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TOPIC HIGHLIGHT

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Pneumo-CT assessing response to neoadjuvant therapy in esophageal cancer: Imaging-pathological correlation

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Abstract

Pneumo-computed tomography (PnCT) is a technique primarily developed and used to study stenotic lesions of the esophagus, gastroesophageal junction and stomach for pre-surgical planning. It helps to define both upper and lower borders of neoplasms located in the aforementioned areas. It achieves maximum lumen distension with CO_2 highlighting thickened areas of the esophageal wall, thus allowing an accurate quantification of their extents. Although there are other alternatives for distension (oral contrast agents, water and effervescent granules), they may be suboptimal. Patients with locally advanced esophageal cancer have a dismal prognosis despite surgical resection. Therefore, neoadjuvant treatment strategies using radiation therapy and chemotherapy were developed to improve survival. Neoadjuvant therapy improves esophageal tumor prognosis in a substantial proportion of patients, and the use of imaging techniques is mandatory to detect their response. PnCT combined with virtual endoscopy and multiplanar reconstruction enhances morphologic details in esophageal cancer, and thus would allow an improved assessment of response to neoadjuvant treatment. Therefore, more information could be provided to assess the efficacy of pre-surgical treatment. We describe the potential use of PnCT to assess the response to neoadjuvant therapy in esophageal cancer with an imaging pathologic correlation.

Key words: Esophagus; Cancer; 64-multidetector computed tomography; Neoadjuvant treatment; Assessment response

Core tip: Pneumo-computed tomography may be a useful technique to monitor neoadjuvant therapy response as it enhances morphologic details. Besides, it provides key information for surgical planning as it helps to define both upper and lower borders of esophageal or gastro-esophageal neoplasms in a single examination.

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INTRODUCTION

Esophageal carcinoma is the sixth most common cause of cancer deaths worldwide[1]. There are approximately 14000 new cases of esophageal cancer per year in the United States, half of which are adenocarcinomas[2]. It is currently the most rapidly increasing cancer in the United States and Western Europe[3]. Prognosis is poor, with an overall survival of less than 10% within 5 years[4,5]. There-

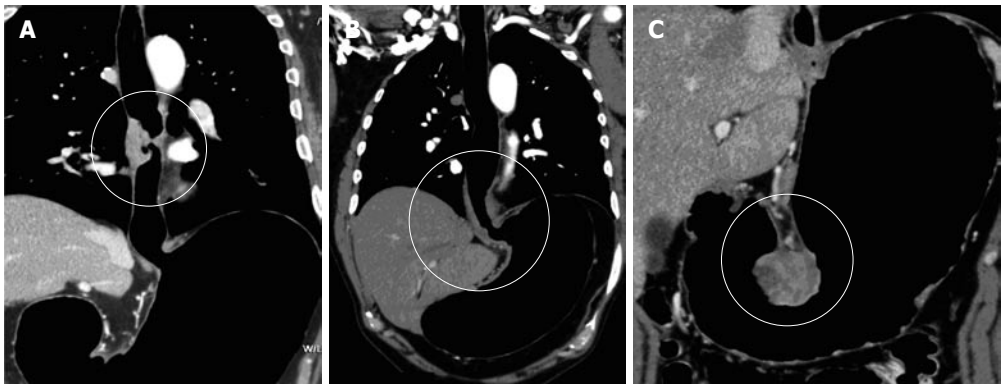

Figure 1 Pneumo-computed tomography in esophageal and gastric neoplasms. A: Pneumo-computed tomography (PnCT) multiplanar reconstructions (MPR) coronal soft tissue window reconstruction depicting involvement of mid-thoracic esophagus. Note detailed demonstration of location; B: PnCT MPR coronal soft tissue window reconstruction depicting involvement of the gastroesophageal junction; C: PnCT MPR coronal soft tissue window shows a GIST tumor arising from gastric wall.

fore, there is need to improve the survival rate for patients with this disease, by earlier diagnosis when prognosis is more favorable, and/or by improving its therapy[6].

Neoadjuvant treatment strategies have been developed to improve survival[7]. Under current standards, chemoradiation is administered preoperatively in the majority of patients with advanced locoregional disease[8]. Thence, the ability to predict response to this combined therapy is clearly desirable.

Despite the importance of accurate pre-operative staging of esophageal neoplasm, there isn't a well accepted method to do so by imaging[9]. The spectrum of diagnostic modalities most commonly used used besides computed tomography (CT), includes endoscopic ultrasound, positron emission computed tomography (PET)/CT and magnetic resonance imaging (MRI). The strength of endoscopic ultrasound is in its role in the initial staging of esophageal cancer. One weakness is its inaccuracy for staging after neoadjuvant therapy because of its inability to distinguish inflammation and fibrosis from residual cancer[10].

