Cancer Letters 379 (2016) 225–229

Contents lists available at ScienceDirect

Cancer Letters

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

Mini-review

Application of stereotactic body radiation therapy to cancer liver metastasis

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ARTICLE INFO

Article history:
Received 14 August 2015
Received in revised form 24 October 2015
Accepted 27 October 2015

Keywords:
SBRT
Liver
Metastasis and radiotherapy

ABSTRACT

As an accurate external beam irradiation method, stereotactic body radiotherapy (SBRT) has been increasingly used to deliver high dose in less fractions. The liver is one of the most common organs for cancer metastasis. Recently, there have been several trials applying SBRT to cancer liver metastasis and have proved to be effective and safe with local control (LC) rates ranging from 70% to 100% within one or two years and 2-year overall survival (OS) rates ranging from 30% to 38%. Many published studies indicate that SBRT for cancer liver metastasis results in good outcomes without severe toxicities. However, the validated contribution of SBRT to an improved progression-free survival is still missing and more randomized trials should be conducted.

Introduction

Systemic therapy, including chemotherapy and molecular-targeted therapy, has prolonged the survival of advanced tumor recently. Enhanced, local treatment for metastasis plays an important role on patients' survival. Among all of the organs, the liver is one of the most common metastatic sites for colorectal, breast, pancreatic adenocarcinoma, and other tumors [1–7]. The gastrointestinal (GI) tract cancers are responsible for a large part of liver metastasis since their draining blood supply is funneled into the portal circulation. Colorectal cancer (CRC) is the most common source of primary subtype of liver metastasis. Hepatic resection remains the mainstay of curative treatment for these patients. A complete surgical resection is considered the best chance for long term survival with a 5-year and 10-year survival rate of 40% and 17%, respectively [5,8]. However, 80–90% of liver metastatic patients are not suitable for resection because of poor general condition, inoperative anatomic tumor location, without sufficient volume of normal liver left or patient's refusal [9]. For medically or technically inoperable patients, other therapies, such as radiofrequency ablation (RFA) and transarterial chemoembolization (TACE), could provide partial palliation of symptoms and prolongation of survival. Combined with surgery or taken alone, RFA is another treatment option with a wide variability in the 5-year survival rate (14–55%) and local tumor recurrence rate (3.6–60%) [10]. Limitation of this method is that tumors adjacent to large hepatic vessels or at the edge of liver present unique problems for performance of RFA because the risk of injury to large blood vessels and adjacent organs, such as bowel, diaphragm and abdominal wall [11].

Traditional liver radiotherapy is considered to be a palliative therapy because of low tolerance of the whole liver. In recent years, due to development in radiation technology, partial liver radiotherapy has acted as a non-invasive therapeutic method for cancer liver metastasis. Stereotactic body radiotherapy (SBRT) is an accurate external beam irradiation method to deliver high dose in as few fractions as less than five [12]. It is characterized by high tumor target dose distribution, steep dose falloff at the target border and small dose distribution in normal tissues. The preliminary application of SBRT to liver tumors can be retrospected to the work of Blomgren and Lax in 1995 who observed an encouraging result with a local rate of no progressive disease of 80% during a follow-up period of 1.5–38 months [13]. Guided by advanced imaging systems, SBRT presents satisfactory efficiency for cancer liver metastasis with local control (LC) rates widely ranging from 70% to 100% at one or two years [6,9]. For selected patients with high risk characteristics said above, inoperative anatomic tumor location, nearby major vessels or difficult to access percutaneously, for example, SBRT might be delivered carefully as a non-invasive approach which offers a therapeutic alternative to lesions near large blood vessels, patients with portal vein thrombosis, inoperative locations and those who refuse surgery. Its excellent dose distribution lead to improved precision and minor liver or surrounding organ toxicities, providing rationales for the increased use of SBRT [14].

Patient selection

Being a parallel organ, the adult's normal liver occupies a volume of about 1250 ± 141 cm^3, which determines the dose distribution

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http://dx.doi.org/10.1016/j.canlet.2015.10.029
0304-3835/

it can tolerate in radiotherapy [15]. Accepted criteria for applying SBRT to liver metastasis are: the number of liver metastases ≤ 3 [15] and the maximum tumor diameter ≤ 6 cm [1,16,17]. Other indexes include [5,16]: Eastern Cooperative Oncology Group (ECOG) ≤ 2 or Karnofsky performance score (KPS) ≥ 70, serum liver enzyme levels less than 3 times of normal, normal coagulation function, Child–Pugh status A or B, stable primary lesion without extrahepatic metastasis or small extrahepatic metastasis without progression and patient's expected survival period more than 3 months. Published clinical trials also suggest metastatic lesions treated with SBRT should not be immediately adjacent to the GI tract (distance > 6 mm) or portal structures [18]. Considering lack of large prospective studies evaluating the clinical results of SBRT for liver, patient selection should be cautiously at present stage.

Effect of liver metastasis SBRT

SBRT for liver metastasis demonstrates a satisfactory LC and overall survival (OS) with respectable side effects observed.

