

ORIGINAL ARTICLE

Is it necessary for patients with potentially resectable esophageal squamous cell cancer to receive routine preoperative brain MRI/CT?

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Abstract

Background: This study aimed to investigate the value and efficiency of routine brain MRI or CT in the preoperative workup for patients with potentially resectable (cT_{1-4a}N₀₋₃) thoracic esophageal squamous cell cancer (ESCC).

Methods: This was a prospective cross-sectional clinical trial (ChiCTR1800020304). A total of 385 patients with potentially resectable (cT_{1-4a}N₀₋₃) thoracic ESCC diagnosed from October 2018 to August 2020 were included. Plain brain MRI or CT was performed preoperatively to detect brain metastases (BrM). The primary endpoint was BrM detected by imaging.

Results: Of all 385 patients, the rate of positive brain MRI/CT findings was 1% ($n = 4$). BrM Patients received chemoradiotherapy, and the median OS was 6 months (95% CI: 4.303–7.697). All 381 remaining patients with initial negative brain MRI/CT diagnosis revealed no brain-associated symptoms within 6 months. The median follow-up for patients without BrM was 20 months (range, from 6 to 32). The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of plain MRI or CT to detect BrM were all 100%.

Conclusions: Preoperative plain MRI or CT is an effective method to detect BrM for potentially resectable (cT_{1-4a}N₀₋₃) thoracic ESCC. However, due to the low incidence, the value of brain MRI/CT as a routinely preoperational examination in potentially resectable esophageal squamous cell cancer is rather limited. Therefore, preoperative brain MRI/CT should not be recommended as a routine preoperative examination for ESCC.

KEYWORDS

brain MRI/CT, esophageal cancer, squamous cell carcinoma, metastasis, preoperative workup

INTRODUCTION

The brain is one of the most common metastatic sites for malignancies. Moreover, the incidence of brain metastases (BrM) is rising, probably owing to the development of imaging and improved tumor control outside the brain.^{1–4}

Esophageal cancer (EC) is a highly lethal malignancy, ranking as the eighth most common carcinoma worldwide.⁵ The treatment stratagem for EC mainly depends on clinical staging, where the presence of BrM indicates a terminal stage. Considering the relatively low incidence of BrM in EC (1.4%–3.9%),^{6,7} brain imaging before surgery is not recommended in the NCCN or ESMO guidelines.^{8,9}

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However, guidelines followed in western medicine may not be completely translatable to those followed in China since esophageal adenocarcinoma (EAC) is the predominant pathological subtype found in western countries, whereas esophageal squamous cell carcinoma (ESCC) dominates in China.⁸ Moreover, there has been no agreement on the means and scale of pretreatment examinations in China. In 1995, Gabrielsen et al. reported that in a cohort of 230 patients, preoperative enhanced brain computed tomography (CT) was not cost-effective due to the rarity of BrM.¹⁰ Nevertheless, the research was underpowered due to its retrospective nature. Therefore, the value of brain imaging before surgery remains unclear. Nowadays, enhanced magnetic resonance imaging (MRI) has been acknowledged as the preferred choice for BrM, with enhanced CT only recommended for those with contraindications to MRI.^{11–14}

In this prospective cross-sectional study, we aimed to investigate the value and effect of routinely preoperative MRI or CT in patients with potentially resectable (cT_{1–4a}N_{0–3}) ESCC.

METHODS

Patients

This single-center, prospective, cross-sectional trial was conducted in the National Clinical Research Center for Cancer in Beijing, People's Republic of China. Between October 2018 to August 2020, 385 consecutive patients were enrolled in our study and had staging investigations for biopsy-proven ESCC. Clinical staging was based upon routine preoperative examinations, including clinical examination, peripheral blood tests, cardiac functional tests, pulmonary functional tests, chest (including neck, chest, and upper abdomen), contrast-enhanced computed tomography (CT), endoscopic ultrasound gastroscopy, and biopsy. Recommendations for clinical staging (cTNM) of cancer of the esophagus and esophagogastric junction were applied according to the eighth edition AJCC (American Joint Committee on Cancer)/UICC staging manuals.¹⁵

The inclusion criteria for this trial comprised: (i) Patients aged between 18 and 75 years; (ii) a Karnofsky performance score ≥ 90 ; (iii) a final pathological diagnosis of thoracic ESCC, clinically staged as T_{1–4a}N_{0–3} before treatment; and (iv) antitumor therapy for esophageal cancer has not been performed. The exclusion criteria were: (i) Patients with a history of malignancy, and (ii) patients with brain-associated symptoms.

