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Mini-review

Innovative therapy for hepatocellular carcinoma: Three-dimensional high-dose photon radiotherapy

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ABSTRACT

The development of three-dimensional conformal radiotherapy (3DCRT) has enabled high dose radiation to be directed to tumour with a frank sparing of the non-tumour surrounding liver parenchyma without restriction due to tumour topography and size, presence of peritumourous satellite nodules or associated segmental portal vein thrombosis. 3DCRT can be safely delivered alone or concomitantly with transarterial chemoembolization (TACE), giving very encouraging results. Efficacy is strongly related to a smaller tumor size and higher dose of radiation while toxicity closely correlates to the pre-radiotherapy liver functions and the dose delivered to the uninvolved liver. These data has led to integrate 3DCRT in the multimodal treatment of HCC as a possible curative-intent option as well as surgical resection or percutaneous procedures although phase-III controlled studies are warranted to clarify this point. This may represent a promising approach in patients who are inoperable or for whom other ablation therapies are not feasible. The next steps will be the optimization of delivery modes of this type of photon therapy, taking account that other radiation modalities such as proton beam therapy for instance might be shown as of great interest within the next few years.

1. Introduction

Hepatocellular carcinoma (HCC) is the most frequent primary malignant liver tumour that commonly arises in advanced chronic hepatopathies such as cirrhosis, and is one of the leading causes of cancer [1]. Its most prevalent etiologic factors are hepatitis virus B (HBV) and C (HCV) chronic infections that accounts for three quarters of cases worldwide, and at a lesser extent nonvirus-related hepatopathies such as alcoholic liver disease for instance. Noteworthy, HCC incidence is currently rising, especially in western countries, due to the HCV endemia [2–5]. In addition to its high prevalence, HCC is a challenging problem of public health since it carries a rather poor prognosis, ranking third in terms of death by cancer worldwide [1]. These pejorative features of HCC originate in its delay to diagnosis, in its intrinsic high resistance to standard commonly available anti-cancerous treatments (systemic chemotherapy and conventional external beam radiotherapy), and finally in the cirrhotic underlying liver disease that leads towards hepatic insufficiency which results in contraindication to anti-cancerous therapy and foretells a rapid fatal outcome [1,6,7]. In this review, we will introduce an innovative therapy – i.e. three-dimensional high-dose photon radiotherapy – and we will focus on its potential interest for the management of a subset of difficult to treat HCCs.

2. Principle of three-dimensional high-dose photon radiotherapy for HCC

Conventional external beam radiotherapy (RT) fails in accurately targeting a limited tumour volume within a

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breathing-related moving organ such as the liver, thus leading to the need of including the whole liver volume within the radiation fields. In this view, the maximal tolerated dose delivered to the whole liver does not exceed 28–35 Gray (Gy) in conventional fractionation (2 Gy *per* fraction), while this dose is far from reaching efficiency for substantial anti-tumour effect against HCC. Above this dose delivered to the whole liver, severe side-effects such as cytolysis and increment of alkaline phosphatases as well as hepatomegaly and ascites/edema syndrome frequently occur, and can lead towards a fatal outcome. In addition to the liver volume, adjacent organs can be involved within the large radiation fields of conventional RT, thus giving potential toxicity especially to stomach, duodenum and kidneys [8–10].

Modern technology has allowed the development of the computer-assisted three-dimensional conformal high-dose photon radiotherapy (CRT) [11]. Due to its ballistic characteristics, CRT has the potential to be analogous to surgical tumourectomy without restriction linked with anatomic localization. Indeed, the CRT technique has the potential to accurately deliver high dose of radiation within a well defined HCC tumour volume while sparing the surrounding non-tumour liver parenchyma and the adjacent organs. Thus, CRT can limit the radiation-induced complications through a strict quantification of the relation between the dose, volumes of the tumour and the irradiated non-tumour liver parenchyma, as well as non-dosimetric factors included in a model of iatrogenic complication probability in non-tumour tissues (NTCP) [12,13].