Even though PET/CT is primarily indicated to look for distant metastases, it has also been used as a noninvasive test to evaluate response after neoadjuvant therapy before surgical resection[11,12]. One of its drawbacks lies in the fact that it does not provide accurate information for surgical planning because of lack of distension of the esophageal lumen.

MRI studies using routine clinical protocols have demonstrated a limited ability to evaluate esophageal anatomy[6]. Dynamic contrast-enhanced MRI is an emerging approach that needs further validation to be used in daily practice.

PneumoCT (PnCT) is a recently described technique that optimizes tumor visualization in the esophageal wall, gastroesophageal junction (GEJ) and stomach[13] (Figure 1). It achieves maximum lumen distension, highlighting thickened wall areas[13,14].

The purpose of this review is to present a correlation between PnCT findings and post surgical pathology in order to evaluate the response of esophageal cancer to neoadjuvant therapy.

First, we discuss the basic technique of how to perform PnCT. Second, we describe the reconstruction steps followed by the classification and CT parameters used to assess response to neoadjuvant therapy. Finally, we present clinical examples of pre- and post-neoadjuvant cases with imaging-pathological correlation.

PNCT TECHNIQUE

Patients are given before their imaging appointment an information sheet describing the procedure in detail including mention of slight discomfort that may be experienced by the esophageal distension. Patients with an 8-h pre-procedural fasting are received in the radiology department by a nurse, and a peripheral venous line is placed. Once in the CT suite, after administration via spray of a local anesthetic a lubricated Foley catheter is introduced transorally or transnasally, placing its distal tip below the cricopharyngeal muscles (Figure 2).

Continuous and sustained supply of CO_2 is maintained during the CT acquisition, with a pressure between 10 and 20 mmHg. We use the the same CO_2 pump as in CT-Colonography (Protocol pump, PROTOC02L, E-Z-EM, Inc., Lake Success, NY, United States). Patients are instructed to hold the air and avoid burping during the procedure.

Pn6CTs are performed at our institution with Aquilion 64-row multidetector computed tomography (MDCT) (Toshiba Inc, Tokyo, Japan) with the following technical parameters: 0.5 mm slices, 0.25 mm table feed, 50 mAs, 120 kV, 0.75 s rotation time and 0.875 pitch. Anterior and lateral scout views are obtained to protocol the scans. We perform two cervico-thoraco-abdominal phases, the first non-enhanced and the second enhanced. The time required for each acquisition is approximately of 8 seconds. Nonionic iodinated contrast (Iobitridol, Xenetix® 350; Guerbet, France) at a dose of 1 mL/kg is infused using an automatic injection pump at a flow of 2.5 mL/s. No oral contrast is used. We haven't experienced a major adverse events specific to the CO_2 insufflation. The typical effective radiation dose is 18 mSv.

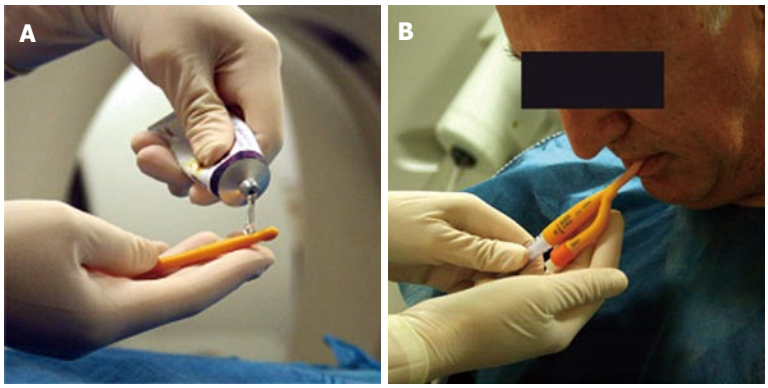

Figure 2 Pneumo-computed tomography technique. A: The tip of the Foley catheter is lubricated with gel anesthesia; B: The Foley catheter is introduced transorally.