This trial conformed to the principles of the Declaration of Helsinki. The protocol received approval from the Institutional Review Board of the National Clinical Research Center for Cancer, and the trial was registered in Chinese Clinical Trials (ChiCTR1800020304). Written informed consent was received from all patients.

Image acquisition and analysis

Brain MRIs and CTs were performed using our standard protocols. Brain MRI scans were obtained with 1.5 or 3.0 T MRI scanners (GE), and the MRI protocol comprised axial T2-weighted fluid-attenuated inversion recovery (FLAIR) images (repetition time [TR], 8000 ms; [time to echo] TE, 130 ms; [inversion time] TI, 2350 ms; NEX, 1; slice thickness, 5 mm and slice space, 1 mm), and axial T2-weighted fast spin echo (FSE) images (TR/TE, 2520/109 ms; slice thickness, 5 mm and slice space, 1 mm) and sagittal FSE T1WI images (TR/TE, 270/9.4 ms; slice thickness, 5 mm). The enhanced images with intravenous injection of Gd-DTPA contrast (TR/TE 450/10 ms; NEX, 1; slice thickness, 5 mm and slice space, 1 mm).

The CT images were obtained using an eight- (LightSpeed Ultra, GE Medical Systems), 16- (ProSpeed or Discovery ST, GE Medical Systems), or 64- (LightSpeed VCT, GE Medical Systems or Toshiba Aquilion, Toshiba Medical Systems) slice spiral CT scanner. CT images were obtained with 120 kVp, 250–350 mA, and a standard algorithm reconstruction kernel. Reconstruction thicknesses were 1.25 mm, and the intervals were 0.8 mm.

Follow-up and identification of brain metastases

Plain brain MRI was the preferred choice for patients included in this study. However, plain CT was conducted for those where MRI was contraindicated, such as patients with pacemakers or metal implants. Upon detection of BrM by plain MRI or CT, enhanced MRI or CT was performed to confirm the findings. All images were assessed by two experienced imaging specialists with the aid of additional senior imaging specialists whenever the two specialists failed to reach an agreement.

All patients were followed up at the outpatient clinic at 3–6 months intervals during the first 2 years. During each follow-up visit, the patient underwent a thorough physical examination, and contrast-enhanced CT (including neck, chest, and upper abdomen). Follow-up extended until March 2021, ensuring a minimal potential follow-up of 6 months. The primary endpoint for this clinical trial was the rate of change of surgical plan on account of positive brain MRI/CT results. This was defined as the number of patients whose treatment strategy was changed due to positive brain MRI/CT results divided by the total number of patients. The secondary endpoint was the rate of positive brain MRI/CT results.

Sample size estimation

Without prior knowledge of the incidence of BrM in the potentially resectable thoracic ESCC clinically staged as T_{1–4a}N_{0–3}, the prevalence was set to 0.5, and survey accuracy d was set to 0.05, with a confidence level of 0.95.