3. A need for innovative approaches and potential place of CRT in the management of a specific subset of difficult to treat HCCs

As mentioned above, CRT is particularly relevant for HCC tumours which topography allows radiation beams at focalizing onto a small part of the liver and sparing as much as possible the surrounding non-tumourous area. In this way, it clearly appears that single HCC nodules, or at worse a few adjacent small nodules closely located within a restricted volume of the liver parenchyma, are the best candidates for CRT. Single HCC nodules can be divided in large (>5 cm) or small size ($\leqslant$5 cm) tumours. In contrast, multifocal HCC nodules scattered in both hepatic lobes do not seem suitable for CRT due to the potential huge ratio of irradiated non-tumourous liver parenchyma, thus prohibiting at delivering high-dose CRT due to the risk of post-radiation hepatitis.

Concerning small size single HCC nodules ($\leqslant$5 cm), surgical resection has long been the treatment of choice in curative intent to treat, giving more than 50% overall survival at 5 years. However, surgical resection can not usually be applied when patients have poor liver functions (non-A Child-Pugh staging) or present extra-hepatic or vascular spreading [14–16]. Additionally to surgical resection, orthotopic liver transplantation (OLT) is the treatment of choice for patients with poor liver functions and a single HCC nodule $\leqslant$5 cm or 1–3 nodules $\leqslant$3 cm each, and radiofrequency ablation (RFA) has shown great efficiency for HCC nodules $\leqslant$3–4 cm, these two therapeutic approaches leading to 5-year overall survival rates ranging from 50% to 80% [14,17–20]. Unfortunately, a substantial number of patients with small size HCCs can not be treated by OLT due to the patient characteristics (bad general conditions, old age, etc.) or to unavailability of grafts. Additionally, RFA may be contra-indicated due to tumour topography, gross ascites, coagulopathy or obstructive jaundice [21]. Furthermore, increased risks of bleeding and peritoneal tumour seeding must be considered when tumours are situated at, or protruding from the liver surface. Tumours hiding under the diaphragm or too close to vital structures (bile ducts, major blood vessels, stomach, and gut) represent significant problem for RFA.

Patients with a large single HCC nodule (>5 cm) have a worse prognosis after surgical resection than with small ones, with an overall survival <30% at 5 years due to a high risk of tumour recurrence (50–100% at 5 years) [16,22–24]. Predictive factors of early recurrence post-surgery are the size of the tumour (>5 cm), macroscopic or microscopic vascular invasion, a non-anatomic type of resection, invasion of surgical margins, alpha-fetoprotein level >2.000 ng/dL, and poorly differentiated histological grade [16,25,26]. Furthermore, OLT or RFA are not recommended for these large HCC tumours.

Concerning all these patients who can not benefit from curative options – i.e. OLT, surgical resection or RFA – solely two palliative options, transarterial chemoembolization (TACE) and sorafenib administration, have shown a significant benefit on survival. However, the benefit from TACE gives a <10% 5-year survival rate, and sorafenib improves the median overall survival of three months only by comparison to placebo [27]. In summary, many HCC patients are ineligible for potential curative options due to stringent criteria for OLT, liver resection or RFA. Palliative options are often limited and bring modest benefit. Due to the ballistic characteristics of CRT, this approach should be specifically assessed on difficult to treat single HCC nodules.

4. First published results on efficacy and tolerance of CRT for difficult to treat HCC nodules

The first striking data were reported in 1993 from a pilot study where 11 patients with focal HCC (median 14.5 cm; range 5–22 cm) were treated by CRT (66–72 Gy, 1.5 Gy twice daily) combined to arterial infusion of the fluorodeoxyuridine radiosensitizer. Interestingly, patients presented an excellent objective response rate (100%) and a fairly good outcome with a tumour-free survival of 72% at 24 months, and 10% patients only with acute toxicity $\geqslant$ grade 3 [28]. Later on, other non-controlled studies confirmed the high efficacy and safety of CRT (28.5–90 Gy, 1.5 Gy twice daily) combined to arterial infusion of fluorodeoxyuridine, showing objective response rates ranging from 56% to 68% for 10 cm mean sized HCC tumours. The median survival times seemed exciting for such large size tumours (11–15.2 months). Interestingly, multivariate analysis clearly showed that higher CRT doses were independently associated with improved progression-free and overall survival rates [29,30].