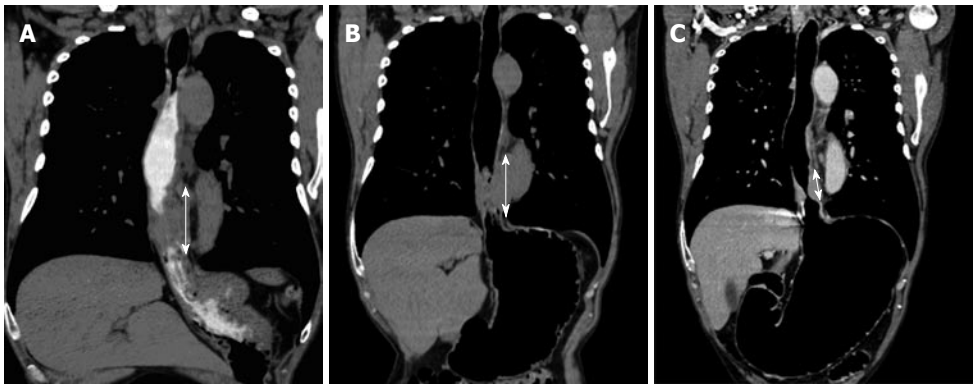

Figure 3 Comparison of different distention options in the same patient with diagnosis of adenocarcinoma. A: Distension with positive oral contrast, the double arrow shows the extent of the lesion, which is larger than b and c, thus overestimating the neoplasm size; B: Distension with effervescent granules, the double arrow shows the tumor extent which is larger than c, still overestimating its size; C: Distension with pneumo-computed tomography technique, the double arrow shows the extent of the wall thickening which is shorter than a and b in accordance with the surgical specimen.

DISTENSION OPTIONS

Other well-known alternatives for esophageal and gastric lumen distension (*i.e.*, oral contrast agents or effervescent granules) are used in daily practice[15]. However, distention may be suboptimal due to rapid transit of contrast and the required esophageal distension cannot always be achieved[16]. Oral contrast enhancement may generate confusing images, with the same density as the tumor[17,18]. Moreover, a suboptimal distension can cause distortion both in the quantification of the extension and in the degree of wall thickening (Figure 3).

RECONSTRUCTION STEPS AND INTERPRETATION

Once acquired, images are sent to a Vitrea 2 working station (Vital Images, Inc, Minnesota, United States) for evaluation. Multiplanar reconstructions (MPR) and curved MPRs are performed with different window settings in order to characterize the lesion. In addition, we performed 3D reconstructions with different window settings (surface-shaded and transparent modes similar to the images obtained in single- and double-contrast barium studies). These images are easy to understand and allow visualization of the tumor. Finally, we obtain fly through views of the esophageal lumen and generate endoluminal views akin to esophagoscopy, to further asses lesion morphology.

A description of shape and location of the lesion as well as measurements of size and wall thickening are performed. Also, we evaluate for presence of periesophageal fat stranding, adenopathy, and extraesophageal disease Information regarding panoramic and longitudinal extent of the esophageal lesion is obtained.

INDICATIONS

This technique was originally developed for GEJ stenosis, since the GEJ is a known difficult area to distend with traditional double contrast esophagograms[13,14]. The obtained gastric distension led to an adequate definition of both the upper and lower borders of GEJ lesions and in turn proved to be helpful for surgical planning[13,14].

We then extended its use to all cases of esophageal stenosis impeding the passage an endoscope and also to cases were endoscopy was contraindicated. The latter include cases in which a noninvasive method for endoluminal lesion characterization stenosis grading, and beyond stricture visualization of the esophagus and/or the stomach is needed.

Palliation therapy with self-expandable stenting is the method of choice[19] both in unresectable esophageal tumors due to distant metastasis or local invasion, and

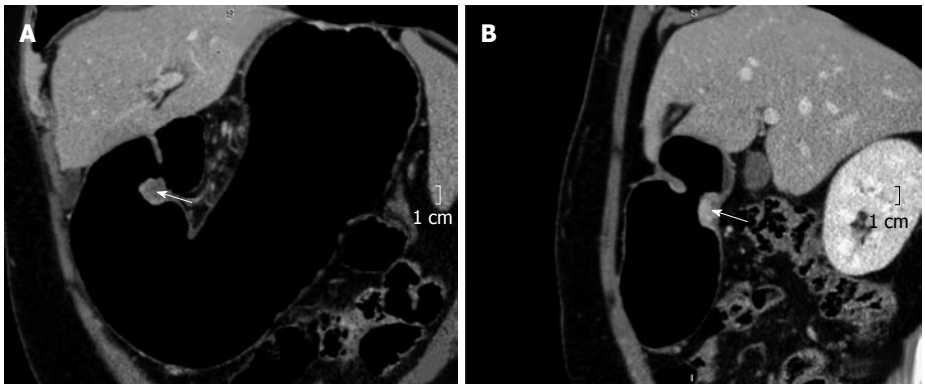

Figure 4 Adenocarcinoma of the pylorus. A: Coronal multiplanar reconstructions (MPR) reconstruction, the arrow shows the tumor and its relationship with the pylorus; B: Sagital MPR reconstruction, the arrow shows the tumor and its relationship with the pylorus.

