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Efficacy of Radiotherapy for Hepatocellular Carcinoma, Liver Cancer and Three-Dimensional Conformal Radiation Therapy

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Abstract:

Intrahepatic cholangiocarcinoma (10–15%) and hepatocellular carcinoma (HCC, 75–85%) are the two main types of primary liver cancer. Surgical removal of primary HCC is not an option for most individuals. Patients with early-stage liver cancer have effective and potentially curative treatment options, including surgical resection, liver transplantation, and percutaneous puncture. Although radiation therapy's usage in the potentially curative context is on the rise, it is still primarily reserved for patients with advanced liver cancer as a non-surgical alternative treatment. Radiotherapy uses ionising radiation to treat certain areas without invading those areas. For primary liver cancer (specifically HCC), this review describes the safety and effectiveness of various radiotherapy methods, including three-dimensional conformal radiotherapy (3DCRT), intensity modulated radiation therapy (IMRT), stereotactic body radiotherapy (SBRT), volume-modulated arc therapy (VMAT), and internal radiation therapies.

Keywords: Radiotherapy, Hepatocellular Carcinoma, Three-Dimensional Conformal Radiation Therapy.

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Introduction

Hepatocellular carcinoma (HCC) accounts for 75–85% of cases, intrahepatic cholangiocarcinoma for 10–15% of cases, and fibrolamellar HCC and other less frequent tumours make up primary liver cancer. The prognosis and likelihood of arterial and metastatic dissemination are both poor in primary liver cancer. After surgery, patients with early stage HCC have a 3-year survival rate of 72% and a 5-year survival rate of 50%; after liver transplantation, the 5-year survival rate ranges from 48% to 61%; and the usual life span after diagnosis is 6-20 months (2-4). On a global scale, HCC ranks high among cancer-related killers. South-east Asia and Sub-Saharan Africa, regions where hepatitis B (HBV) and hepatitis C (HCV) are prevalent, have the highest incidence of this virus. About 42,030 new instances of liver cancer will be detected in 2019, with 31,780 deaths attributable to the disease, according to the GLOBOCAN forecast. The use of radiation in HCC is the primary topic of this review. Liver cirrhosis is a frequent scenario for hepatocellular carcinoma to develop [1-3]. Hepatitis B and C, alcoholic cirrhosis, gene hemochromatosis, non-alcoholic steato-hepatitis (NASH), alpha-1-antitrypsin deficiency, and stage 4 primary biliary cirrhosis are common causes of cirrhosis that should be checked for. Without cirrhosis, hepatocellular carcinoma (HCC) can occur in people who carry the hepatitis B virus. Screening ultrasounds and blood tests for alpha-fetal protein (AFP) should be included of a 6-monthly HCC surveillance plan. Even though AFP has been used for a long time to diagnose HCC and is also included in surveillance algorithms, it is neither sensitive or specific enough to be utilised as an assay for surveillance. Imaging and histology are thus essential for HCC diagnosis. Histological confirmation of HCC was once the gold standard, but today there is consensus on a set of non-invasive criteria that can be used to diagnose the disease in patients with cirrhosis. Current radiological methods allow for the diagnosis of HCC in the absence of a biopsy as long as the characteristic imaging features are present; this is in contrast to earlier recommendations that relied on the AFP level and the lesion's radiological appearance on dynamic CT or MRI scans. A dynamic CT scan or magnetic resonance imaging (MR) with contrast is necessary for this. During the arterial phase, the enhancement of HCC is more pronounced compared to the surrounding liver. This is due to the fact that HCC includes solely arterial blood, in contrast to the diluted arterial blood in the liver, which is composed of venous blood that does not contain contrast. Compared to the surrounding liver, the HCC shows less enhancement in the venous phase. The reason behind this is that portal blood in the liver still contains contrast, while arterial blood travelling through the lesion in HCC does not, and this is due to the absence of a portal blood supply in the tumour. The phrase used to describe this phenomenon is "washout," however it fails to adequately characterise the actual chain of events. The occurrence of "washout" continues throughout the delayed phase [4, 5]. It is possible that "washout" is exclusive to the delayed phase in certain cases. A highly specific indicator of HCC is the presence of arterial absorption followed by washout. Even for lesions as small as 1 cm, this has been proven. Thus, a four-stage analysis consisting of an unenhanced, arterial, venous, and delayed phase is necessary to adequately establish the presence of HCC. While venous washout is necessary, arterial hypervascu larity is not enough on its own. According to Bruix et al. (2005), the current guidelines for the diagnosis of HCC are: 1. Advice for lesions less than 1 cm has not changed. Since the majority of these nodules will be cirrhotic rather than HCC, a thorough study is unnecessary. Nevertheless, it is advised to closely monitor the nodules every three months using the same method that initially identified their presence. It is advised to use ultrasound as the method of follow-up if these were identified during screening on ultrasonography. Once two years have passed with no change, regular monitoring can be resumed. Additional imaging using a dynamic contrast enhanced MRI or a 4-phase multidetector CT scan is warranted for lesions larger than 1 cm in diameter. No more testing is necessary to confirm the diagnosis of HCC if the MRI or CT scan findings are consistent with the typical findings of HCC, as mentioned above. One of two approaches might be considered if the symptoms do not fit the profile of HCC (and do not indicate hemangioma) [6, 7]. It is recommended to do a second contrast-enhanced investigation using the alternate imaging method. Assuming there are no out-of-the-ordinary symptoms, the diagnosis is solid. Another possibility is that a biopsy will be ordered due to an unusual research .

