Cancer Letters 357 (2015) 69–74

Contents lists available at ScienceDirect

Cancer Letters

journal homepage: www.elsevier.com/locate/canlet

Mini-review

Involved field irradiation for the treatment of esophageal cancer: Is it better than elective nodal irradiation?

Liyang Jiang [a,1], Xin Zhao [b,1], Xue Meng [a], Jinming Yu [a,*]

[a] Department of Radiation Oncology, Shandong Cancer Hospital and Institute, Shandong Academy of Medical Sciences, Jinan, China
[b] Department of Cardiothoracic Surgery, Qilu Hospital, Shandong University, Jinan, China

ARTICLE INFO

Article history:
Received 9 October 2014
Received in revised form 19 November 2014
Accepted 19 November 2014

Keywords:
Esophageal cancer
Involved field irradiation
Elective nodal irradiation

ABSTRACT

Esophageal cancer (EC) is an extremely aggressive and lethal malignancy with an increasing incidence worldwide. Currently, the combination of radiotherapy and concurrent chemotherapy is performed for nonsurgical EC. However, there is no clear consensus on the accurate definition of the clinical target volume. Still, elective nodal irradiation (ENI) is the conventional remedy adopted for EC patients, while severe radiotherapy-related toxicities would occur in at least half of patients. Involved field irradiation (IFI) is a selective way to decrease the irradiation volume and thereby to decline toxicities. This review centers on the modality of IFI and compares the treatment efficacy between IFI and ENI.

Introduction

Esophageal cancer (EC) is the sixth leading cause of cancer-related mortality worldwide, and an estimated 18,170 new cases were diagnosed in the United States, with 15,450 deaths, in 2014 [1,2]. The standard treatment for patients with localized EC who choose nonsurgical management involves combined-modality treatment with radiotherapy plus concurrent chemotherapy, as established by the results of Radiation Therapy Oncology Group (RTOG) trials [3,4].

However, there is no international consensus regarding the accurate definition of the clinical target volume (CTV), because EC is greatly capable of metastasising with an extensive and not clearly defined range of invasion [5]. Taking into consideration microscopic spread, the radiation fields of many trials involve larger ranges and have included elective nodal irradiation (ENI), i.e., nodal target volume that covers both metastatic lymph nodes and regional nodes. Although the choice of ENI may seem logical when considering the benefit from three-field lymphadenectomy of EC [6] and it theoretically provides a better local tumor control, radiotherapy-related toxicities cannot be ignored, and severe toxicities would appear in at least 50% of patients if ENI were adopted [3,4,7,8].

Theoretically, treatment-related toxicities would decline if the irradiation volume was diminished. Involved field irradiation (IFI, i.e., nodal target volume that includes only the metastatic nodes) is a selective way of decreasing the irradiation volume. Moreover, there have been studies of a series of cases treated with IFI, and these studies have shown that administration of IFI is feasible [9–17]. In light of the ongoing controversy over the scope of the CTV, in this review we summarize the available data on the modality of IFI compared with ENI and the following questions are discussed: What is the theoretical foundation of IFI? How should IFI be implemented? Which is superior, IFI or ENI? What is the suitable patient population for adopting IFI?

The theoretical foundation of IFI

As is well known, EC is associated with multicentric disease or submucosal "skip" invasion due to the extensive and longitudinal interconnecting system of lymphatics. However, many studies have reported a low incidence of isolated out-field nodal failure, which is discrepant with the above notion. The reason for the inconsistency might be that many patients have died before the regional disease becomes clinically apparent or that micro-metastases are adequately controlled by the immune system or incidental nodal irradiation.

Abbreviations: EC, esophageal cancer; ENI, elective nodal irradiation; IFI, involved field irradiation; RTOG, Radiation Therapy Oncology Group; CTV, clinical target volume; MHCI, major histocompatibility complex class I; CTL, cytotoxic lymphocyte; GTV, gross target volume; CT, computed tomography; PET, positron emission tomography; GTVt, gross target volume of visible primary tumor; GTVn, gross target volume of metastatic lymph nodes; CTVt, clinical target volume of visible primary tumor; CTVn, clinical target volume of metastatic lymph nodes; LRC, locoregional control; PFS, progression-free survival; DFS, disease-free survival; CFRT, conventional fractionated radiation; LCAHRT, late-course accelerated hyperfractionated radiotherapy; HFR, hypofractionated radiation; OS, overall survival; CR, complete response; NEIL1, nei endonuclease VIII-like 1; EAC, esophageal adenocarcinoma.

* Correspondence author. Tel.: +86 531 87984729; fax: +86 531 87984079.
E-mail address: sdyujinming@126.com (J. Yu).

[1] Equal contributors (co-first author).

http://dx.doi.org/10.1016/j.canlet.2014.11.045
0304-3835/

Radiotherapy to enhance body immunity

The tumor microenvironment is a sophisticated collection of cells that includes a number of leukocytes. The overall effect of the microenvironment is to support tumor growth and restrain immune responses. Radiation treatment can modify the tumor microenvironment. The modifications result in induction of the expression of inflammatory cytokines and the upregulation of death receptors, such as Fas, which can boost the availability and presentation of antigen, normalize vessels, increase the expression of major histocompatibility molecules, increase localization of T cell and induce danger signals [18].

Radiation can also upregulate other immunologically important molecules such as major histocompatibility complex class I (MHCI). Moreover, radiation works in conjunction with adoptive transfer of tumor-specific cytotoxic lymphocyte (CTL) to improve the antitumor effect of transferred cells [19,20]. Additionally, novel proteins that are brought forth by the tumor can be presented on the MHCI molecules and recognized by the CTL. With radiation treatment, well-established tumors that are expressing low levels of antigen will produce transient upregulation of major histocompatibility complexes on stromal cells and the appearance of tumor antigen. Therefore, it is the combination of tumor antigen and the adoptive transfer of pre-activated CTL that causes tumor regression.

