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Original article

Adjuvant radiotherapy for positive lymph nodes of oesophageal squamous cell carcinoma: Can it earn promising benefits at long-term follow-up?

Radiothérapie adjuvante pour les ganglions atteints du carcinome épidermoïde œsophagien : peut-elle générer des avantages prometteurs lors d'un suivi à long terme ?

Y. Ren[a,1], J. Ye[b,1], W. Xiong[b], J. Zuo[b], Y. He[b], M. Tan[b], Y. Yuan[b,*]

[a] *Department of radiation oncology, The First Affiliated Hospital, Sun Yat-Sen University, 58, 2nd Zhongshan Road, 510080 Guangzhou, PR China*
[b] *Center of gastrointestinal surgery, The First Affiliated Hospital, Sun Yat-Sen University, 58, 2nd Zhongshan Road, 510080 Guangzhou, PR China*

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ABSTRACT

Purpose. – The value of adjuvant radiotherapy for patients with positive lymph nodes after curative resection of oesophageal squamous cell carcinoma is controversial. This study aims to investigate its long-term benefits in a specific cohort.
Patients and Methods. – The charts between 1990 and 2003 from patients with positive lymph nodes were retrospectively reviewed. Those subjects were divided into adjuvant radiotherapy and surgery alone groups, with two subgroups defined by radiation dose (cutoff value: 50 Gy). Overall survival, disease-free survival and locoregional recurrence-free survival were compared between two groups, with predictive factors of overall survival analysed meanwhile.
Results. – In sum, 175 matched patients with 1:2 ratios for group balance were enrolled for final analysis. During the follow-up (median: 37.0 months), 143 (81.7%) deaths were recorded, with 70.6% of deaths from cancer progression. The median overall survival time (19.5, 4 to 172 months) was not significantly different between the two groups (18.9 vs. 20.0 months, $P = 0.179$). However, the disease-free survival time was significantly shorter in the adjuvant radiotherapy group than that in the control group (median, 11.5 vs. 14.9 months; $P = 0.001$), with the locoregional recurrence-free survival time impressively prolonged (median: 18.3 vs. 16.5 months; $P = 0.022$). Age ($P = 0.030$), number ($P = 0.005$) and ratio ($P = 0.002$) of positive lymph nodes were associated with overall survival, but radiation dose was not ($P = 0.204$).
Conclusion. – Adjuvant radiotherapy with low- or high-dose did not improve survival compared with surgery alone. However, radiotherapy was effective to control locoregional recurrence, and could be applied as salvage therapy when recurrence event occurred.

Mots clés :
Cancer de l'œsophage
Radiothérapie
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Survie

RÉSUMÉ

Objectif de l'étude. – La valeur de la radiothérapie adjuvante de sites ganglionnaires atteints après la résection à visée curative d'un carcinome épidermoïde œsophagien est controversée. Cette étude visait à étudier ses avantages à long terme dans une cohorte spécifique.
Patients et méthodes. – Les dossiers entre 1990 et 2003 des patients chez qui les ganglions étaient atteints ont été rétrospectivement examinés. Des sous-groupes de patients ont été comparés, un de ceux seulement opérés et un de ceux opérés et irradiés (en distinguant ceux qui ont reçu moins de 50 Gy et ceux qui

* Corresponding author.
E-mail address: condor.yyj@gmail.com (Y. Yuan).
[1] Y. Ren and J. Ye equally contributed to this study.

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ont reçu plus de 50 Gy. La survie globale, la survie sans maladie et la survie locorégionale sans récidive ont été comparées entre deux groupes, avec des facteurs prédictifs de survie globale analysés pendant ce temps.

Résultats. – Parmi les 175 patients, 59 ont été irradiés. Au cours du suivi (en médiane 37,0 mois), 143 décès (81,7 %) ont été enregistrés, avec 70,6 % dus à une progression du cancer. La durée médiane de survie globale (19,5, 4 à 172 mois) n'était pas significativement différente entre les deux groupes (18,9 contre 20,0 mois, $p = 0{,}179$). Cependant, celle de survie sans maladie était significativement plus courte dans le groupe irradié que dans le groupe témoin (médiane de 11,5 contre 14,9 mois, $p = 0{,}001$), avec une durée de survie sans récidive locorégionale plus longue (médiane de 18,3 contre 16,5 mois, $p = 0{,}022$). L'âge ($p = 0{,}030$), le nombre ($p = 0{,}005$) et le taux ($p = 0{,}002$) des ganglions atteints étaient liés à la survie globale, mais non la dose de rayonnement ($p = 0{,}204$).