Small lesions (defined as less than 2 cm in diameter) pose the sole diagnostic challenge when there is a hypo-vascular lesion, which is described as an area that does not enhance as much as the surrounding liver on arterial and venous phase imaging. According to pathological research, these lesions really have two blood supplies, which is why they

seem hypovascular. On the other hand, dysplastic nodules can exhibit diminished portal supply and unpaired arteries. Thus, in order to differentiate dysplastic nodules from HCC, a biopsy is necessary. Regrettably, stromal invasion—the defining characteristic that differentiates a high-grade dysplastic tumour from HCC—may remain undetectable even after a needle biopsy. Hypovascularity can also be present in larger HCCs. Biopsies may be necessary for these as well, however in most cases a diagnosis can be made without one. Biopsies of tiny lesions should be examined by a skilled pathologist when a histological diagnosis is required. To enhance diagnostic accuracy, it is recommended to stain non-HCC tissue with all available markers, including as CD34, CK7, glypican 3, HSP-70, and glutamine synthetase. Imaging of the lesion should be performed every three to six months until the nodule either goes away, grows, or shows diagnostic signs of HCC in individuals whose [8, 9] biopsies come back negative for the cancer. If the lesion grows larger but still doesn't look like HCC, it's best to get a second opinion. Following the confirmation of HCC, further laboratory testing should consist of the following: a hepatitis B and C panel, baseline tests for liver and renal function, coagulation tests (PT/INR), albumin, a full blood count with differential and platelet levels, chest imaging (ideally a chest CT scan), and a bone scan if clinically indicated. In addition to predicting therapeutic response and recurrence in HCC, positron emission tomography (PET) scans can identify extra-hepatic illness. Prior research has shown that a multidisciplinary team should be included in determining the best course of treatment for a patient with HCC. Members of the liver transplant team, interventional radiologists, medical and radiation oncologists, hepatologists, and hepatobiliary surgeons should make up this team. Indeed, specific patient and tumour traits, together with the severity of preexisting liver disease, must be considered when deciding on the best course of treatment for every particular HCC patient. A hepatologist's role includes making a diagnosis, evaluating the patient's liver function, deciding on the best course of treatment based on that evaluation, and managing the patient's liver illness both before and throughout treatment .

Cancer Staging

The usage of any certain HCC staging method is not agreed upon by all countries. Although tumour stage is a major factor in solid tumour prognosis, underlying liver dysfunction is also a major factor in HCCit. Patients with HCC should have their tumour stage, liver function and performance status, therapy effects, and overall health evaluated using a staging approach that accounts for all of the above. Traditionally, the TNM or Okuda staging systems have been used to classify HCC. Especially for individuals in the early to middle stages of their disease, none of these can help determine a prognosis with the best treatments. Model for End-Stage Liver Disease (MELD) and Child-Turcotte-Pugh's Class (CTP), often known as the Child-Pugh class, are two systems that solely take liver function into account. The most popular schemas out of all the ones [10] offered are the BCLC system and CLIP (Cancer of the Liver Italian Programme). Tumour stage, liver function, physical, and cancer-related condition are all factors that make up the BCLC system. The biggest perk is that it connects staging to treatment options and life expectancy estimates. For patients with CTP-A and a solitary nodule less than 2 cm in size, this is considered very early stage HCC .

Managing initial

The primary methods for achieving a cure for hepatocellular carcinoma (HCC) include radical treatment, which includes surgical removal of the cancerous tumour and/or liver transplantation. It is not until the tumour has progressed to an advanced and frequently incurable stage that the majority of patients with HCC experience symptoms. Surgical procedures are not an option for most people. At now, only 20% of cases are surgically resected. Surgery, liver transplantation, and percutaneous puncture are effective treatments for individuals with very early or early stage hepatocellular carcinoma (Child-Pugh A, tumour diameter), according to the American Association for the Study of Liver Diseases (AASLD) Guide on the Treatment of Hepatocellular Carcinoma.

