Conformal and stereotactic radiotherapy in hepatocellular carcinoma

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Historically, Radiation Therapy (RT) has played a minor role in the treatment of hepatocellular carcinoma, especially because of toxicity related to conventional techniques. However, high radiation doses can now be given safely by means of 3D-conformal techniques and other more specialized techniques. 3D-conformal RT, in which both target definition and treatment planning are based on three-dimensional image data sets, provided good local control in several series. As an evolution of cranial radiosurgery, stereotactic body radiation therapy (SBRT) is currently being employed as a new tool for the treatment of HCC, as it offers the opportunity of achieving radioablation for tumors up to 6 cm in diameter with a minimal risk of radiation induced liver disease. SBRT is distinguished by the fact that both planning and treatment are guided by reference to a system of external stereotactic coordinates. As a consequence, SBRT may succeed in minimizing geometric treatment uncertainties, thus allowing the delivery of high doses to the target, given in a small number of fractions. In several published series of SBRT for HCC, actuarial 5-year local control rates higher than 80% have been achieved. In short, radiation therapy should be considered as a useful addition to the treatment spectrum of HCC.

KEY WORDS: Conformal radiotherapy, Hepatocellular carcinoma, Stereotactic radiotherapy.

Introduction

Historically, radiation therapy (RT) has played a minor role in the management of hepatocellular carcinoma (HCC), owing to the low tolerance of the whole liver to RT and difficulties in delivering high doses conformally to limited volumes inside the liver [19].
The most common liver toxicity is radiation-induced liver disease (RILD), which is a syndrome of anicteric hepatomegaly, ascites, and elevated liver enzymes that occurs from 2 weeks to 3 months after RT [2]. Eventually RILD can evolve to liver failure. Precipitation of underlying liver disease as well as reactivation of viral hepatitis also can occur after RT for HCC. RILD occurs in 5–10% of patients treated with 30–35 Gy to the whole liver. However, a partial volume of the liver may be treated safely to much higher doses (up to 90 Gy) as long as an adequate volume of normal liver is spared. HCC patients have a lower liver tolerance to RT than patients with liver metastases, due to their underlying liver disease. The risk of RILD can be estimated from the mean radiation dose to uninvolved liver, according to the Lyman normal tissue complication probability model of partial tolerance. The mean liver doses associated with a 5% risk of RILD for primary and metastatic liver cancer are 28 Gy and 32 Gy, respectively, in 2 Gy per fraction [7,10].
Nowadays high radiation doses can be given safely, thanks to technical advancements, including 3D-conformal planning techniques and some more advanced techniques.

Conformal RT

3D-Conformal RT is characterized by target delineation and treatment planning based upon three-dimensional imaging data sets as well as by individualized field shaping by means of multileaf collimators. Contouring of clinical target volume (CTV) on contrast-enhanced CT should take into account data showing that in most

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instances imaging by CT or MRI overestimates true gross pathologic size. In fact a 0.5 cm margin around the gross radiographic tumor has been estimated to cover more than 90% of pathologic gross lesions [21].
Also, a margin has to be added to CTV, thus defining a planning target volume allowing for both liver motion and set up inaccuracies. Margins associated with both sources of inaccuracies can be kept to a minimum by adequate patient immobilization, while respiratory motion can be addressed by more advanced techniques such as breath hold and/or respiratory gating of the RT. Treatment plans are individualized and make use multiple fields or arcs from different angles, including non-axial beams.
In several single-center experiences of conformal RT a strong dose-response relationship has been observed, with improved local control and survival when doses exceeded 50 Gy conventionally fractionated [2,28,29]. Wide ranges of 5-year local control and survival rates have been reported, due to substantial heterogeneity in patient selection and treatment delivered.
There is a large Asian experience in combining conformal RT with trans-arterial chemoembolization (TACE) in patients with advanced HCC. Different strategies have been studied [2,18,22,25,39]. One logical approach is to deliver RT as a "consolidation" planned procedure after TACE to target residual cancer cells at the tumor periphery.

Advanced techniques

Recent technological developments in the field of radiation oncology have the potential to improve radiation treatments compared to conformal RT, by conforming dose distribution more tightly to the tumor [14].

INTENSITY-MODULATED RT (IMRT)
With IMRT, radiation is delivered with a non-homogeneous modulated fluence pattern for each beam angle. The optimal dose distribution is achieved by computer-aided automated optimization ("inverse planning") of beams modulation. Clinical experience with IMRT for the treatment of HCC is limited. Planning studies have suggested some benefit in selected categories of patients [11,14].

PROTON AND HEAVY-ION RT
Protons and carbon-ion have physical properties, which makes them well suited for the treatment of deep-seated tumors surrounded by normal tissues. A peak area (Bragg-peak) exists in which rapidly increasing doses are deposited at the end of the beam range, at a depth depending on the beam energy. It thus permits greater sparing of normal tissues surrounding the tumor than conformal photon therapy.
In several trials of carbon-ion and proton beam RT, 5-year local control rates higher than 80% have been achieved. Pathologic complete responses were reported in 2/6 patients with HCC who underwent liver transplantation 6 to 18 months after proton therapy [5].

IMAGE-GUIDED RT (IGRT)
The term IGRT refers to imaging techniques ensuring spatial precision of treatment in each daily fraction. As a result, IGRT allows for a reduction of added safety margins designed to account for setup variability.
Image-guided verification on the linear accelerator couch may be achieved by different modalities: use of electronic portal imaging devices to assess the position of implanted radio-opaque fiducial markers; in-room CT units linked by rail systems with the treatment delivery unit; cone-beam on-board CT units, physically mounted on the linear accelerator gantry [14]. Both IMRT and SBRT should be combined with IGRT tools in order to derive greatest benefits in terms of geometric accuracy.

