

World Journal of *Gastroenterology*

World J Gastroenterol 2017 December 14; 23(46): 8109-8262



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World Journal of Gastroenterology (*WJG*) is now indexed in Current Contents[®]/Clinical Medicine, Science Citation Index Expanded (also known as SciSearch[®]), Journal Citation Reports[®], Index Medicus, MEDLINE, PubMed, PubMed Central and Directory of Open Access Journals. The 2017 edition of Journal Citation Reports[®] cites the 2016 impact factor for *WJG* as 3.365 (5-year impact factor: 3.176), ranking *WJG* as 29th among 79 journals in gastroenterology and hepatology (quartile in category Q2).

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NAME OF JOURNAL
World Journal of Gastroenterology

ISSN
ISSN 1007-9327 (print)
ISSN 2219-2840 (online)

LAUNCH DATE
October 1, 1995

FREQUENCY
Weekly

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7901 Stoneridge Drive, Suite 501,
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PUBLICATION DATE
December 14, 2017

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Retrospective Study

Endoscopic ultrasound staging for early esophageal cancer: Are we denying patients neoadjuvant chemo-radiation?

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Author contributions: Luu C provided the conception and design; Fontaine JP contributed to acquisition, analysis, or interpretation of data; all authors drafted, revised and finally approved of the manuscript.

Institutional review board statement: This study was reviewed and approved by the Institutional Review Board at Moffitt Cancer Center.

Informed consent statement: This is a retrospective study using de-identified clinical data that was obtained after approval from the institution's IRB. Since all information was anonymous and does not impact patients in any way, no patient consent was required.

Conflict-of-interest statement: We have no financial relationships to disclose.

Data sharing statement: No additional data are available

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Manuscript source: Unsolicited manuscript

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Received: January 23, 2017

Peer-review started: January 27, 2017

First decision: May 12, 2017

Revised: July 4, 2017

Accepted: August 2, 2017

Article in press: August 2, 2017

Published online: December 14, 2017

Abstract

AIM

To evaluate the accuracy of endoscopic ultrasound (EUS) in early esophageal cancer (EC) performed in a high-volume tertiary cancer center.

METHODS

A retrospective review of patients undergoing esophagectomy was performed and patients with cT1N0 and cT2N0 esophageal cancer by EUS were evaluated. Patient demographics, tumor characteristics, and treatment were reviewed. EUS staging was compared to surgical pathology to determine accuracy of EUS. Descriptive statistics was used to describe the cohort. Student's *t* test and Fisher's exact test or χ^2 test was used to compare variables. Logistic regression analysis was used to determine if clinical variables such as

tumor location and tumor histology were associated with EUS accuracy.

RESULTS

Between 2000 and 2015, 139 patients with clinical stage I or II A esophageal cancer undergoing esophagectomy were identified. There were 25 (18%) female and 114 (82%) male patients. The tumor location included the middle third of the esophagus in 11 (8%) and lower third and gastroesophageal junction in 128 (92%) patients. Ninety-three percent of patients had adenocarcinoma. Preoperative EUS matched the final surgical pathology in 73/139 patients for a concordance rate of 53%. Twenty-nine patients (21%) were under-staged by EUS; of those, 19 (14%) had unrecognized nodal disease. Positron emission tomography (PET) was used in addition to EUS for clinical staging in 62/139 patients. Occult nodal disease was only found in 4 of 62 patients (6%) in whom both EUS and PET were negative for nodal involvement.

CONCLUSION

EUS is less accurate in early EC and endoscopic mucosal resection might be useful in certain settings. The addition of PET to EUS improves staging accuracy.

Key words: Esophageal cancer; Endoscopic ultrasound; Staging; Early esophageal cancer; Endoscopic mucosal resection

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Core tip: Endoscopic ultrasound (EUS) is an important and widely used staging modality in esophageal cancer. However, our study corroborates other reports that EUS is less accurate in early cancer. The use of positron emission tomography in this setting improves rates of accurate staging. Also, more liberal use of endoscopic mucosal resection will potentially improve staging in early esophageal cancer. Further evaluation of the under-staged group in this review is needed to determine if unrecognized nodal disease by preoperative staging workup in early stage esophageal cancer affects long-term survival or disease-free interval.