Thus, it might be possible that the radiation treatment changes the tumor microenvironment, and then, the enhanced body immune system destroys the established tumors and the pre-clinical niduses. Therefore, by the mechanisms described above, it might be possible for IFI to restrain the development of micro-metastases.

The effect of incidental nodal irradiation

Among the possible reasons why micro-metastases can be controlled, incidental nodal irradiation cannot be omitted. Ji et al. [10] quantified the incidental irradiation doses to esophageal lymph node stations when treating T1-4N0M0 EC patients using IFI and provided a convincing evidence of micro-metastatic control from incidental nodal irradiation.

In that study, the mean equivalent uniform dose was greater than 40 Gy in most high-risk nodal regions under a prescribed 60 Gy dose, but all these regions likely do not acquire high enough incidental irradiation doses in all patients studied. It has been reported that worthwhile treatment benefits can be achieved by lower doses and that a radiation dose as low as 24 Gy could reduce metastases by 30–50% [21–23], so the low out-field failure might be attributed to the incidental irradiation of elective nodal regions. Additionally, with patients who had positive lymph node metastases, the incidental irradiation dose to high-risk regions would be much higher. To conclude, incidental irradiation may also play a role in the control of micro-metastases.

The current implementation pattern of IFI

Determining the adequate radiotherapy target volume in radiotherapy planning

When patients are treated with radiotherapy, it is crucial for the delineation of the target volume to be accurate because inaccurate or inappropriate delivery could potentially cause locoregional recurrence attributed to missed nodes within a CTV or excess toxicity attributed to unnecessarily large treatment volumes.

With the development of examination techniques, the gross target volume (GTV) has been localized using techniques that range from computed tomography (CT) and esophagogastroduodenoscopy to endoscopic ultrasonography and positron emission tomography (PET)/CT, which can more accurately identify the submucosal extension and lymphadenopathy and exclude metastatic disease [24,25]. In regard to the delineation of IFI, the GTV is any visible primary tumor (GTVt) and includes metastatic lymph nodes (GTVn). The metastatic node criteria were as follows: Nodes greater than 1.0 cm in the shortest axis in the intrathoracic and intra-abdominal region [9,13,15] and greater than 0.5 cm beside the recurrent nerve [9,13] on CT scans or with a high standardized uptake value-max of ^{18}F-deoxyglucose avid on PET/CT images [15]. The CTV encompasses an adequate margin around the GTV. As for the definition of adequate margins, there is still no globally concordant opinion or high-quality evidence-based medical definition for this. To date, most trials define the CTVt as 3 cm superoinferior margins and a 0.5–1.0 cm lateral margin from the GTVt, and the CTVn is defined as the GTVn plus a 0.5–1.0 cm radial margin. Moreover, prophylactic nodal irradiation should not be included.

The dose of the radiation regimen

Although RTOG 94-05 demonstrated that patients did not benefit from 64.8 Gy compared with 50.4 Gy, this trial did not give a clear reason for this finding. Moreover, the majority of patients were of non-Asian race; only one Asian person participated in this trial. Since then, some East Asian researchers have determined that high-dose radiotherapy (≥60 Gy) was associated with improved locoregional control (LRC), progression-free survival (PFS) and/or disease-free survival (DFS) without a remarkable increase in treatment-related mortalities or toxicities [26,27]. Accordingly, the radiation dose of the East Asian patients was higher than that of the Western patients because of the non-conformity of tumor radiosensitivity and histological types between East Asian and Western populations, regardless of whether they were prescribed ENI or IFI. Thus, in trials using IFI, a dose of 60 Gy in 30 fractions was given for the majority of Chinese and Japanese patients [10,12,13,15,17], while Button et al. from the United Kingdom [11] treated patients with a dose of 50 Gy in 25 fractions. In our opinion, to receive a better therapeutic effect, prescribing a higher dose might be more reasonable because of the shrunken radiation field and decreased treatment-related toxicities which are described below.

Radiotherapy with different types of fractionation

For the treatment of EC, many trials have adopted conventional fractionated radiation (CFRT), that is, 2.0 Gy per day, 5 fractions weekly, for a total dose of 50–60 Gy. However, other types of fractionation have come into existence through demonstrations of some researches.

Improved local control and relatively long-term survival have been reported in patients receiving late-course accelerated hyperfractionated radiotherapy (LCAHRT) compared with CFRT [28]. Some papers have attributed one of the major reasons for the treatment failure of EC to rapid proliferation of surviving tumor clonogen during CFRT [29,30]. Moreover, three independent meta-analyses from China have illustrated that LCAHRT was favorable in EC and had benefits compared with CFRT for EC [31–33]. Of the available studies on IFI, Zhao et al. [9] achieved a satisfactory result by applying LCAHRT, which consisted of receiving CFRT at 1.8 Gy per day for the first two-thirds of treatment for a dose of 41.4 Gy in 23 fractions, followed by LCAHRT using reduced fields, at 1.5 Gy per fraction twice daily, with an interval of ≥6 hours between fractions, for a dose of approximately 27 Gy. The total dose was 68.4 Gy in 41 fractions.

Some studies have reported that radiation enhanced the expression of cancer stem cell markers of radiation resistance [34,35], which could result in local failure. In addition, CFRT has been shown to have reduced radiobiologically tumoricidal effects in radioresistant EC [36]. Thus, increasing the fraction dose (i.e., hypofractionated radiation [HFR]) might be theoretically possible. At present several papers suggested that HFR for locally advanced