Table 1 Dworak classification for gastrointestinal tumors

	Dworak classification
Dworak grade 0	Is define as no regression
Dworak grade 1	Is define as prevalence of active cells and fibrosis/necrosis
Dworak grade 2	Is define as many of fibrosis or necrosis with active cells easier to find
Dworak grade 3	Is define as scarce neoplastic cells, hard to detect
Dworak grade 4	Is define as absence of tumor cells

in high-risk patients. In these patients, the definition of both upper and lower limits of the lesion in the longitudinal axis provided by PnCT allowed determining the stent graft length and the need for a valved stent. Thus no further barium studies are required.

Although the stomach can be well distended with other contrasts, such as water, milk, effervescent granules, the pyloric area is also a known difficult area to distend. Due to the optimal distension obtained with PnCT, we began to use this technique for distal stomach pathology with suspected pyloric involvement (Figure 4).

TOMOGRAPHIC PARAMETERS USED TO ASSESS RESPONSE TO POST-NEOADJUVANT THERAPY

Esophageal tumors exhibit increased expression of proangiogenic factors such as basic fibroblast growth factor (bFGF) and vascular endothelial growth factor[20,21]. This form of malignancy is associated with greater vascularization and has a higher microvascular density compared with normal esophageal tissue and precancerous lesions[20-23]. These properties suggest a valid pathologic basis upon which quantifying the density with PnCT could not only detect esophageal tumors and but also evaluate their response to neoadjuvant therapy.

The following CT parameters are measured to evaluate (or restage) response to neoadjuvant therapy: wall thickening, density, and presence of adenopathy.

We compare the maximum diameters of pre- and post-neoadjuvant therapy for wall thickening evaluation. To analyze its density, we make the same pre- and post-neoadjuvant therapy comparison by placing a region of interests (ROI) at the same site of greatest wall thickening, excluding areas of low density representing wall necrosis. Finally, we compare adenopathy sizes as well before and after neoadjuvant therapy.

IMAGING-PATHOLOGIC CORRELATION

The use of neoadjuvant therapy began to be practiced for rectal cancer[24]. Its use was extended to esophageal and other gastrointestinal cancers[24]. Since neoadjuvant therapy changes the internal structure of tumor, pathologists have been faced to reconsider the staging of these neoplasms resected after receiving chemo-radiation. The appearance of fibrosis and necrosis confirms the action of therapy and constitutes the basis for several new staging classifications[24].

In 1997, Dworak *et al*[24] presented a pathological classification for rectal cancer based mainly on the difficulty of highlighting viable tumor cells in a fibronecrotic stroma. Thus, five categories were identified (Table 1). Due to its usefulness, this classification, has also been extrapolated to other gastrointestinal tumors[25].

CORRELATION BETWEEN THE PN64MDCT AND DWORAK CLASSIFICATION

We use clinical examples to show the change observed in the CT findings comparing pre- and post-therapy PnCT scans with correlation with the Dworak classification obtained after surgery.

Wall thickening persistence is evident in the pre- and post-neoadjuvant therapy measure comparison at the same level (Figure 5). Placing the ROI on the site of maximum wall thickening, the density in Hounsfield Units (HU) increases from (90.8 HU) before to 95.7 HU after therapy. The increase in the density may be given by the persistence of active cells containing proangiogenic factors (Figure 5). Additionally, an adenopathy monitor-

