantly decrease the risk of malignancy, remaining a good point of discussion.

From this perspective, total esophagectomy appears more "recommended" than bypass, which apparently offers no protection against the development of cancer (*Fig. 7*). Moreover, the exclusion from the digestive transit, with the abandonment of the caustic damaged esophagus by bypass, deprives the patient of an early diagnosis of esophageal malignancy, by limiting endoscopic access. Also, the clinical elements directly related to the appearance of cancer will be limited to semiotic elements specific to an advanced stage (recurrent paresis due to invasion of the aortic arch, esophago-bronchial fistulas, chest pain due to invasion of mediastinal nerve structures), weight loss. The surgeon's reluctance to resect the stenotic esophagus is due to laborious operative techniques, with negligible morbidity and mortality, in a patient with definitively benign disease that, at least up to a point, can be effectively managed with dilating endoscopic treatment. If we also consider the low rates of scar malignancy, it becomes obvious why most authors agree that routine esophagectomy should be avoided (13).

Failure or impossibility of endoscopic therapy requires surgical intervention. In some studies, patients with scar cancer had a higher resection rate (68% vs. 56%) compared to patients without a history of caustic injury, although the difference was not statistically significant. Interestingly, the percentage of patients with esophageal cancer confined to the muscle layer was more than double compared to the other esophageal cancers. Also, the percentage of pT1 or pT2 patients with lymph node involvement was lower - 8% in post caustic cancers versus 34% in the group with no history of caustic ingestion. It can be speculated that chronic and repetitive inflammatory insult to the esophageal wall (dilation, food stasis, reflux) may lead to fibrosis and possible occlusion of superficial lymphatic channels, which prevents early

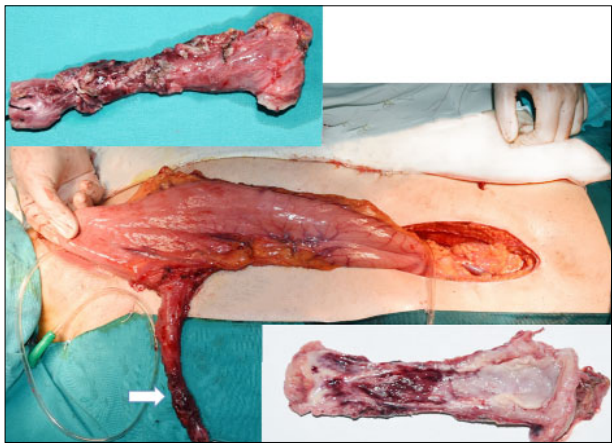


Figure 7. Intraoperative appearance of a transhiatal esophagectomy and mobilization of the stomach in the Sloan-Orringer manner. Indicated by arrow, the site of neoplastic degeneration at the level of a postcaustic stenosis. In the two cartridges, the appearance of the esophagectomy specimen.

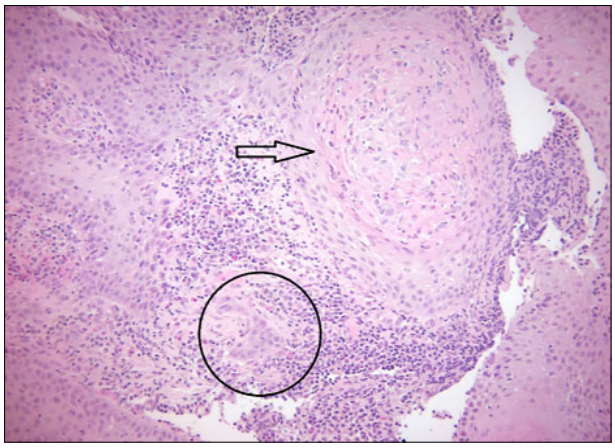


Figure 8. HE 20x: Minimally invasive esophageal squamous carcinoma (black circle); areas of tumor keratinization (black arrow) and marked lympho-plasmacytic inflammatory infiltrate with frequent eosinophils are identified. The appearance is suggestive of a tumoral degeneration of a postcaustic esophageal stenosis (26 years post-ingestion)

dissemination of tumor cells along the rich submucosal lymphatic network (*Fig. 8*). Only 12% of patients who underwent esophageal resection had loco-regional lymph node metastases and only 6% in distant lymph nodes. In addition, it should be noted that in patients with the indication of unresectable, 63% presented a fistula with the respiratory tract, lymph node metastases only in 37.5% of cases and visceral metastases only in 12.5%, which leads to the hypothesis that these tumors have mainly a local aggressiveness (13).