Luu C, Amaral M, Klapman J, Harris C, Almhanna K, Hoffe S, Frakes J, Pimiento JM, Fontaine JP. Endoscopic ultrasound staging for early esophageal cancer: Are we denying patients neoadjuvant chemo-radiation? *World J Gastroenterol* 2017; 23(46): 8193-8199 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v23/i46/8193.htm> DOI: <http://dx.doi.org/10.3748/wjg.v23.i46.8193>

INTRODUCTION

In the United States, an estimated 16910 cases

of esophageal cancer will be diagnosed each year and 15690 deaths are expected from the disease^[1]. Approximately 50% of patients initially present with unresectable or metastatic disease^[1]. Early stage disease carries a better prognosis with five-year overall survival (OS) ranging from 80%-93% in stage I disease after esophagectomy^[2,3]. For locally advanced disease (T3N0 or TxN+), the addition of neoadjuvant therapy to surgical resection improves survival and is currently standard of care in the United States^[4]. Management of T2N0 esophageal cancer is more controversial. In the randomized trial by van Hagen *et al*^[5] which demonstrated a survival benefit to neoadjuvant therapy, T2N0 patients were included in the trial; however, Mariette *et al*^[6] did not demonstrate a survival benefit for neoadjuvant chemoradiotherapy in stage I and II esophageal cancer.

Therefore, clinical staging is critical in determining optimal therapy for esophageal cancer. Modalities for clinical staging include computed tomography (CT), positron emission tomography (PET), and endoscopic ultrasound (EUS). Magnetic resonance imaging (MRI) is not generally used for staging at our institution though it may be useful in certain circumstances. In a systematic review of PET staging, the reported sensitivity and specificity for locoregional metastasis was 0.51 and 0.84, respectively^[7]. Specificity for distant metastasis was higher at 0.97. EUS is another key component of clinical staging and is routine in evaluating locally advanced esophageal cancer^[8]. When compared to various staging modalities, EUS is more accurate in assessing locoregional disease. In a meta-analysis of EUS studies by Puli *et al*^[9], the sensitivity and specificity of EUS for defining tumor depth was 80%-90% and more than 90%, respectively, with increased accuracy for more advanced T stage. In the same study, the pooled sensitivity of EUS for nodal staging was 84.7% and the specificity was 84.6%. The addition of fine needle aspiration (FNA) of equivocal lymph nodes increased the sensitivity and specificity of nodal staging to 96.7% and 95.5%, respectively^[7].

Despite its utility in locoregional staging, EUS is reported to be less accurate in early disease. A review of studies of EUS in early esophageal cancer reported a 65% tumor stage concordance between EUS and pathology^[9]. It is especially challenging to differentiate between T2 tumors that invade the muscularis propria and T3 tumors, which invade the adventitia. The distinction is critically important, as it determines which patients should undergo upfront surgery and which would benefit from neoadjuvant therapy prior to curative resection. In addition, distinguishing between benign reactive lymph nodes and lymph node metastasis can be challenging, although FNA can improve accuracy. This study explores our institution's experience with early stage cT1N0 and cT2N0 esophageal cancer and evaluates variables which affect EUS staging. In this manner, we aim to elucidate

Table 1 Clinicopathologic characteristics *n* (%)

Characteristics	
Mean 64.9 yr (range 40-83)	
Gender	
Male	114 (82)
Female	25 (18)
Tumor location	
Middle 1/3 of esophagus	11 (8)
Lower 1/3 of esophagus and GEJ	128 (92)
Tumor histology	
Adenocarcinoma	129 (92.8)
Squamous cell carcinoma	10 (7.2)
Clinical stage	
T1N0	110 (79.1)
T2N0	29 (20.9)
Type of esophagectomy	
Three-field	2 (1.4)
Transhiatal	26 (18.7)
Ivor-Lewis	111 (79.9)
Adjuvant therapy	
Chemotherapy	6 (4.3)
Chemoradiation	3 (2.2)
None	130 (93.5)

factors which can improve staging and allow for optimal treatment of esophageal carcinoma.