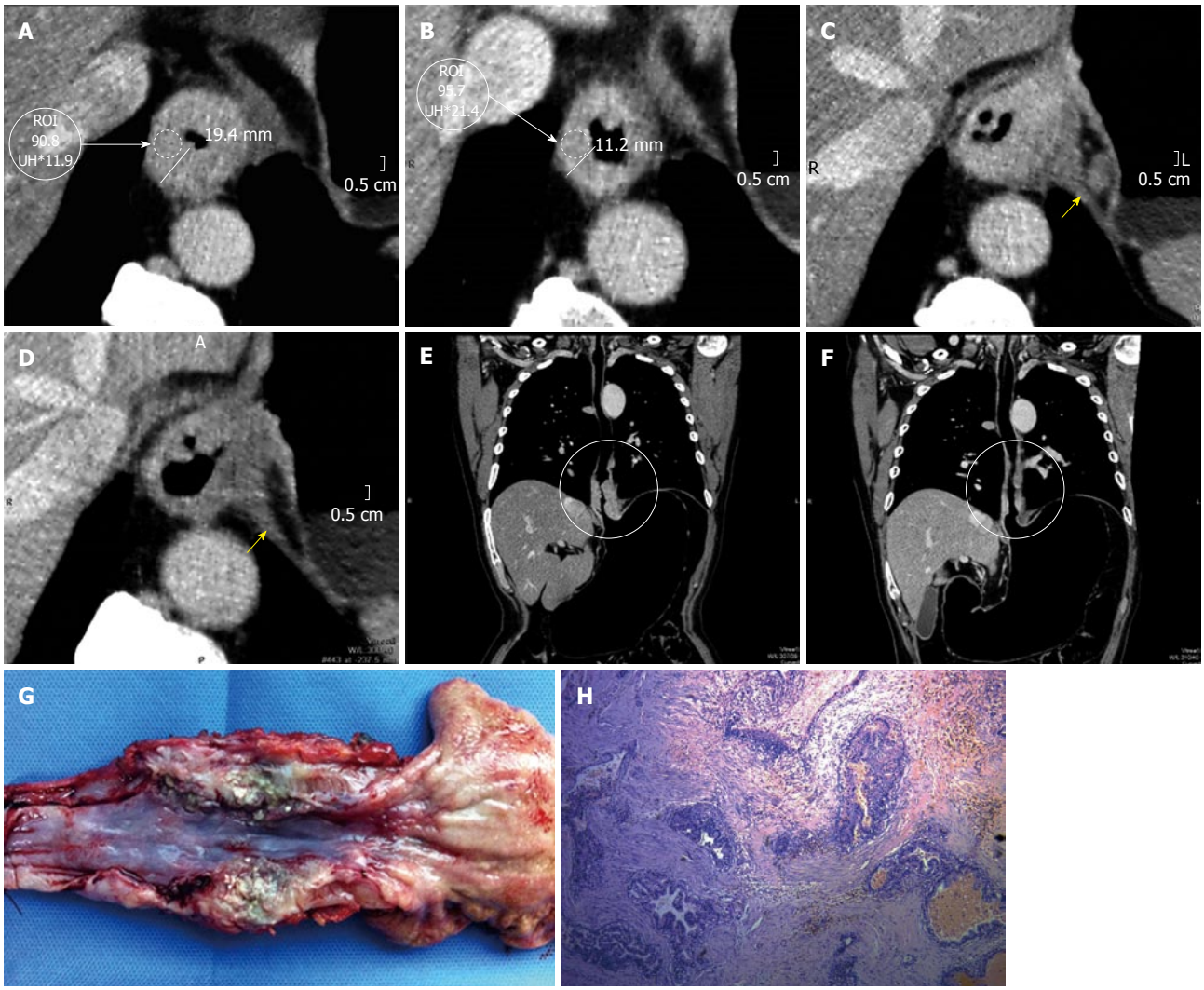

Figure 5 Advanced adenocarcinoma. Dworak grade I, prevalence of active cells. A: Axial pre neoadjuvant therapy image. Both wall thickness and density are measured; B: Axial post-neoadjuvant therapy image reveals persistence of the wall thickening and almost no variation in density; C: Axial pre-neoadjuvant therapy image, the arrow is pointing to a lymphadenopathy; D: Axial post-neoadjuvancy image reveals resolution of the adenopathy; E: Coronal multiplanar reconstructions (MPR) pre-neoadjuvancy reconstruction. The circle shows the long axis compromise of the tumor; F: Coronal MPR post-therapy reconstruction. The circle shows the long axis of the tumor and its precise location; G: Surgical specimen of total esophagectomy and upper polar gastrectomy. Open piece shows an important thickening of the lower esophagus, at squamo-columnar junction recognizes a polypoid lesion and poorly defined borders. The remaining gastric mucosa presents edematous folds; H: Section shows at gastroesophageal junction one degrade injuries ranging from low-grade dysplasia to invasive adenocarcinoma. The primary lesion is below the squamocolumnar junction. Generally infiltrates shaped surface (submucosa) with occasional foci in muscle layer and extends in the form of multiple separate foci below esophageal epithelium. Proximal margin: adenocarcinoma foci observed at adventitia and submucosa layers. Tumor is seen infiltrating striated muscle tissue.

ing can be performed, determining it's evolution.

On the other hand, the pre- and post- comparison of the wall thickness in Figures 6 and 7 at the same level demonstrate a decrease of over 50% in the measured density, for instance before 85.7 HU and after 36.4 HU chemotherapy and radiotherapy (Figures 6-8). This decrease in density could be explained by the presence of extensive areas lacking proangiogenic factors. The disappearance of the lymphadenopathy can also be observed.

In patients without response to neoadjuvant therapy (Dworak I), there was no change in the density of the tumor when we compared the PnCT pre- and post- therapy. This finding could be explained by the presence in the active cells of bFGF and vascular endothelial growth factor. Conversely, there is reduction in the thickness and in the Hounsfield Units density (between 33% and 46% less) of the tumor in those patients with a good response to therapy, correlating well with a significant regression in the post-surgical pathological staging of Dworak Ⅲ or Ⅳ neoplasms.