Different from non-caustic cancer, the long-term survival for the patient with cicatricial carcinoma appears to be very good: 45.6% of patients after resection survive at 5 years and 14.4% at 10 years (32).

Conclusions

Malignancy of caustic esophageal scar, although rare, is a reality. The management must be customized for each individual case, keeping the oncological objectives.

The favorable prognosis can be theoretically attributed to several factors. First of all, patients with caustic injuries are carefully monitored and this can contribute to a diagnosis of cancer at an early stage, despite the fact that information from clinical and paraclinical investigations is difficult to interpret. Second, esophageal carcinoma that develops after caustic ingestion can be diagnosed earlier because the tumor tends to develop only intramurally, limited by the perilesional fibrous scar. Thus, although the lesion is small, being developed on a post caustic stenotic esophagus, it will cause early dysphagia or the obvious worsening of a pre-existing dysphagia. Thirdly, intra- and peri-tumoral fibrosis, through subsequent changes in the loco-regional lymphatic and microvascular network, could prevent the early spread of cancer with the late development of nodal or visceral metastases.

Author's Contributions

Conceptualization: D. P., F. A., S. C., A. C.; Investigation: D. P., F. A., S. C., A-C. M., C. G. R., D-V. S, A. R., A. C.; Writing - original draft preparation: D. P., F. A., S. C., A-C. M., C. G. R., D-V. S., A. R., A. C.. All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

Funding

This research received no external funding.

Institutional Review Board Statement

This study was conducted in accordance with the Declaration of Helsinki. and approved by the Saint Mary Hospital Ethics Committee (approval form no. 253/1 june 2024).

References

1. Contini S, Scarpignato C. Caustic injury of the upper gastrointestinal tract: a comprehensive review. World J Gastroenterol. 2013;19(25):3918–30.
2. Chirica M, Kelly MD, Siboni S, Aiolfi A, Riva CG, Asti E, et al. Esophageal emergencies: WSES guidelines. World J Emerg Surg. 2019;4:26.
3. De Lusong MAA, Timbol ABG, Tuazon DJS. Management of esophageal caustic injury. World J Gastrointest Pharmacol Ther. 2017;8(2):90–8.
4. Rafeey M, Ghojazadeh M, Sheikhi S, Vahedi L. Caustic ingestion in children: a systematic review and meta-analysis. J Caring Sci. 2016;5(3):251–65.
5. Andreollo NA, Tercioti V Jr, Coelho Neto JS, Ferrer JAP, Lopes LR. Caustic