MATERIALS AND METHODS

A retrospective chart review was performed and patients who underwent esophagectomy for malignancy from 2000 to 2015 at a single institution were identified. Patients who were clinically staged as T1N0 (cT1N0) and T2N0 (cT2N0) were identified. Over this time period, there were also 70 patients with cT1a esophageal carcinoma who underwent endoscopic mucosal resection (EMR). These patients were not included into the study because complete pathologic staging, *i.e.*, nodal staging, would not be obtainable. Patient demographics, tumor characteristics, operative treatment and perioperative outcomes, surgical pathology, and long term outcomes were recorded.

Clinical staging was performed by EUS for all patients in addition to a combination of CT and PET imaging. The majority of patients (128/139) underwent EUS at our institution. EUS was performed by two gastroenterologists (Harris C and Klapman J) who have advanced training in EUS and have seven and 12 years of EUS experience, respectively. Each endoscopist performed an average of 150 EUS procedures a year. The radial echoendoscope was used by both endoscopists, but CH also adds the linear echoendoscope to evaluate the nodal mediastinal stations: 2R, 2L, 4R, 4L, 5, 6, 7, 8, and 9. Of note, the processor was updated within the last 3 years from an Aloka SSD-5000 (Aloka Co., Ltd., Tokyo, Japan) to an Aloka alpha 10 (Aloka Co., Ltd., Tokyo, Japan). Ultrasound-guided fine needle aspiration of lymph nodes was also performed during the procedure for equivocal or suspicious lymph nodes. EUS and other clinical

Table 2 Comparison of clinical and pathologic staging for cT1N0 and cT2N0 sub-groups

	Clinical stage		Pathologic stage		
	cT1N0	pTisN0	pT1N0	pT2-3N0	pN+
	110	22	67	9	12
	cT2N0	pTis-1N0	pT2N0	pT3N0	pN+
	29	15	6	1	7
Total	139	37	73	10	19

staging modalities were not repeated for patients who had completed the procedure at an outside facility.

After complete preoperative evaluation, all patients underwent esophagectomy without any neoadjuvant chemotherapy, radiation, or chemoradiation. Type of esophagectomy was determined by the judgment of the operating surgeon and included minimally invasive and open approaches. For Ivor-Lewis esophagectomies, thoracic lymphadenectomy was also performed to include mediastinal lymph node stations 7-9. Surgical specimens were staged by the tumor-node-metastasis (TNM) classification according to American Joint Committee on Cancer guidelines. Accuracy rates of EUS were determined by comparing EUS tumor depth and nodal staging to depth and nodal status on surgical pathology. Patients who were found to have more advanced disease on surgical pathology than suggested by preoperative work-up were referred to medical and radiation oncology for discussion of adjuvant therapy.

Statistical analysis was carried out by SPSS software version 23 (Chicago, IL, United States). Descriptive statistics was used to describe the cohort, with means and medians for continuous variables and frequencies and percentages for categorical variables. Student's *t* test and Fisher's exact test or χ^2 test was used to compare variables. Two-sided *P*-value was used with *P* < 0.05 considered statistically significant. Logistic regression analysis was used to determine if clinical variables such as tumor location and tumor histology were associated with EUS accuracy. Institutional review board approval was obtained prior to initiation of the study.

RESULTS

Between 2000 and 2015, 139 patients with early stage esophageal carcinoma (cT1N0 and cT2N0) were identified. Patient demographics and tumor characteristics are outlined in Table 1. Briefly, there were 25 (18%) female and 114 (82%) male patients with tumors predominantly in the lower third of the esophagus and the gastroesophageal (GE) junction. Ninety-three percent of patients had adenocarcinoma and 7% had squamous cell carcinoma on final pathology. Clinical staging was as follows: 110 (79%) patients had cT1N0M0 and 29 (21%) patients had cT2N0M0 tumors. Type of surgical resection included three-field

esophagectomy (2/139), transhiatal esophagectomy (26/139), and Ivor-Lewis esophagectomy (111/139). Fifty-three (38%) procedures were by a minimally invasive approach (laparoscopic or robotic-assisted). The median lymph node count was 12 (range 1-63).