STEREOTACTIC BODY RADIOTHERAPY (SBRT)
As an evolution of cranial radiosurgery, SBRT is currently being explored as a new tool in radiation oncology for the treatment of extra-cranial primary and metastatic localized tumors. HCC is one of the main topics of research in the field of abdominal SBRT, as it offers the opportunity of achieving radioablation with a negligible risk of RILD [6,17,30,31,33].
SBRT is distinguished by the fact that both planning and treatment are guided by reference to a system of external stereotactic coordinates [30,33,37]. Usually in SBRT a body frame is employed in which the patient is immobilized with the use of a vacuum pillow and an abdominal compression device to reduce diaphragmatic excursion. As a consequence stereotactically guided RT may succeed in minimizing geometric treatment uncertainties and decrease the volume of uninvolved hepatic tissue, thus allowing the delivery of high doses to the target with a high degree of precision, given in a small number of fractions [12,13,24,36].
Although liver motion because of breathing may be substantial (from < 5mm up to 3 cm in some patients), active breathing control techniques such as breath hold and/or respiratory beam gating can minimize the adverse effects of breathing motion, allowing higher precision in tumor position during the delivery of treatment [4,38].
The typical beam arrangement is a combination of at least five non-coplanar conformal arcs with 6-18 MV photons [26]. Strict normal tissue constraints must be satisfied in treatment planning. In particular several dose/volume criteria have been established as a constraint for uninvolved liver: for example at least 700 cc of uninvolved liver should receive less than 15 Gy total dose when given in 3 fractions.
Since the extra-target dose distribution depends on the dose delivered to the periphery of the target, an inhomogeneous dose distribution with about a 50% higher dose to the central part of the target was chosen in most studies, a strategy also supported by the high probability of hypoxic areas bearing more radioresistant clonogens in

the central part of the lesion. Total doses up to 26 Gy in a single fraction to 60 Gy in 3 fractions have been prescribed in several series without excess toxicity [3,8,20,23,32,34,35,38].

Eligibility criteria for SBRT in HCC patients usually include: number of lesions less than or equal to three; tumor size lower than 5 cm; early or intermediate stage HCC; Child A or B cirrhosis [1].

Following SBRT, contrast enhanced CT at least 4 weeks after the treatment is the standard imaging modality for evaluating response. Non-enhanced tumoral areas reflect tissue necrosis. In patients with a single lesion, tumor control should be defined as a stable or decreasing AFP level and liver tumor either stable or smaller in size at CT/MRI evaluation.

At least seven series of liver SBRT have been published, totalling more than 150 patients. Most series included both primary liver cancers and hepatic metastases. The median tumor volume ranged from 6 to 78 mL. In patients with HCC, SBRT has shown actuarial 5-year local tumor control rates higher than 80%. Since anyway most patients develop new lesions, the 5-year survival rate rarely exceed 25%-50%, depending also on the severity of underlying cirrhosis [27].

Conclusions

While surgery remains the standard of care for early HCC, it is limited to only a minority of patients. Currently non-surgical treatment options include several well-established ablative modalities, as well as chemo-embolization. Each of them has shown efficacy, but also suffers from being invasive at some degree [15].

Lately, RT has evolved to a potentially curative treatment option in patients with HCC. High-dose conformal RT delivered in a variety of fractionation schedules has been used safely with good results, particularly in patients who receive higher doses of RT. Toxicity is related mainly to pre-treatment liver function and to the dose given to uninvolved liver. On the whole toxicity from SBRT seems comparable to any of non-surgical ablative techniques [6,16]. Hypofractionated SBRT can now be regarded as an established technique achieving rates of local tumor control higher than 80% in selected cases. Thus, SBRT stands out as a possible non surgical alternative in patients with small solitary tumors, candidates for a radical approach. In selected cases it can also contribute to allow a "bridge" to transplantion.

Therefore radiation therapy should be considered as a useful addition to the treatment spectrum of HCC.

Riassunto

Storicamente la Radioterapia (RT) ha avuto un ruolo marginale nel trattamento dell'epatocarcinoma, soprattutto a causa della tossicità associata a tecniche di trattamento convenzionali. Tuttavia esistono oggi modalità di trattamento più selettive che consentono di somministrare dosi elevate con rischi limitati. La RT conformazionale, che si basa su una definizione del bersaglio e pianificazione dosimetrica su immagini tridimensionali, in diverse esperienze ha prodotto importanti risultati clinici in termini di controllo locale e di sopravvivenza. Tra le modalità tecniche più avanzate, la RT stereotassica corporea ipofrazionata (SBRT) realizza una radioablazione superselettiva, fattibile per lesioni fino 6 cm di diametro con minimo rischio di danno epatico. Nella SBRT sia la pianificazione che il trattamento fanno riferimento a un sistema di coordinate stereotassiche esterne solidali al paziente mediante un sistema di immobilizzazione dedicato. Ciò si traduce in un elevato livello di precisione che permette la somministrazione di dosi elevate in poche frazioni. In alcune esperienze di SBRT si è ottenuto un controllo locale fino all'80%. In sintesi la RT effettuata con modalità avanzate costituisce una efficace alternativa non invasiva nel trattamento dell'epatocarcinoma.

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