stenosis of the esophagus and malignant neoplasia: A dilemma. Front Oncol. 2022;12:1059524.
6. Mowry JB, Spyker DA, Cantilena LR Jr., McMillan N, Ford M. 2013 Annual Report of the American Association of Poison Control Centers, National Poison Data System (NPDS): 31st Annual Report 2013. Clin Toxicol (Phila). 2014;52(10):1032-283.
7. Andreollo NA, Lopes LR, Inogutti R, Brandalise NA, Leonardi LS. Conservative treatment of benign esophageal strictures using dilation. analysis of 500 cases. Rev Assoc Med Bras. 2001;47(3):236–43.
8. Mamede RCM, Mello Filho FV. Ingestion of caustic substances and its complications. Sao Paulo Med J;2001.119(1):10–5.
9. Mu HW, Chen CH, Yang KW, Pan CS, Lin CL, Hung DZ. The prevalence of esophageal cancer after caustic and pesticide ingestion: A nationwide cohort study. PloS One. 2020;15(12):e0243922.
10. Bonavina L, Chirica M, Skrobic O et al: Foregut caustic injuries: Results of the world society of emergency surgery consensus conference. World J Emerg Surg. 2015;10:44.
11. Zargar SA, Kochhar R,Mehta S, Mehta SK. The role offiberoptic endoscopy in the management of corrosive ingestion and modified endoscopic classification of burns. Gastrointest Endosc. 1991;37(2):165-9.
12. Lupa M, Magne J, Guarisco JL, Amedee R. Update on the diagnosis and treatment of caustic ingestion. Ochsner J. 2009;9(2):54-59.
13. Ntanasis-Stathopoulos I, Triantafyllou S, Xiromeritou V, Bliouras N, Loizou C, Theodorou D. Esophageal remnant cancer 35 years after acidic caustic injury: A case report. Int J Surg Case Rep. 2016;25:215-7. Erratum in: Int J Surg Case Rep. 2016;29:16.
14. Tustumi F, Seguro FCBDC, Szachnowicz S, Bianchi ET, Morrell ALG, da Silva MO, et al. Surgical management of esophageal stenosis due to ingestion of corrosive substances. J Surg Res. 2021;264:249–59.
15. Kochhar R, Sethy PK, Kochhar S, Nagi B, Gupta NM. Corrosive induced carcinoma of esophagus: report of three patients and review of literature. J Gastroenterol Hepatol. 2006;21:777-780.
16. Appelqvist P, Salmo M. Lye corrosion carcinoma of the esophagus: a review of 63 cases. Cancer. 1980;45:2655-2658.
17. Gerami S, Booth A, Pate JW. Carcinoma of the esophagus engrafted on lye stricture. Chest. 1971;59:226–227.
18. Levine M, Finkelstein Y, Trautman WJ, Cao D, Schwarz E, Filip A, et al. Is EGD Needed in all Patients after Suicidal or Exploratory Caustic Ingestions? J Med Toxicol. 2024;20(3):256-262.
19. Bigger IA, Vinson PP. Carcinoma secondary to burn of the esophagus from ingestion of lye; report of a case. Surgery 1950; 28:887–889.
20. Imre J, Kopp M. Arguments against long-term conservative treatment of oesophageal strictures due to corrosive burns. Thorax 1972;27:594–598.
21. Lu F, Yang L, Luo Z, He Q, Shangguan L, Cao M, Wu L. Laboratory blood parameters and machine learning for the prognosis of esophageal squamous cell carcinoma. Front Oncol. 2024;14:1367008.
22. Keh SM, Onyekwelu N, McManus K, McGuigan J. Corrosive injury to upper gastrointestinal tract: Still a major surgical dilemma. World J Gastroenterol. 2006;12(32):5223–8.
23. Kalayarasan R, Durgesh S. Changing trends in the minimally invasive surgery for corrosive esophagogastric stricture. World J Gastrointest Surg. 2023;15(5):799-811.
24. Stoica A, Lionte C, Palaghia MM, Gîrleanu I, Sorodoc V, Ceasovschih A, et al. Severe Intentional Corrosive (Nitric Acid) Acute Poisoning: A Case Report and Literature Review. J Pers Med. 2023;13(6):987.
25. Hopkins RA, Postlethwait RW. Caustic burns and carcinoma of the esophagus. Ann Surg. 1981;194(2):146–8.
26. Tarazi M, Chidambaram S, Markar SR. Risk Factors of Esophageal Squamous Cell Carcinoma beyond Alcohol and Smoking. Cancers (Basel). 2021;13(5):1009.
27. Jain R, Gupta S, Pasricha N, Faujdar M, Sharma M, Mishra P. ESCC with metastasis in the young age of caustic ingestion of shortest duration. J Gastrointest Cancer 2010;41:93-95
28. Kim YT, Sung SW, Kim JH. Is it necessary to resect the diseased esophagus in performing reconstruction for corrosive esophageal stricture? Eur J Cardiothorac Surg. 2001;20(1):1-6.