For the entire cohort, preoperative EUS staging matched the final surgical pathology in 73 of 139 patients for a concordance rate of 53% (Table 2). Thirty-seven patients (27%) were over-staged and 29 (19%) were under-staged. Of these, 10/139 (7%) were under-staged by tumor depth and 19/139 (14%) had nodal disease unrecognized pre-operatively (pN+) (Table 2). Of patients with cT1N0 disease who were clinically over-staged, 22 had carcinoma *in-situ* or Barrett's with high grade dysplasia on final surgical pathology. Of patients with nodal disease, 17/19 were pN1 and 2/19 were pN2. We could not ascertain from pathology reports whether microscopic or macroscopic nodal metastasis was present in these cases. By clinical stage, preoperative ultrasound was less reliable in identifying nodal disease for tumors with greater depth, though this was not statistically significant. EUS missed nodal disease for 12/110 (11%) of cT1 tumors and 7/29 (24%) of cT2 tumors ($P = 0.075$).

Other factors which could influence ability of EUS to predict pathological staging were also analyzed. We examined the time period in which patients underwent EUS. Patients were divided by whether they underwent EUS between 2000 and 2010 or between 2011 and 2015. Of patients who underwent EUS in 2010 or earlier, 17/110 (16%) had unrecognized nodal disease compared to 2/29 (7%) of patients who had EUS performed in 2011 or later ($P = 0.363$). In our series, PET was used for clinical staging in addition to EUS in 62 of the 139 patients. Of 62 patients that had both EUS and PET, only 4 (6%) had occult nodal involvement on surgical pathology compared to 15/77 (19%) of patients that did not undergo PET preoperatively ($P = 0.028$).

Logistic regression was performed to evaluate whether tumor location, tumor histology, time period of EUS, and whether EUS was performed at our institution were associated with accurate staging by EUS. None of these variables were related to the ability of EUS to accurately stage patients ($P > 0.05$). Factors such as tumor length, presence of Barrett's dysplasia, presence of strictures, and traversability of lesions were not evaluated in this study due to incomplete or missing data.

Of the cohort, 29 patients (21%) were under-staged. Nine patients underwent adjuvant therapy, with six undergoing chemotherapy and three undergoing chemoradiation. The remaining patients did not undergo adjuvant therapy. Median follow-up was 51 mo (range 1-186 mo). Median overall survival was 107 mo for the entire cohort.

DISCUSSION

The current standard of care for early stage esophageal cancer includes EMR for T1aN0 disease and upfront surgery for T1bN0 and T2N0 disease. Trimodality therapy is the standard of care in patients with more advanced disease^[10]. The staging of esophageal cancer, therefore, is important not only as a prognostic indicator, but also as a means by which we may determine the best therapeutic approach.

EUS is believed to offer improved sensitivity and specificity to the clinical staging process. However, in our cohort the concordance of EUS with pathological stage was lower than prior reports of EUS staging for esophageal cancer, though these studies included early and locally advanced disease. There is a degree of operator dependence with EUS, but this is an unlikely explanation. The accuracy of EUS for the evaluation of early stage esophageal cancer has been examined in multiple recent retrospective reviews and they demonstrate similar findings^[11-14]. These studies identified the limited ability of EUS to accurately stage T1N0 and T2N0 disease. In their study, Young *et al*^[9] cited a 56% concordance rate with EUS and surgical pathology in early esophageal cancer. These limitations may be related to the anatomy of the esophagus and its complex lymphatic system. Other cited factors which decrease EUS accuracy include tumor length, tumor location (specifically tumors at the gastroesophageal junction and cardia), and presence of Barrett's esophagus^[8,10].

Tumors may be under-staged by either underestimating the depth of invasion (T stage) or the presence of nodal involvement (N stage). In our series, EUS underestimated the depth of invasion in 10 (7%) patients without pathological lymph node involvement. In the study by van Hagen *et al*^[5], neoadjuvant treatment increases the rate of complete resection with negative margins. Despite this fact, all patients in this series were able to undergo complete surgical resection with negative margins. The more problematic issue is when clinical under-staging presents as unrecognized nodal involvement. This leads to unreliable prognostication and inappropriate treatment selection. The importance of this issue is demonstrated in the dismal 5-year survival rate for patients with lymph node metastasis^[15]. Furthermore, several studies have established a survival advantage to neoadjuvant therapy before surgery in patients with lymph node involvement^[16,17]. In our series, 19 of 139 (14%) patients had unrecognized nodal disease pre-operatively. Had their clinical staging been accurately assessed, neoadjuvant chemoradiation would have been recommended prior to proceeding with surgical resection. The role of adjuvant therapy in these patients is controversial and the delivery of

concurrent chemotherapy and or radiation therapy following surgical resection might be challenging due to concerns of decreased efficacy and poor tolerance^[18,19]. In a randomized trial of preoperative vs postoperative chemotherapy for esophageal squamous cell carcinoma, five-year overall survival was 43% for the adjuvant chemotherapy group vs 55% for the neoadjuvant chemotherapy group^[19]. In addition, rates of treatment after surgery may be lowered due to poor postoperative performance status or patient refusal, as seen in the present series in which only half of the patients who met criteria for adjuvant therapy received it.