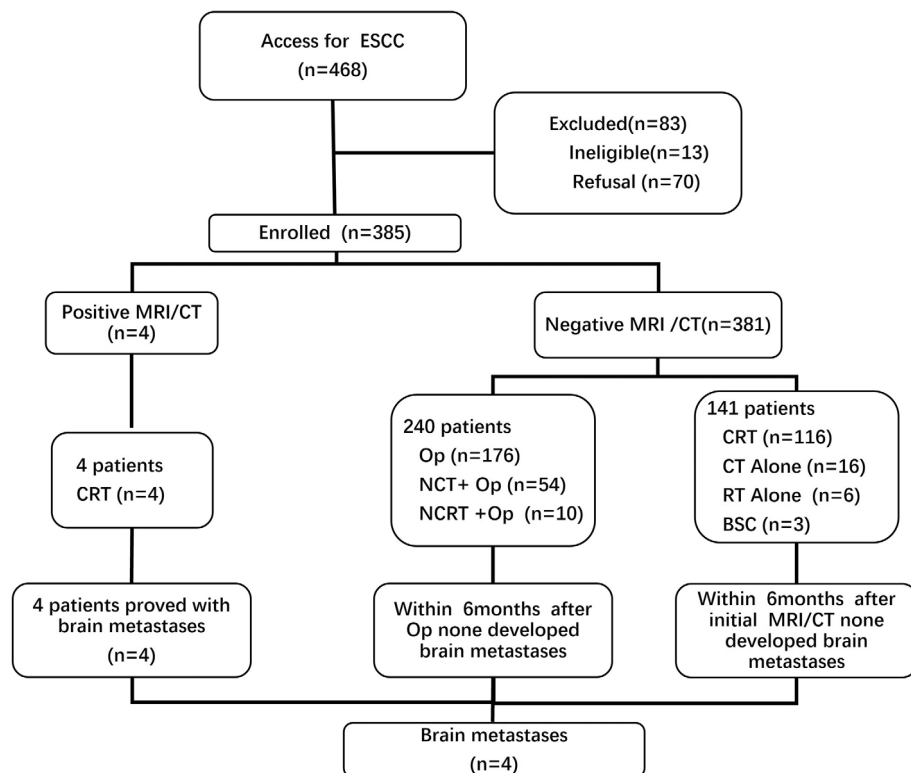


FIGURE 1 BSC, best supportive care; CRT, chemoradiotherapy; CT, chemotherapy; ESCC, esophageal squamous cell carcinoma; MRI/CT, magnetic resonance imaging/computed tomography; NCRT + Op, neoadjuvant chemoradiotherapy followed by operation; NCT + Op, neoadjuvant chemotherapy followed by operation; Op, operation; RT, radiotherapy.

Assuming a normal distribution, the α was set to be 0.05, from which it followed that the $z_{1-\alpha/2}$ was 1.96. We calculated a conservative sample size of 385 patients using the following formula.

$$N = \left(\frac{z_{1-\alpha/2}}{d} \right)^2 \times p \times (1 - p)$$

Statistical analysis

The association between BrM and clinicopathological variables was evaluated via the Pearson X^2 or Fisher's exact test, with a statistical significance level set at $p < 0.05$. SPSS (SPSS 26.0) was utilized to perform all statistical analyses.

RESULTS

Based on the inclusion and exclusion criteria, 468 patients with potentially resectable (cT1-4aN0-3) thoracic ESCC were diagnosed at the National Clinical Research Center for Cancer from October 2018 to August 2020 were initially selected. Of these, 13 patients could not withstand operation due to underlying diseases, and 70 refused brain imaging. This resulted in a total of 385 patients being included in this study (Figure 1).

The average age of the cohort was 61.9 ± 7.7 years (ranging from 36 to 75 years old), with the majority (53.8%) older than 63. Patient tumors were typically located in the middle thoracic esophagus ($n = 189$, 49.1%) or lower

thoracic esophagus ($n = 140$, 34.8%). A primary tumor of T3 or T4a was most commonly diagnosed ($n = 266$, 69.1%). The numbers of patients with clinical negative (N0) and clinical positive (N1-3) regional lymph nodes were 190 (49.3%) and 195 (50.7%), respectively. According to the eighth AJCC staging system, 53.5% ($n = 206$) had stage I or stage II disease, while 46.5% ($n = 179$) had stage III or IV disease. From Pearson's X^2 test, the incidence of BrM was found not to be statistically associated with age, gender, tumor site, T stage, N stage, or eighth AJCC stage ($p > 0.05$). Details are listed in Table 1.