29. Ruol A, Rampado S, Parenti A, Portale G, Giacomelli L, Battaglia G, et al. Caustic ingestion and oesophageal cancer: intra- and peri-tumoral fibrosis isassociated with a better prognosis. Eur J Cardiothorac Surg. 2010; 38(6):659-64.
30. Csıkos M, Horvath O, Petri A, Petri I, Imre J. Late malignant transformation of chronic corrosive oesophageal strictures. Langenbecks Arch Chir. 1985; 365(4):231–8.
31. El-Asmar KM, Allam AM. Predictors of successful endoscopic management of caustic esophageal strictures in children: When to stop the dilatations? J Pediatr Surg. 2021;56(9):1596-1599.
32. Pennachi CMPS, Moura DTH, Amorim RBP, Guedes HG, Kumbhari V, Moura EGH. Lugol's iodine chromoendoscopy versus narrow band image enhanced endoscopy for the detection of esophageal cancer in patients with stenosis secondary to caustic/corrosive agent ingestion. Arq Gastroenterol. 2017;54(3):250-254.
33. Collins MH, Alexander ES, Martin LJ, Grotjan TM, Mukkada VA, Sheil A, et al. Acquired Esophageal Strictures in Children: Morphometric and Immunohistochemical Analyses. Pediatr Dev Pathol. 2022;25(2):124-133.
34. Fassan M, Volinia S, Palatini J, et al.MicroRNA expression profiling in the histological subtypes of Barrett's metaplasia. Clin Transl Gastroenterol 2013;4:e34.
35. Nagaich N, Sharma R, Nijhawan S, Nijhawan M, Nepalia S, Rathore M. Histopathological Profile of Caustic Oesophageal Strictures on Chronic Endoscopic Dilatation: What is the Safe Limit? J Cancer Prev Curr Res 2015; 2:23.
36. Eskander A, Ghobrial C, Mohsen NA, Mounir B, Abd El-Kareem D, Tarek S, et al. Histopathological changes in the oesophageal mucosa in Egyptian children with corrosive strictures: A single-centre vast experience. World J Gastroenterol. 2019;25(7):870–9.
37. Attila T, Fu A, Gopinath N, Streutker CJ, Marcon NE. Esophageal papillomatosis complicated by squamous cell carcinoma. Can J Gastroenterol 2009; 23:415-419.
38. Allam AR, Fazili FM, Khawaja FI, Sultan A. Esophageal carcinoma in a 15-year-old girl: a case report and review of the literature. Ann Saudi Med 2000;20:261-264.
39. Kavin H, Yaremko L, Valaitis J, Chowdhury L. Chronic esophagitis evolving to verrucous squamous cell carcinoma: possible role of exogenous chemical carcinogens. Gastroenterology 1996;110:904-914.
40. Spechler SJ, Schimmel EM, Dalton JW, Doos W, Trier JS. Barrett's epithelium complicating lye ingestion with sparing of the distal esophagus. Gastroenterology. 1981;81:580-583.
41. Rolim I, Rodrigues RV, Bettencourt A, Barros R, Camilo V, Dias Pereira A, et al. Mid-Esophagus Columnar Metaplasia: What Is the Biopathogenic Pathway? Int J Surg Pathol. 2017;25(3):262-265.
42. Ismail-Beigi F, Horton PF, Pope CE 2nd. Histological consequences of gastroesophageal reflux in man. Gastroenterology. 1970;58:163-174.
43. Han JS, Lee SW, Suh KH, Kim SY, Hyun JJ, Jung SW, et al. Pseudoepitheliomatous hyperplasia mimicking esophageal squamous cell carcinoma in a patient with lye-induced esophageal stricture. Korean J Gastroenterol. 2014;63(6):366-8.
44. Barbosa B, Santos B, Mesquita I, Marcos M, Nogueira C, Santos J. Adenocarcinoma arising in a colonic interposition after esophagectomy for benign stricture and review of the literature. J Surg Case Rep. 2018; 2018(10):rjy264.
45. Simões C, Moura M, Noronha Ferreira C, Rosa R, Freire JP, Carrilho Ribeiro L, Tato Marinho R. Lateral Spreading Tumor Arising in an Interposed Colonic Segment. ACG Case Rep J. 2019;6(10):e00245.
46. Kobayashi T, Kimura T, Yoshida M, Sakuramachi S, Ohishi M, Harada Y, et al. Carcinoma of the reconstructed stomach tube following esophageal resection for a benign stricture: report of a case and review of the literature. Surg Today. 1995;25(3):257-60.
47. Theilen TM, Chou AJ, Klimstra DS, LaQuaglia MP. Esophageal Adenocarcinoma and Squamous Cell Carcinoma in Children and Adolescents: Report of 3 Cases and Comprehensive Literature Review. J Pediatr Surg Case Rep. 2016;5:23-29.
48. Liang H, Fan JH, Qiao YL. Epidemiology, etiology, and prevention of esophageal squamous cell carcinoma in China. Cancer Biol Med. 2017;14: 33-41.