CONCLUSION

PnCT is a useful non-invasive imaging technique for evaluating esophageal and gastroesophageal tumors, allowing a precise evaluation of their size, location, local extension and regional adenopathy a single examination[13,14].

Further, PnCT provides key pre-surgical planning information, since it defines both upper and lower borders of neoplasms located in the GE junction[13,14].

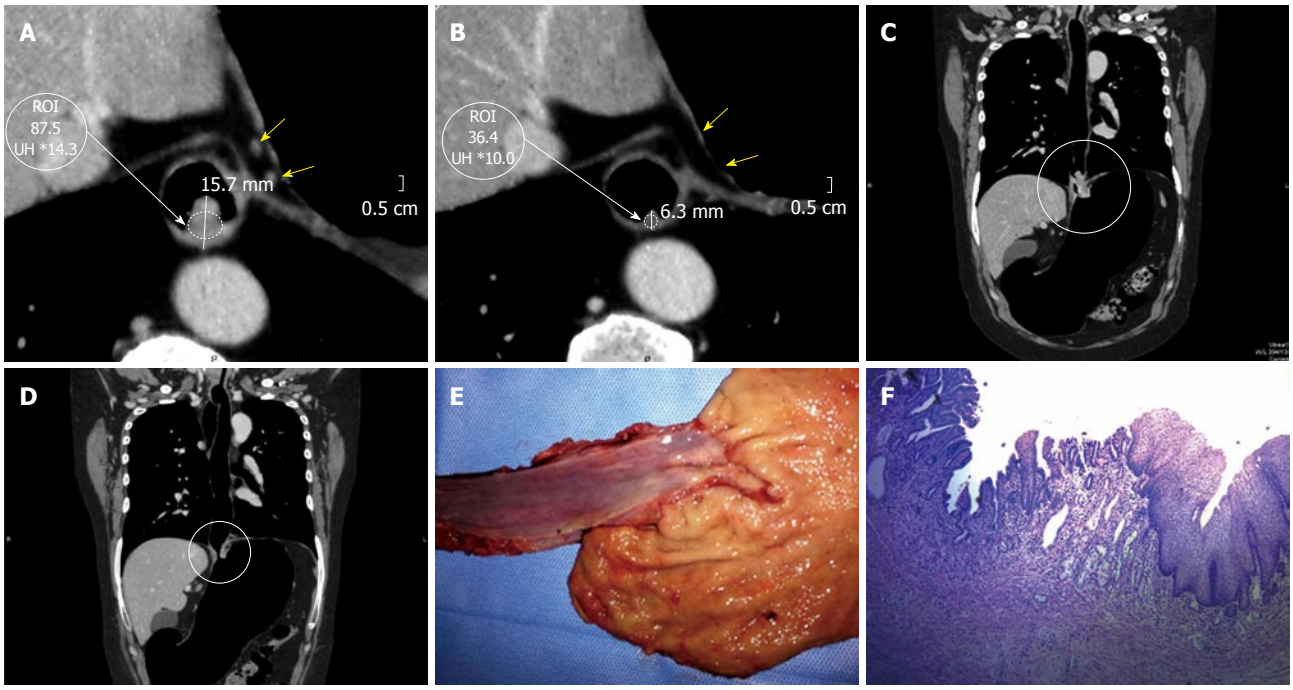

Figure 6 Advanced adenocarcinoma of the gastroesophageal junction. Dworak grade 2, large areas of fibrosis or necrosis with active cells. A: Axial pre-therapy image. Both wall thickness and density are measured. Yellow arrows indicate two small lymph nodes; B: Axial post-therapy image reveals a clear decrease of tumor size and in density. Lymph nodes are not visible; C: Coronal multiplanar reconstructions (MPR) pre-therapy reconstruction. The circle shows the long axis of the tumor; D: Coronal MPR after therapy reconstruction. Note marked decrease in tumor size; E: Surgical specimen of total esophagectomy and upper polar gastrectomy correlating well with the lesion demonstrated with pneumo-computed tomography. Open piece, is recognized at the level of the gastro-esophageal junction an indurated area with diminished mucosal folds and elevated edges with whitish nodule and firm consistency; F: Submucosal layer with nodular accumulations of atypical epithelial cells scant cytoplasm that are arranged in small tubular structures, cords or dispersed. Nodules are found at the distal esophagus and cardia underlying mucosa. Linfovasculares tumor emboli are observed. In small area is observed submucosal fibrosis, chronic inflammation and congestion. At the level of the gastro-esophageal junction is observed extensive intestinal metaplasia to intramucosal carcinoma focus. Preserved oxyntic gastric mucosa.