Conclusion. – La radiothérapie adjuvante de dose faible ou élevée n'a pas amélioré la probabilité de survie par rapport à la chirurgie seule. Cependant, la radiothérapie s'est avérée efficace pour contrôler la récidive locorégionale et pourrait servir de traitement de rattrapage en cas de récidive.

1. Introduction

Oesophageal cancer is one of the most lethal malignancies. The 5-year overall survival is roughly 10–35% [1,2]. The majority of oesophageal cancers present with squamous cell carcinoma and adenocarcinoma [3]. As for the treatment, a complete surgical resection is associated with improved overall survival and decreased risk of recurrence [4,5]. Recent evidence suggests that initial chemoradiation treatment followed by curative surgical resection is an optimal therapeutic theme for locally advanced oesophageal cancer [6]. However, a poorly characterized, but clearly identifiable subgroup of oesophageal SCC patients would suffer from positive nodal disease after radical esophagectomy. This subset of patients with metastatic lymph nodes continues to predominate in Asia, especially in China [7]. For this specific population, numerous adjuvant therapy studies have been carried out, but no consensus has been reached due to poor characterization or weak study design [8,9].

Adjuvant radiation therapy has demonstrated a survival benefit in several gastrointestinal malignancies including gastric and gastroesophageal cancer, pancreatic cancer and rectal cancer [10–12]. However, its role in improving the survival is not well established for oesophageal squamous cell carcinoma with positive lymph nodes. The JCOG 9907 study of 330 patients with squamous cell carcinoma indicates that induction chemotherapy was superior to adjuvant chemotherapy, but delivered futile care for node-positive patients [13]. Adjuvant radiotherapy often regarded as a local control measure is now preferred to deliver in specific patients with high risk of locoregional recurrence, and can be performed more safely and efficiently. However, there is conflicting evidence as to whether this treatment could improve long-term outcomes of such specific population.

Therefore, the aim of current study was to explore the impact of adjuvant radiation on long-term results of oesophageal squamous cell carcinoma with lymph nodes metastasis. More importantly, it aimed to evaluate the value of two different radiation doses on improving the survival in this disease.

2. Patients and methods

2.1. Patient population

In this retrospective study, specific patients, who were diagnosed as oesophageal cancer and underwent a definitive esophagectomy operation between 1st January 1990 and 31st December 2003, were identified first from our database. Patients 18 years or older, with stage I–IV squamous cell carcinoma according to the American Joint Committee on Cancer (AJCC; the 6th edition), treated with adjuvant therapy or not, were included for assessment of enrolment. The histological subtype of oesophageal cancer was restricted to squamous cell carcinoma (keratinizing, non-keratinizing and basaloid) in the current study.

Patients were excluded from the final analysis if they had less than 3-month survival, unresectable tumour with distant organ metastasis, positive resection margin (R1 and R2), neoadjuvant or intraoperative radiation, adjuvant chemotherapy, and unclear record of radiation therapy or surgery (missing data). Patients were also excluded if they had negative lymph nodes on pathologic examination.

2.2. Treatment schemes

As for the treatment, a radical esophagectomy with an extended lymphadenectomy was the procedure of choice at the discretion of the surgeon. Several surgical approaches were employed to achieve curative R0 resection, which were mainly decided according to surgeon's preference. After 4 to 6 weeks of operation, a total radiation dose of 45 to 70 Gy with daily fractions of 1.8 to 2.0 Gy was given to selected cases. The radiation dose was mainly determined by individual factors (personal context). Of note, three-dimensional radiotherapy was mainly performed for included patients during the study period.

Follow-up was typically every three months for the first year after the surgery, every six months for the second year and twice a year thereafter [14]. Similar follow-up procedures took place with a medical oncologist or radiation oncologist. There was no protocol on obtaining imaging, but contrast-enhanced computed tomography (CT)-scan, endoscopic ultrasound or positron emission tomography (PET)-CT scan were selected for recurrence surveillance during the first three years postoperatively.

In the current study, patients with positive lymph nodes who received adjuvant radiation therapy (radiotherapy group, also labelled as treatment group) were compared with similar patients who had no further treatment after primary surgery (surgery alone group, also labelled as control group). Patients receiving adjuvant radiotherapy can be further divided into low-dose (less than 50 Gy) and high-dose (at least 50 Gy) subgroups, as previously published [15]. Those patients were not encouraged to attempt salvage chemotherapy or radiotherapy, unless they had confirmed disease recurrence within the follow-up period. Disease recurrence was defined as locoregional (oesophageal bed or anastomotic or regional lymph nodes) or metastatic (supraclavicular lymph nodes or distant organs) tumour invasion on evidence.

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