49. Karwasra RK, Yadav V, Bansal AR. Esophageal carcinoma in a 17-year-old man. Am J Gastroenterol. 1999;94:1122-1123.
50. Zhen YZ. Isolation and culture of fungi from the cereals in counties of Henan Province--5 with high and 3 with low incidences of esophageal cancer. Zhonghua Zhong Liu Za Zhi. 1984;6:27-29.
51. de Oliveira Junior WE, Felix TF, Pires GDV, Lapa RML, Severino FE, Terra SA, et al. MicroRNA expression profiles in the esophagus of children with caustic stenosis: A pathway towards esophageal cancer? J Pediatr Surg. 2020;55(10):21449.
52. Kasinski AL, Slack FJ. Epigenetics and genetics. MicroRNAs en route to the clinic: progress in validating and targeting microRNAs for cancer therapy. Nat Rev Cancer. 2011;11:849–64.
53. Setrerrahmane S. Xu H. Tumor-related interleukins: old validated targets for new anti-cancer drug development. Mol Cancer 2017;16:153.
54. Sreedharan A, Rembacken BJ, Rotimi O. Acute toxic gastric mucosal damage induced by Lugol's iodine spray during chromoendoscopy. Gut. 2005;54:886-7.
55. Marchand P. Caustic strictures of the oesophagus. Thorax. 1955;10: 171-181.
56. Tustumi F, de Moura DTH, Waisberg J, Herbella FAM. Editorial: Premalignant conditions in the esophagus and stomach. Front Oncol. 2022; 12:1091911.
57. Chaber-Ciopinska A, Kiprian D, Kawecki A, Kaminski MF. Surveillance of patients at high-risk of squamous cell esophageal cancer. Best Pract Res Clin Gastroenterol. 2016;30(6):893–900.
58. Millar AJ, Cox SG. Caustic injury of the oesophagus. Pediatr Surg Int. 2015; 31(2):111–21.
59. Saftoiu A, Hassan C, Areia M, Bhutani MS, Bisschops R, Bories E, et al. Role of gastrointestinal endoscopy in the screening of digestive tract cancers in Europe: European society of gastrointestinal endoscopy (ESGE) position statement. Endoscopy. 2020;52(4):293-304.
60. Olsen AM. Chevalier Jackson lecture. Esophagology: an update. Ann Otol Rhinol Laryngol. 1982;91(6 Pt 1):551-7.
61. Yamasaki Y, Takenaka R, Hori K, Takemoto K, Kawano S, Kawahara Y, et al. Tolerability of magnifying narrow band imaging endoscopy for esophageal cancer screening. World J Gastroenterol. 2015;21:2793-9.
62. Yoshida T, Inoue H, Usui S, Satodate H, Fukami N, Kudo SE. Narrow-band imaging system with magnifying endoscopy for superficial esophageal lesions. Gastrointest Endosc. 2004:288-95.
63. Kiviranta N. Corrosive carcinoma of the esophagus. Acta Otolaryngol. 1952;102:1-9.
64. Valencia C, Prieto J, Jara J, Pesantez P. Esophagogastric Complications After Caustic Ingestion: A Case Report. Cureus. 2022;14(7):e26762.
65. Haefliger L, Jreige M, Du Pasquier C, Ledoux JB, Wagner D, Mantziari S, et al. Esophageal cancer T-staging on MRI: A preliminary study using cine and static MR sequences. Eur J Radiol. 2023;166:111001.
66. Rana SS, Sharma R, Kishore K, Gupta R. High-frequency miniprobe endoscopic ultrasonography in the management of benign esophageal strictures. Ann Gastroenterol. 2020;33(1):25-29.
67. Daniel P, Samanta J, Gulati A, Gupta P, Muktesh G, Sinha SK, et al. Can high-frequency mini-probe endoscopic ultrasonography predict outcome of endoscopic dilation in patients with benign esophageal strictures? Endosc Int Open. 2020 Oct;8(10):E1371-E1378.
68. Rana SS, Sharma R, Gupta R. High-frequency miniprobe endoscopic ultrasonography for evaluation of indeterminate esophageal strictures. Ann Gastroenterol 2018;31:680–684.
69. Wu LF, Wang BZ, Feng JL, Cheng WR, Liu GR, Xu XH, et al. Preoperative TN staging of esophageal cancer: Comparison of miniprobe ultrasonography, spiral CT and MRI. World J Gastroenterol. 2003;9(2):219-24.