Plain brain MRI and CT were conducted on 340 and 45 patients, respectively. BrM was detected by MRI in four patients, with zero cases detected by CT. The mean age of the four patients with BrM was 63.7 years, with most patients experiencing advanced T stage at initial diagnosis, including three (75%) patients with T3 stage disease and tumor locations typically within the middle thoracic esophagus ($n = 2$, 50%). All four patients with BrM received chemoradiotherapy, and the median OS was 6 months (95% CI: 4.303–7.697). Details of the four cases with BrM are shown in Table 2.

The median follow-up for the 381 patients without BrM was 20 months (range, from 6 to 32). All 381 patients demonstrated no brain-associated symptoms within 6 months after diagnosis. Plain MRI or CT identified four (1.0%) patients with BrM and 381 patients without BrM. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of plain MRI or CT to detect BrM were all 100% (Table 3).

TABLE 1 Clinicopathological features of 385 esophageal squamous cell carcinoma patients with brain MRI/CT

Factors	Overall number (%)	Without brain metastases (%)	With brain metastases (%)	p-value
Age (years)				1.000
≥63	207 (53.8%)	205 (99.0%)	2 (1.0%)	
<63	178 (46.2%)	176 (98.9%)	2 (1.1%)	
Gender				0.462
Male	330 (85.7%)	327 (99.1%)	3 (0.9%)	
Female	55 (14.3%)	54 (98.2%)	1 (1.8%)	
Tumor site				0.799
Upper	56 (14.5%)	55 (98.2%)	1 (1.8%)	
Middle	189 (49.1%)	187 (98.9%)	2 (1.1%)	
Lower	140 (36.4%)	139 (99.3%)	1 (0.7%)	
T stage				0.423
T1 + T2	119 (30.9%)	119 (100%)	0 (0%)	
T3 + T4a	266 (69.1%)	262 (98.5%)	4 (1.5%)	
N stage				1.000
N0	190 (49.3%)	188 (98.9%)	2 (1.1%)	
N1-3	195 (50.7%)	193 (99.0%)	2 (1.0%)	
Eighth AJCC stage				0.098
I + II	206 (53.5%)	206 (100%)	0 (0%)	
III + IV	179 (46.5%)	175 (97.8%)	4 (2.2%)	

Abbreviations: CT, computed tomography; Low, lower esophagus; Mid, middle esophagus; MRI, magnetic resonance imaging; Upp, upper esophagus.

TABLE 2 Details of four patients with brain metastases

Patient	Sex	Age (years)	Location	Clinical T stage	Clinical N stage	Treatment	OS (months)
Case 1	Male	71	Lower	3	1	CRT	4
Case 2	Female	56	Middle	3	2	CRT	6
Case 3	Male	55	Upper	3	0	CRT	6
Case 4	Male	69	Middle	3	0	CRT	8

Abbreviations: Low, lower esophagus; Mid, middle esophagus; Upp, upper esophagus.

TABLE 3 Sensitivity, specificity, PPV, NPV, and accuracy of brain MRI in 385 patients with esophageal squamous cell carcinoma

Eighth AJCC stage	Brain metastasis	Abnormal			PPV	NPV	Accuracy
		MRI/CT finding	Sensitivity	Specificity			
All (<i>N</i> = 385)	4	4	100% (4/4)	100% (381/381)	100% (4/4)	100% (381/381)	100.0% (385/385)
I–III (<i>N</i> = 350)	0	0	– (0/0)	100% (350/350)	– (0/0)	100% (350/350)	100% (350/350)
IV (<i>N</i> = 30)	4	4	100% (4/4)	100% (26/26)	100% (4/4)	100% (26/26)	100% (30/30)

Abbreviations: MRI, magnetic resonance imaging; NPV, negative predictive value; PPV, positive predictive value.

DISCUSSION

As the eighth most common malignancy, more than half of esophageal cancers are diagnosed in China.¹⁶ ESCC has high malignancy and is notorious for early lymph node metastases.¹⁷ However, with squamous cell carcinoma found in most cases, western guidelines may not be directly applicable in China. To our knowledge, this research represents the first study to explore the value and effect of routinely

preoperative brain MRI or CT in patients with potentially resectable (cT_{1-4a}N₀₋₃) thoracic ESCC.