Due to the potential for understaging and missed opportunities for neoadjuvant therapy, consideration for neoadjuvant therapy in T2 esophageal carcinoma has been examined, though controversy exists. As mentioned above, the rate of nodal metastasis in clinical T1 and T2 disease is not negligible. Bergeron *et al.* demonstrated that 15% of cT1a and 18% of cT1b tumors were under-staged by nodal status^[14]. Keeping in mind the relationship between tumor depth and nodal status in esophageal cancer, tumors that penetrate the submucosal layer may be able to also invade the network of lymphatic channels that course the length of the esophagus^[20]. In the evaluation of depth of tumor as a predictor of regional lymph node involvement by Rice *et al.*^[20], up to 40% of T2 lesions were identified to have lymph node involvement. In this series, 24% of cT2N0 patients had nodal involvement on surgical pathology. In the randomized trial by van Hagen *et al.*^[5] that established a benefit for neoadjuvant chemoradiation, T2 patients were included in the study. Similarly, a propensity matched study of stage I and II patients demonstrated that stage I and II patients who underwent neoadjuvant chemotherapy had a 47.7% five-year OS rate compared to a 38.6% rate in patients who underwent upfront surgery ($P = 0.016$). However, when upfront surgery vs neoadjuvant chemoradiation was evaluated in this population in a randomized trial, there were no survival differences ($P = 0.94$) but increased postoperative mortality ($P = 0.049$)^[5].

Since 2009, our center has added the routine use of PET with EUS for staging early esophageal cancer. This has improved accuracy of staging, as confirmed in other series^[21]. Of the 139 patients with clinical T1N0 or T2N0 esophageal cancer, 62 patients had a PET included as part of their clinical workup. Only four patients were found to have nodal disease on pathologic specimen when their EUS and PET imaging showed negative nodal involvement. Seventy-seven patients in this series did not undergo PET imaging as part of their clinical staging. Of that group, 15 patients (19%) were identified as having occult nodal disease. These findings suggest that the combination of both EUS and PET for staging of early esophageal cancer improves clinical accuracy. We cannot definitively predict that a PET would have

demonstrated hypermetabolic activity in those understaged lymph nodes, as many patients had low volume nodal disease with only one positive lymph node on final pathology. Interestingly, in a SEER study, the authors noted that EUS and/or CT-PET was associated with improved overall survival, probably due to the improvement in staging and receipt of therapies for patients undergoing these procedures^[22].

Although the consequences of clinically understaging may seem evident, over-staging by EUS also has important ramifications. Over-staging may lead to unnecessary surgical procedures. In clinical series, the mortality and morbidity rate of esophagectomy are 2%-6% and 50%-64%, respectively^[23-25]. In this series, the 30-d mortality rate was 2.2%. Of 110 patients with cT1N0 tumors, 22 had carcinoma *in situ* (Tis) or Barrett's with high grade dysplasia (HGD) on final surgical pathology. These disease processes could have been treated with a less invasive endoscopic mucosal resection rather than esophagectomy. EMR has been proven to be an effective treatment option for patients with Tis and Barrett's with HGD, as long as deep radial and deep margins are free of tumor^[26]. For this reason, our institution now utilizes EMR not only as a therapeutic tool when appropriate, but also as a diagnostic tool which can evaluate pathologically and more accurately the depth of invasion of the tumor.

The decreased accuracy of EUS in early stage disease is unlikely related to evolving technology or improved technique over time at our institution. In similar studies, retrospective data collected over a decade time span has proposed technology to be a limitation, contributing to possible EUS inaccuracy if obtained during the early 2000s^[11]. This was evaluated in our review by grouping patients into two separate time periods. Endoscopes used for the majority of patients in this review ranged in frequencies from 5-10 MHz. Of note, the processor was updated within the last 3 years from a 5 MHz endoscope to a 10 MHz endoscope. No significant difference was identified between patients whose EUS was performed before or after 2010 with respect to unrecognized nodal disease by EUS.