Chemotherapy for early-stage liver cancer

employs ionising radiation to induce direct and indirect DNA double strand breaks; it is a non-invasive local treatment. Radiation therapy can target liver tumours, which have a moderate to high radio sensitivity, alongside lymphatic tissue tumours, bone marrow tumours, and normal tissues including the kidney and bone marrow. Ionising radiation's mechanical effects include reducing or disabling the normal function of biological macromolecules like nucleic acids, proteins, enzymes, etc., and eventually leading to irreparable double strand DNA breaks through ionisation of water. The healthy liver can recover from radiation-induced localised liver damage thanks to its

remarkable regenerative capacity and the hepatic cell proliferation of the healthy tissue that was spared. Over the years, there have been numerous technological advancements in radiotherapy for HCC, allowing for more precise conformal delivery of radiation around specific liver tumours. These include local field irradiation, moving strip radiotherapy, hyper-fractionation radiotherapy, and whole-liver wide field low dose irradiation. Before the 1990s, radiation-induced liver disease (RILD), liver failure, or death could result from large-volume liver irradiation, which damaged normal liver tissue. Thus, the application of targeted radiation therapy with the goal of curing the disease was postponed. By utilising three-dimensional conformal radiotherapy (3DCRT) [11, 12], intensity modulated radiation therapy (IMRT), and stereotactic body radiotherapy (SBRT), the radiation dose to normal tissues around the lesion could be greatly reduced while the accuracy of the targeting was greatly enhanced. Serious side effects are much less likely to occur now because to modern radiation treatment and advanced imaging tools. Radiation therapy is now an integral aspect of HCC treatment plans. Although it is reserved as a treatment option only in cases where other standard treatments are not possible, in certain country guidelines it is listed as a prioritised treatment for patients with early, middle, or advanced HCC. There are two main types of radiation treatment: external and internal. The former uses several types of radiation sources (18). Subband, gradient-coated, image-modulated, and volume-modulated arc treatment (VMAT) are the mainstays of photon-based external radiation therapy [13, 14]. Liver cancer patients have also been treated with protons and carbon ions, although these ions are more costly and not as commonly available. Radioactive iodinated oil, 125I particles implanted, 90Y microsphere therapy, and 131I monoclonal antibodies are all part of internal radiation therapy, which is frequently administered through the hepatic artery. Liver cancer has also been treated using percutaneous brachytherapy. This article examines the efficacy and safety of different radiation treatments for various stages of liver cancer, including HCC. Here you may find a compilation of research on radiotherapy's efficacy and overall survival rate in cases of primary liver cancer.

CT scans with three-dimensional conformal radiation

Liver cancer patients have frequently been treated with 3DCRT. New developments in optimisation, computational mathematics, and virtual reconstruction form the basis of this treatment. Using a CT scan of the patient in treatment position, a radiotherapy treatment planning software system determines the dose in a patient model, which is then used to construct radiation target volumes, field shapes, and angles. The target dose is determined by taking into account the tolerance doses of the underlying liver and neighbouring normal tissues [15]. When used to treat patients with liver cancer, CRT significantly enhances the therapeutic ratio while sparing normal tissues like the liver from the treatment's early and late adverse responses. Liver movement caused by respiration is an issue with 3D-CRT since it affects the precision of tumour localisation and radiation. An elevated risk of liver toxicity can result from an excessively large amount of irradiated liver. Newer methods exist to mitigate the effects of the liver's respiratory motion, such as actively holding the breath to immobilise the liver, limiting radiation treatment to a specific phase of the respiratory cycle, or following the radiation beam as it moves across the liver. Results for early stage liver cancer treated with 3DCRT range from 73.6% (40) to 81.1% overall survival after one year, with local control rates between 71.4% and 93.8% after more than one month. Compared to individuals with bigger, multifocal malignancies with vascular invasion, those with a single, tiny HCC (less than 10 cm) had the best chance of a positive outcome. Mornex et al. had treated 25 patients with a single HCC (diameter IMRT IMRT is a newer technology developed on the basis of 3DCRT. Using optimization software, based on multi-field irradiation, the dose intensity of each field within larger fields can be varied, and the radiation dose in the target area may be more evenly distributed, and more tightly surrounding the target volume, sparing concave or convex adjacent normal tissues, which is beneficial for protecting important sensitive organs. It is more suitable for treating tumors with irregular three-dimensional shapes. The disadvantages of IMRT are the longer exposure time and poor tolerance in patients with severe illness. Most of the IMRT series have focused on advanced liver cancer patients, with a local control rate from 30% to 50% for advanced HCC. For tumors with a margin less than 1 cm adjacent to or involved in the hilar vascular trunk, IMRT is helpful for those who will receive surgery. IMRT improved the 3-year OS and disease-free survival in HCC patients receiving narrow margin hepatectomy [16-19]. This treatment strategy is highly effective for patients with a narrow surgical margin. A prospective randomized study was conducted by Yu et al. which recruited 119 HCC patient who had narrow margin (in adjuvant RT group of one-, 3-, and 5-year recurrencefree survival rates than that in control group. Besides, combined application of IMRT and TACE can significantly improve the prognosis of HCC patients. A study observed 26 liver cancer patients with portal tumor thrombus (87% were in III–IV stage) and found the patients under