In this study, based on a cohort of 385 potentially resectable (cT_{1-4a}N₀₋₃) thoracic ESCC patients, we found that the incidence of BrM was only 1% (*n* = 4) at 100% sensitivity, specificity, PPV, and NPV of plain MRI or CT to detect BrM. The incidence of our research was slightly lower than that found in existing data (1.4% to 3.9%).^{6,7} However, we found this difference reasonable considering that most

previous studies consisted of relatively long follow-ups, potentially allowing for the observation of more BrM cases. Moreover, our cohort only incorporated patients with potentially resectable ESCC, and patients with brain-associated symptoms were excluded.

Our data suggest that plain MRI or CT pretreatment performs well, with satisfactory sensitivity and specificity. For patients with brain-associated symptoms, enhanced magnetic resonance imaging (MRI) has been acknowledged as the preferred choice for BrM, with enhanced CT only recommended for those with contraindications to MRI.^{11–14} Davis et al. reported a case series of 23 patients who had undergone enhanced MRI to verify ambiguous findings on double-dose delayed CT (DDD-CT) studies. They found that enhanced MRI and T2-weighted MRI, respectively demonstrated more than 67 and 40 definite metastatic sites, while DDD-CT revealed only 37 typical metastatic lesions.¹²

Conventional MRI effectively reveals the accurate anatomical information of BrM.¹⁸ Previous studies revealed that MRI showed advantages over CT in diagnosing intracranial parenchymal tumors, including higher sensitivity in detecting pathological alteration of normal tissue constituents, more detailed and accurate description of tumor extent, and superior delineation of associated abnormalities.¹⁹ In recent years, advanced MRI methods such as MR spectroscopy (MRS), perfusion-weighted imaging (PWI), and diffusion-weighted imaging (DWI) have presented more valuable information in terms of tumor biology.¹⁸ On the other hand, positron emission tomography-CT (PET-CT) has demonstrated its strength in oncological imaging.²⁰ PET-CT works via the principle of metabolic activity of tumor cells; thus, radionuclide-marked molecules (such as glucose) will concentrate in the tumor once injected into the human body. However, the active glucose metabolism of normal brain tissue confounds the delineation of brain metastases.^{21,22} Moreover, MRI can detect smaller lesions (5 mm in diameter) than PET-CT (10 mm in diameter) due to better scanning resolution.¹⁸

Although our data indicate the good performance of pretreatment plain MRI or CT in detecting BrM, the incidence of potentially resectable (cT_{1-4a}N₀₋₃) thoracic ESCC was merely 1%, which meant that up to 99% of patients received unnecessary examination, resulting in extra expense and unwarranted patient discomfort. Therefore, a predictive model that can aid in identifying those with higher BrM probability would be valuable. Using a cohort from the surveillance, epidemiology, and results (SEER) database, Cheng et al. found that younger age (<65 years), American Indian/Alaskan Native race, primary tumor of overlapping location, EAC, higher N stage, and liver metastases were all independent risk factors associated with BrM. The author constructed a model predicting the likelihood of BrM in patients with EC.²³ However, the data were retrospectively obtained from a public database, and as a result, the value of the predictive model was not powerful enough. Therefore, it could not be used to aid in clinical decision-making. Based on our data, two patients with BrM had N0 disease, and all patients presented with local tumors of T3. Consequently, we found that

brain MRI/CT does not significantly affect the preoperative workup in patients with potentially resectable thoracic ESCC, even though it remained difficult to determine which patient types should be recommended for brain imaging.

Despite the interesting findings of this study, several shortcomings should be addressed. First, all four patients with BrM were identified by MRI. The value of plain CT in patients with BrM could therefore not be assessed. Second, only four patients were diagnosed with BrM, making it difficult to analyze the characteristics of patients with BrM. Third, our study was limited by the narrow population coverage, and thus there is a need for larger prospective multicenter studies to confirm our findings.

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CONFLICT OF INTEREST

The authors report no conflicts of interest.

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