70. Wang Z, Guo J, Qin J, Zhang H, Zhao Y, Lu Y, et al. Accuracy of 3-T MRI for Preoperative T Staging of Esophageal Cancer After Neoadjuvant Chemotherapy, With Histopathologic Correlation. AJR Am J Roentgenol. 2019;212(4):788-795.
71. Giganti F, Ambrosi A, Petrone MC, Canevari C, Chiari D, Salerno A, et al. Prospective comparison of MR with diffusion-weighted imaging, endoscopic ultrasound, MDCT and positron emission tomography-CT in the pre-operative staging of oesophageal cancer: results from a pilot study. Br J Radiol. 2016; 89(1068):20160087.
72. Yuan Y, Chen L, Ren S, Wang Z, Chen Y, Jin A, et al. Diagnostic performance in T staging for patients with esophagogastric junction cancer using high-resolution MRI: a comparison with conventional MRI at 3 tesla. Cancer Imaging. 2019; 19(1):83.
73. Alves IPF, Tercioti Junior V, Coelho Neto JS, Ferrer JAP, Carvalheira JBC, Pereira EB, et al. Neoadjuvant chemoradiotherapy followed by transhital esophagectomy in locally advanced esophageal squamous cell carcinoma: impact of pathological complete response. Arq Bras Cir Dig. 2022; 34(3):e1621.
74. Noh SY, Kim HJ, Lee HJ, Park SH, Lee JS, Kim AY, et al. Corrosive-induced carcinoma of esophagus: Esophagographic and CT findings. AJR Am J Roentgenol. 2017;208(6):1237-43.
75. Ramasamy K, Gumaste VV. Corrosive ingestion in adults. J Clin Gastroenterol. 2003;37(2):119-24.
76. Lagergren J, Smyth E, Cunningham D, Lagergren P. Oesophageal Cancer. Lancet. 2017;390:2383–2396.
77. Mukkamalla SKR, Recio-Boiles A, Babiker HM. Esophageal Cancer. In StatPearls; StatPearls Publishing: Treasure Island, FL, USA; 2022.
78. Zhang X, Wang M, Han H, Xu Y, Shi Z, Ma G. Corrosive induced carcinoma of esophagus after 58 years. Ann Thorac Surg. 2012;94(6):2103–5.
79. Yang J, Liu X, Cao S, Dong X, Rao S, Cai K. Understanding Esophageal Cancer: The Challenges and Opportunities for the Next Decade. Front Oncol. 2020;10:1727.
80. Li J, Xu J, Zheng Y, Gao Y, He S, Li H, et al. Esophageal Cancer: Epidemiology, Risk Factors and Screening. Chin. J. Cancer Res. 2021;33: 535–547.
81. Noordzij IC; Curvers WL; Schoon EJ. Endoscopic Resection for Early Esophageal Carcinoma. J Thorac Dis. 2019;11:S713–S722.
82. Vellayappan BA, Soon YY, Ku GY, Leong CN, Lu JJ, Tey J.C. Chemoradiotherapy versus chemoradiotherapy plus surgery for esophageal cancer. Cochrane Database Syst Rev. 2017;8(8):CD010511.
83. Stahl M, Stuschke M, Lehmann N, Meyer HJ, Walz MK, Seeber S, et al. Chemoradiation with and without Surgery in Patients with Locally Advanced Squamous Cell Carcinoma of the Esophagus. J Clin Oncol. 2005;23: 2310–2317.
84. Mann C, Berlth F, Hadzijusufovic E, Lang H, Grimminger PP. Minimally Invasive Esophagectomy: Clinical Evidence and Surgical Techniques. Langenbecks Arch. Surg. 2020;405:1061–1067.
85. Sheikh M, Roshandel G, McCormack V, Malekzadeh R. Current Status and Future Prospects for Esophageal Cancer. Cancers (Basel). 2023; 15(3):765.
86. Chen YJ, Seak CJ, Cheng HT, Chen CC, Chen TH, Sung CM, et al. Evaluation of a diagnostic and management algorithm for adult caustic ingestion: New concept of severity stratification and patient categorization. J Pers Med. 2022;12(6):989.
87. Okonta KE, Tettey M, Abubakar U. In patients with corrosive oesophageal stricture for surgery, is oesophagectomy rather than bypass necessary to reduce the risk of oesophageal malignancy? Interact Cardiovasc Thorac Surg. 2012;15(4):713-5.