the combined treatment of IMRT and TACE (the median dose of radiotherapy was 50 Gy, 44–70 Gy) had an effective rate of 64. 8 percent, with a median survival rate of 20.2 months.

Therapeutic arc volumetric modulation

The benefits of administering radiation via a revolving gantry make VMAT a dynamic IMRT approach. When used with active breathing coordinator (ABC), it can render the liver immobile. Its dose compliance is better than that of 3DCRT and IMRT. With VMAT, the target area is more precisely defined, and there is less radiation that can harm organs and less radiation that could harm the liver (8,54,55). After administering 138 patients with HCC (88.4% of whom were in AJCC stage III or IV) VMAT with 45, 60, and 66 Gy of radiation (either 1.8 or 2 Gy once), Wang et al. assessed 108 patients. Each subject was assigned a BCLC stage between A and C. After a maximum of 28 months of follow-up, they demonstrated 11% CR, 53% PR, 29% SD, and 6% PD instances. There were no major toxic events, the local control rate was 93.7% at 12 months and 95% at 6 months, and the median survival time was 10.6 months.

The SBRT

is a form of radiation treatment that makes use of three-dimensional conformal radiotherapy (3DCRT). By utilising image guidance and respiratory motion management technologies, SBRT is able to precisely target the tumour area. Within the tumour, a high dosage is launched, while the dose beyond the target area falls significantly. This allows the radiation to avoid damaging the healthy tissue immediately surrounding the tumour. SBRT necessitates precision administration with daily imaging guidance and permits irradiation to be administered in fewer fractions (1–6) over one to two weeks, as opposed to 25–35 over 5–7 weeks, as is the case with traditional radiation therapy. Early results have concentrated on early stage HCC, and SBRT is most effective in treating smaller liver tumours. Most tumours bigger than 10 cm are controlled after 1 to 2 years with mild dosage SBRT, even though the local control rate is lower in larger tumours [20, 21]. Sixty HCC patients who underwent SBRT were subsequently followed up by Andolino et al. They had a median tumour diameter of 3.2 cm, received a dose of 42 Gy/3 fractions, had a two-year local control rate of 90%, had a two-year PFS rate of 48%, and a two-year OS rate of 67%; naturally, no RILD events happened. Using doses ranging from 30 to 39 Gy/3 portions, Kwon et al. treated 42 patients with HCC; they saw a CR of 60% and PR of 26%; and the 1- and 3-year PFS rates were 72% and 67.5%, respectively. Radiotherapy doses of 40 Gy/5 fractions were administered to patients with Child-Pugh A (n=137) and Child-Pugh B (n=48) liver dysfunction in another retrospective analysis, while patients with Child-Pugh B liver dysfunction received 35 Gy/5 fractions. There was an 89% and 91% local control rate and a 66% OS rate after three years, respectively. Using SBRT, Takada et al. treated fifty patients with small-HCC; they found that 30 Gy/5 fractions was a safe and effective treatment for cirrhosis patients. For minor HCC, SBRT and radiofrequency ablation therapy have similar indications and have been compared in a few studies .