Other non-controlled studies assessed efficacy and tolerance of CRT alone (48.2 ± 7.9 Gy, 1.8 Gy once daily) without concomitant arterial infusion of fluorodeoxyuridine for HCC tumours of variable sizes associating small (⩽5 cm) and large (>5 cm) HCCs. The objective response rates (67.1%) mimicked these encountered with the combination of CRT plus fluorodeoxyuridine (56–68%). Interestingly, most of non-responders showed stable disease without local progression within the irradiated tumour volume. By the way, about 40% patients developed intrahepatic metastasis beyond the radiation fields, or had simultaneous lung metastasis. The higher total radiation dose not only significantly correlated with the tumour response probability as observed in studies cited above, but also correlated with the rate of liver toxicity [31]. Subsequent studies brought additional exciting data by testing the impact of CRT on the outcome of patients with localized HCC that had previously failed or were unsuitable for TACE. These tumours were of variable size, including small and large ones, and some of them had portal vein thrombosis as complication. CRT (39.6–60 Gy, 1.8 Gy daily; or 44–54 Gy, 2–3 Gy daily) confirmed its striking efficacy since leading towards 54.3–61.4% objective response rates, and most of non-responders did not present progression of the disease. Taking account of patients with the most severe prognosis – i.e. advanced HCCs with portal vein thrombosis – CRT gave again exciting data with 39% objective response rates and a few progressions (12.2%). Logically, median survival times were higher in responders without or with portal vein thrombosis (18 or 20.1 months, respectively) than in non-responders without or with portal vein thrombosis (6.8 or 7.2 months, respectively) [32,33]. As described above, the analysis of prognosis factors clearly demonstrated that the total dose of radiotherapy had a significant positive impact on survival.

Finally, recent studies focused specifically on efficacy of CRT (66 Gy, 2 Gy daily) or stereotaxic radiotherapy (50 Gy, 5–10 Gy daily) for small size HCCs (2–6.5 cm). These studies demonstrated huge efficacy of high-dose RT since giving 80–92% objective response rates and very few disease progressions, and acceptable tolerance especially for Child-Pugh A patients before the start of radiotherapy [34–36]. Although these were not some prospective randomized controlled trials, survival rates seemed higher than those observed in previous studies for large size HCC, and close to those of historical cohorts of patients with small size HCC treated by percutaneous ablations. It was postulated that the smaller the tumour size was, the more effective high-dose radiation therapy became.

5. Could combination of TACE improve efficacy of CRT?

TACE alone is of limited efficacy with modest tumour response rates (35% objectives partial responses), although giving a significant advantage on overall survival by comparison to symptomatic care (median 30 *vs*. 13 months) [37]. Within or around the capsule, which is supplied by both arterial and portal blood, tumour cells remain viable, which are often responsible for later recurrence. As the tumour response variable induced by TACE appears as an independent predictor of survival, it seems evident that complementary therapeutic approaches tending to increase response rates would definitely improve survival. The combination of 3D-CRT with TACE may remedy the limitation of each alone and has synergistic effects, and combination therapy may also serve the purpose of eliminating residual cancer cells after TACE.