1 LC rate: most results revealed a 70% to 100% and 60% to 90% LC rate for cancer liver metastasis SBRT at one and two years, respectively [19]. Further studies showed that total dose irradiation, segmentation and BED are closely associated with LC rate [19].
   (1) Total dose irradiation and segmentation method: In dose related phrase I and II clinical trials, a total of 37 patients with 60 liver lesions received SBRT for liver lesions, and most of them were metastases cancer [20]. For patients receiving 22–26 Gy/single fraction, radiotherapy improved LC rate to 81%, yet those receiving 14–20 Gy/fraction improved none at 18 months after SBRT. As a result, the author concluded that total dose irradiation was associated with tumor LC rate in liver SBRT. McCammon et al. reported a higher radiation dose and a smaller GTV were significant predictors of better LC in univariate analysis [21]. The 3-year actuarial LC rate was 89.3% for a dose of ≥ 54 Gy compared to 59.0% for a 36–53.9 Gy dose and 8.1% for a < 36 Gy dose. Bae reported a good LC for 41 CRC patients who had multiple metastatic lesions treated with SBRT [22], with a marked LC rate for those with 48 Gy in 3 fractions or more doses. Chang et al. drew a similar conclusion from their multicenter pooled analysis [15]. By now, the most impressive result is presented by UT southwestern from a trial with 60 Gy in 5 fractions for 26 patients, showing 100% LC at 2 year [23]. In summary, there is a trend for patients with a prescribed dose higher than 48 Gy in 3 fractions, that better LC could be expected compared with lower dose.
   Until now, most studies of liver metastasis SBRT adopt a dose prescription of 30–60 Gy in 2–6 fractions and 14–30 Gy in single fraction [24,25]. Due to the heterogeneity of primary tumor pathologic type, lesion quantity and size, and radiation treatment planning, the exact impact of total dose and radiation schedule to LC rate is still unclear and no universal recommendation is available.
   (2) BED: Investigators have introduced BED as an evaluator to reduce the differences between various irradiation dose and segmentations.
   Heggemann's study including 19 patients with cancer liver metastasis showed actuarial LC rates of 92% at 6 month and 57% at 2 year [26]. The association of higher BED with improved LC rate and low local recurrences was only observed for patients receiving a BED < 75 Gy. Due to small patient size, no formal dose–effect relationship was established. But a trend to significance at a dose cut-off of 78 Gy was found, with a statistical trend to significance ($p = 0.0999$) [26]. Among 42 cancer liver metastasis patients who received very different radiation dose prescriptions (from 40 Gy/4 fractions to 45 Gy/3 fractions), LC rate demonstrated to be similar, with 90% at 1 year and 86% at 2 year, which showed all BED were more than 80 Gy [27]. Meanwhile, Chang's research showed that higher BED of 79 Gy improved LC at 12, 18 and 24 months compared with lower one [15]. Hence they presumed a certain relationship between BED and LC. Although there is still not a definite prescription to recommend, it would be accepted that BED of SBRT for most of liver metastatic lesions should be more than 80 Gy ($\alpha/\beta = 10$) [15,27]. Additional information about LC rate is now available for metastasis. Rusthoven found poor LC associated with a great GTV volume [6]. The 2-year LC rate was 100% for lesions ≤ 3 cm compared with 77% for lesions >3 cm ($P = 0.015$, log-rank test). There was a familiar conclusion in Heggemann's trial which showed lower LC in patients with larger PTV-size when a volume cut-off of 67 cm^3 was used. No local relapse was observed at PTV-sizes <67 cm^3 and BED > 78 Gy [26]. According to the foregoing findings above, patients with oligometastasis ≤ 3 cm and who receive dose of BED more than 80 Gy might achieve long-term control [6,27].
2 OS rate: The OS of cancer liver metastasis treated with SBRT is different. In Hoyer's review, the median survival time ranged from 10 to 34 months, and the 2-year OS rate ranged from 30% to 38% [19]. They reported OS for 67%, 38%, 22%, 13% and 13% after 1, 2, 3, 4 and 5 years, respectively, in a recent follow-up, and the largest metastasis being < 35 mm was significantly related to better OS [3,19]. Schefter [16] and Rusthoven [6] studied 2-year OS rate in perspective phase I–II trial with SBRT dose prescription ranging from 36–60 Gy in 6 fractions and got a 2-year rate of OS for 30%. In Chang's multicenter trials, which treatment dose ranged from 36 to 60 Gy in 1–6 fractions, rate of OS were 72%, 55% and 38% at 12, 18 and 24 months, respectively [15]. For 25 patients in phase I trial with liver metastasis and intrahepatic cholangiocarcinoma, SBRT reached a median survival time of 28.6 months and 1- and 2-year OS rate of 61.8% and 49.4%, which the dose ranged from 18 to 30 Gy in single fraction [28]. Then recently, in a multi-institutional registry, Davis et al. included thirty-nine US centers with patients treated with SBRT/stereotactic radiosurgery [29]. A total of 174 patients with 204 liver metastases were in trial, and most of them had liver metastases from CRC. Median OS was 22 months and OS rates at 6, 12 and 18 months were 91%, 69% and 60%, respectively. Local progression-free survival was 94%, 76% and 70% at 6, 12 and 18 months, respectively.

As aforementioned, besides dose and segmentation, many factors affect patient's survival, such as pathological type of primary tumor, the absence of extra-hepatic disease (35.8 months vs. 11.3 months) [3,20] and metastasis size and number [30]. In Milano's study, it established a benefit for SBRT conferring LC, progression free survival (PFS), and OS in breast cancer patients with liver metastasis than other primary types of tumor (mainly colorectal or lung) [31]. Another retrospective trial also reported a 5-year survival rate of 36% and 10-year survival of 23% for carefully selected non-CRC patients, with liver metastases from breast cancer having the best and melanoma and squamous cell cancers the poorest survival [32]. In addition, Rusthoven et al. found that favorable primary histology included breast cancer, CRC, renal carcinoid and GIST while unfavorable primary sites included lung, ovary and non-CRC GI. The median survival for favorable primary sites was 32 months and 12 months for unfavorable primaries ($p < 0.001$) [6]. Yuan's study got a similar result [33].

Implementation of liver SBRT

1 Target region: In addition to conventional computed tomography (CT) simulation, magnetic resonance imaging (MRI) has