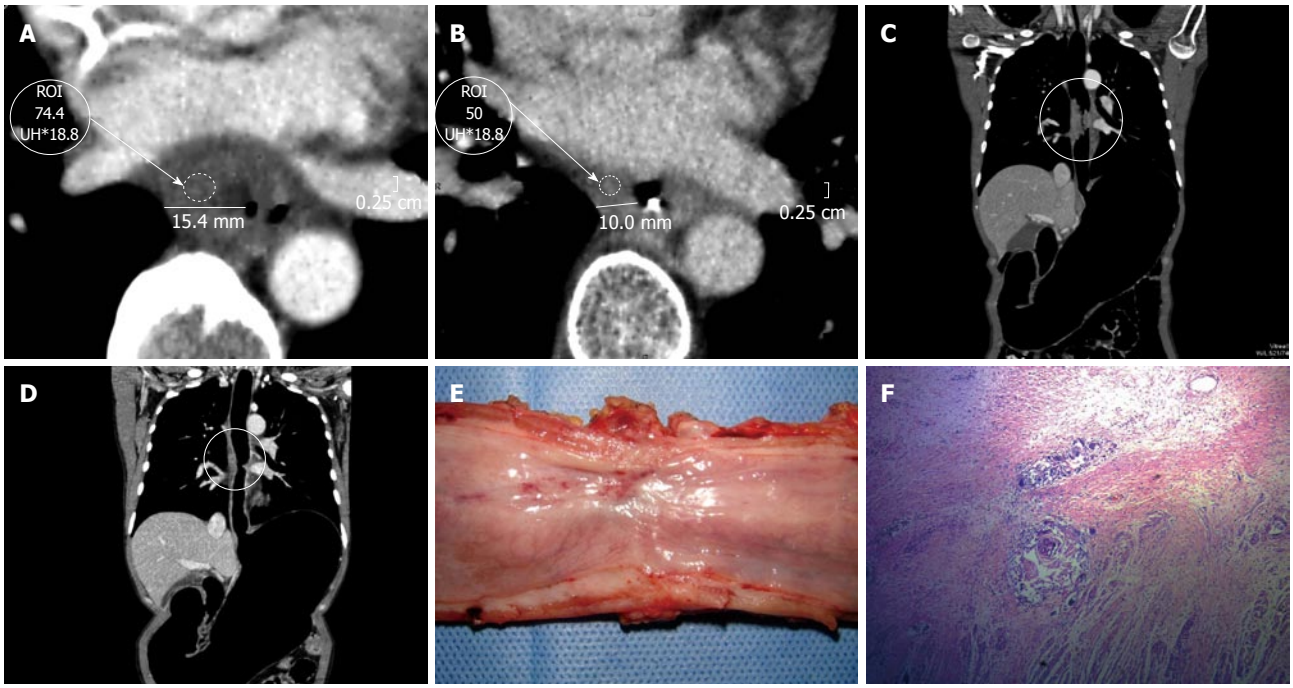

Figure 7 Epidermoid carcinoma. Dworak grade 3, scarce neoplastic cells. A: Axial pre-neoadjuvant therapy image. Both wall thickness and density are measured; B: Axial post- neoadjuvant therapy image reveals a clear decrease of the wall thickening and density; C: Coronal multiplanar reconstructions (MPR) pre-neoadjuvant therapy reconstruction. The circle shows the long axis of the tumor; D: Coronal MPR post-neoadjuvant therapy reconstruction with decrease in tumor size; E: Surgical specimen of total esophagectomy. Open piece, shows thickening at the middle third of the esophagus with an ulcerated area; F: The sections shows at submucosal layer a nodular accumulation of atypical epithelial cells with vesicular nuclei and scant cytoplasm that are arranged in small tubular structures. Also the submucosa presents fibrosis, chronic inflammation and congestion. Mucosal layer shows conserved squamous epithelium and focal fibrosis regression suggesting changes.