This study has several important limitations. There are inherent biases due to the retrospective nature of this study. In addition, though it appears that the concordance rate of EUS with surgical pathology was low in this study, other published studies report similar numbers in the setting of early esophageal cancer. In addition, we did not include patients that underwent endoscopic mucosal resection, which likely would have improved our accuracy rates. The decision to exclude those patients was made because it would not be possible to figure out the true nodal status of those patients without undergoing surgery. Also, one of our study objectives was to demonstrate factors associated with inaccurate EUS, but due to the time span of the study many prior endoscopic reports were missing pertinent information such as length of

the tumor and presence of Barrett's esophagus. Our study had an overwhelming majority of patients with adenocarcinoma, which is more typical of Western populations. Though we could not ascertain from endoscopy reports exactly how many patients had Barrett's esophagus, we speculate that many of our patients diagnosed with carcinoma were undergoing surveillance for Barrett's esophagus. In addition, patients who had EUS at an outside institution were included, but the number was relatively small and likely did not impact the results of this study.

However, this study does bring to light the limitations of one of the more specific and sensitive tools in the staging of esophageal cancer. As suggested by the results of our study, the initial use of endoscopic mucosal resection may be an appropriate diagnostic and possible therapeutic technique for patients with cT1N0 disease. It is especially difficult to distinguish T1a disease from T1b disease by EUS and therefore EMR is even more important as a diagnostic tool. For patients who may be under-staged based solely on depth of invasion (T stage), which carries a 7% risk in our series, meticulous surgical technique with adequate radial resection margins mitigates potential incomplete resections. Also, the addition of PET reduces the rate of finding occult nodal disease in these patients with early disease. When staged with a combination of EUS and PET, the risk of occult nodal disease is only 4% in this group. Therefore, current treatment algorithms of clinical stage T1N0 and T2N0 esophageal cancer should be re-evaluated so that appropriate therapy is administered, without over- or under-treatment. Further evaluation of the under-staged group in this review is needed to determine if unrecognized nodal disease by preoperative staging workup in early stage esophageal cancer affects long-term survival or disease-free interval. As for patients with cT2N0 lesions based on both EUS and PET, a frank and detailed discussion must be undertaken regarding the risks and benefits of neoadjuvant therapy, as 18% of this group of patients will have clinically unrecognized nodal involvement. Further studies are required to elucidate various clinical and pathological risk factors for occult nodal involvement. Future developments in molecular profiling techniques would also aid the diagnosis and treatment of these patients.

COMMENTS

Background

Studies demonstrate the importance of neoadjuvant therapy in esophageal cancer. Accurate staging determines which patients should undergo neoadjuvant treatment and is vital to improved patient outcomes. Computed tomography, magnetic resonance imaging, positron emission tomography, and endoscopic ultrasound (EUS) are important modalities for staging in esophageal cancer. EUS is a widely used modality with high sensitivity and specificity, though studies suggest that it is less accurate in early disease.

Research frontiers

EUS for esophageal cancer is standard practice. The distinction between

tumors that invade the muscularis propria from those that invade the adventitia is critically important as it determines which patient will require upfront surgery vs neoadjuvant treatment. However, reports suggest that EUS staging is less accurate in early esophageal cancer.

Innovations and breakthroughs

This clinical study demonstrates that even in high volume cancer centers, improved staging is necessary. The addition of PET-CT leads to greater improvement in staging accuracy. Endoscopic mucosal resection is another useful diagnostic tool in the setting of early esophageal cancer.

Applications

Based on the findings of this study, we recommend increased use of PET-CT and EMR in addition to EUS in the staging of early esophageal cancer. Continued advances in these modalities will lead to more accurate determination of staging and treatment strategies for patients with early esophageal cancer.

Peer-review

The manuscript describes the experience from an oncologic center with EUS as the main tool, sometimes associated to PET-SCAN for the treatment of esophagus cancer.

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P- Reviewer: Caboclo JLF, Chiba T S- Editor: Ma YJ L- Editor: A
E- Editor: Ma YJ





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ISSN 1007-9327