The first study combining high-dose RT (total 44–69.3 Gy, daily 1.8 Gy fractions) and TACE was published in 1999 and enrolled patients with unresectable large size HCCs (mean 9 ± 3.4 cm). The objective response rate was 63.3%, and survival rates were 67%, 33.3%, and 22.2% at 1, 2, and 3 years, respectively, with a median overall survival of 17 months. Toxicity was reduced, without treatment-related death [38]. Although achieved in uncontrolled settings, subsequent studies compared the high-dose RT + TACE combination to TACE alone, and clearly isolated irradiation as an independent positive predictor of survival. The combination therapy gave higher response rates than TACE alone (47.4% *vs*. 28.1%, $P < 0.05$), and additionally higher survival rates (64%, 28.6%, and 19.3% at 1, 3, 5 years, respectively, median 19 months, *vs*. 39.9%, 9.5%, and 7.2%, respectively, median 10 months, $P = 0.0001$) [39]. Improvement of survival brought by the combination therapy closely correlated to the larger tumour size (63% *vs*. 42% in 5–7 cm HCCs, $P = 0.22$; 50% *vs*. 0% in 8–10 cm HCCs, $P = 0.03$; and 17% *vs*. 0% in >10 cm HCCs, $P = 0.0002$) [40], and the irradiation dose [41]. Therefore, further studies evaluated increasing doses of radiation therapy on HCC in chemoradiation strategies (up to 60 Gy in 7.5 Gy fractions, equivalent to 87.5 Gy in 2 Gy fractions) delivered by conformational hypofractionation. This radiation schedule led to higher response rates (90.5%) and better overall survival rates (93.6%, 53.8%, and 26% at 1-, 2-, and 3-years, median 25 months). On multivariate analysis, radiation dose ($P = 0.001$), and tumour size ($P = 0.0001$) were the significant factors, without increasing side-effects [42]. The same data were obtained by stereotaxic radiotherapy approach, giving 50% complete response, absence of tumour progression within the infield radiation volumes, 100% survival after a mean follow up of 612 days (range 244–994 days) and absence of serious treatment-related toxic manifestations [43].

6. Conclusion

High-dose conformal or stereotaxic radiotherapy enables to deliver high-dose radiation to well defined tumour volumes with a frank sparing of the non-tumour surrounding liver parenchyma without restriction due to tumour topography and size, presence of peritumourous satellite nodules or associated segmental portal vein thrombosis. Thus, HCC has become a radio-sensitive tumour. Efficacy is strongly related to a smaller tumour size and higher dose of radiation while toxicity closely correlates to the pre-RT liver functions and the dose delivered to the uninvolved liver. Moreover, 3D-CRT yields several advantages that make it an attractive treatment option: (1) worldwide routine availability; (2) non-invasive feature; (3) opportunity to treat several lesions in a single course; (4) effective on deeper lesions inaccessible to percutaneous procedures; and (5) possibility to treat patients in poor medical conditions.

These data has led to integrate high-dose conformal or stereotaxic radiotherapy in the multimodal treatment of HCC as a possible curative-intent option as well as surgical resection or percutaneous procedures although phase-III controlled studies are warranted to clearly evidence its benefit. For small HCC tumours (<5 cm), high-dose CRT combined or not with a radiosensitizer is associated with excellent local control. In this setting, high-dose RT might be considered as the first line therapy for patients with early-stage HCCs contra-indicated to liver transplantation, liver resection and percutaneous destructions. However, prospective randomized controlled trials comparing high-dose RT to percutaneous destructions would be warranted. One the other hand, single HCC nodules of large size (>5 cm) frequently relapse after surgery or are non-eligible for surgery, thus leading these patients with palliative options such as TACE in first line therapy. For these patients, combination of TACE and CRT has been used with promising results although randomized controlled trial *vs*. TACE alone are warranted. Since the large size HCCs carry poor prognostic indicators in surgical resection series, prospective controlled trials comparing the RT + TACE combination to surgical resection should be carried out to ascertain the real potential benefit of this approach. However, the optimal scheduling of RT and TACE is unknown. Finally, CRT has a potential role in a wide spectrum of HCC presentations, from early-stage curable disease to advanced HCCs. It should be considered as a new treatment option to be discussed together with the other approaches depending on HCC presentation.

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