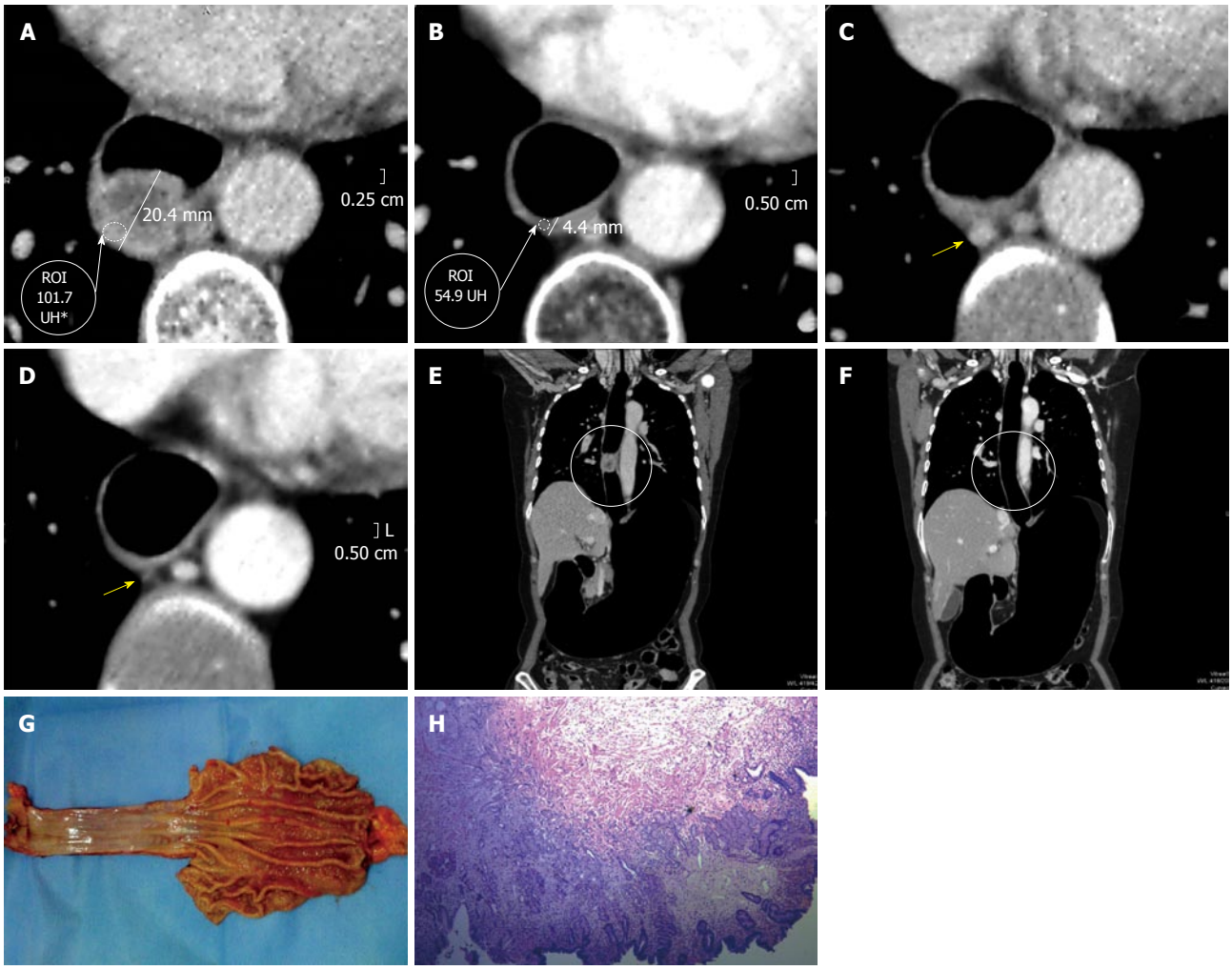

Figure 8 Epidermoid carcinoma of the thoracic esophagus [CME #5]. Dworak grade 4, absence of tumor cells. A: Axial pre-neoadjuvant therapy image. Both wall thickness and density are measured; B: Axial post- neoadjuvant therapy image reveals a clear decrease of the wall thickening and density; C: Axial pre- neoadjuvant therapy image, the arrow is pointing to adenopathy; D: Axial post-neoadjuvancy image reveals disappearance of adenopathy; E: Coronal multiplanar reconstructions (MPR) pre-neoadjuvant therapy reconstruction. The circle shows the long axis of the tumor; F: Coronal MPR reconstruction post- neoadjuvant therapy. The neoplasm is not longer detected; G: Surgical specimen of total esophagectomy and upper polar gastrectomy. Open piece, is recognized at the level of the gastro-esophageal junction an area of white-depressed with elevated edges; H: Squamous epithelium with acanthosis, conserved cell polarity. Fibrohialinosis in lamina propria and submucosa with lymphocytic infiltrate. Absence of atypical cells. At the level of the gastroesophageal junction shows a sector with intestinal metaplasia in the stomach side, negative for dysplasia.

We also demonstrate the PnCT findings correlate with the Dworak pathologic classification and could allow assessing the response of esophageal neoplasms to neoadjuvant therapy. This is crucial regarding the overall prognosis and therapeutic strategy.

Our next goal is to prove in a prospective, blinded and randomized study the accuracy of PnCT to asses response to neoadjuvant therapy in esophageal neoplasms and its correlation with post resection pathological staging.

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