Heavy ion and proton radiation

Deep liver tumours and individuals with compromised liver function may benefit from heavy ion radiation because it has the potential to cause less low dose splash to neighbouring normal tissues. Radiation therapy with protons and carbon ions deposits its doses inside the body in a Bragg peak, with a steep dose decline in healthy tissues outside of the target volume. In addition to the steep dose reduction following the Bragg peak, photons may offer additional benefits in proton and heavy ion radiation, such as reduced oxygen effect, high relative biological effectiveness, and improved line energy transfer. It is possible to kill tumour cells while sparing surrounding normal tissues by directing the Bragg peak to the depth of the tumour using energy adjustment [23, 24]. Nakayama used proton radiation to treat 47 patients with head and neck cancers with doses of 72.6 Gy divided into 22 fractions or 77 Gy divided into 35 fractions. Results showed a median overall survival time of 33.9 months, a local control rate of 88.1% after 3 years, and a total survival rate of 50% after 3 years. Ultimately, 6.4% of patients had grade 2 gastrointestinal symptoms and 2.1% reported grade 3, respectively. The 27 patients with thrombi in their portal veins who had proton radiation therapy (50 to 66 Gy/20 to 22 fractions) were the subjects of the study by Lee et al. At the end, they had 55.6% PR, 37.0% SD, and 7.4% PD. A prospective study was conducted by Imada et al. and involved 64 patients with HCC who had a portal vein tumour thrombus. Near the thrombus, there were 18 liver tumours.

Intraoperative radiation

By using the body's own cavities and tissue spaces, radioactive sources can be implanted or placed directly within a patient as part of internal radiation therapy. The radioactive source was guided into the target via catheters, allowing for the application of high dosage radiation in a small volume. Presently, 90Y microspheres, 131I monoclonal antibodies, radioactive iodinated oil, and 125I particle implantation are the mainstays of selective internal radioembolization therapy (SIRT) for the internal radiation treatment of primary liver cancer. One of these is the use of 90Y microsphere radiation to shrink huge tumours to a level where they can be transplanted, which increases the survival rate of patients with hepatocellular carcinoma. The survival benefit that SIRT can provide is comparable to that of TACE, according to the research. Overall and disease-specific survival benefits in unresectable HCC were comparable across SBRT and SIRT .

Medical Use

Orthotopic liver transplant, surgical resection, and percutaneous radiofrequency ablation are three treatments for primary HCC that have the potential to be curative, according to the American Association for the Study of Liver Diseases. Unfortunately, liver transplantation is only an option for a tiny fraction of HCC patients. On top of that, a lot of individuals won't be able to get their tumours removed or abated because of advanced cirrhosis or an unfavourable placement. There are two main reasons why external beam radiation treatment has not been more widely used to treat HCC. Patients with HCC-complicating liver cirrhosis are especially vulnerable to the dose-limiting problems of liver irradiation and radiation-induced liver disease (RILD). The second option is trans-arterial chemoembolization, which is either less invasive or more efficient than RFA. A more attractive therapy approach that circumvents some of these constraints is SBRT, which has an ever-improving track record of safely delivering hypo-fractionated radiation doses to tumours within radiosensitive organs. There have been a number of series published on the topic of SBRT in liver cancers [25, 26]; however, the vast majority of these studies have included non-cirrhotic patients with liver metastases. Results from a phase II study on SBRT for liver metastases (60 Gy in three fractions) were published by Rusthoven et al., who found that the treatment was effective with a local control (LC) rate of 93% after 2 years and no grade 3 or higher toxicity. Similar evidence for HCC is only now coming to light, although these trials have validated the safety and effectiveness of SBRT for metastatic lesions in an otherwise healthy liver (among others, see "Liver Metastasis" by Stinauer et al. in this volume). Blomgren et al. recorded one of the first investigations on hypofractionated radioablative doses for HCC in a publication. One patient with embryonic cancer and nine individuals with HCC carcinomas received SBRT. One patient also had cancer of the intrahepatic bile ducts. Twelve malignancies were eradicated from the eleven patients. Within the target volume, the total minimum doses ranged from 15 to 45 Gy. Each part of the treatment received 5–15 Gy of energy, with a minimum dose to the target administered over the course of one to three sessions. At the 12-month mean follow-up, five tumours showed stable disease, twelve tumours shrank in size, and two tumours did not form, for a total response rate of 70% (10% CR). After treatment, all patients had nausea for a few hours and a fever of up to 38.5C. Unfortunately, an autopsy was not conducted when one patient passed away two days following a 30-Gy dosage to a massive HCC in the left hepatic lobe. Two patients died (likely due to liver failure) after developing ascites during the first three to six weeks of SBRT. A phase I-II trial with 45 lesions (34 metastatic and 11 HCC) was published by Méndez Romero et al. In contrast, patients with cirrhosis and/or HCC C 4 cm received 59.5 Gy or 39.0 Gy, with a prescription isodose of 65%, whereas patients with metastases, HCC without cirrhosis, or HCC\4 cm with cirrhosis received 3 fractions of 12.5 Gy. At one year, 94% of the group had local control; at two years, that number dropped to 82%. Patients suffering from HCC and CPC-B linked liver cirrhosis had a higher grade of C3. Tse et al. (2008) performed a prospective Phase I trial at the University of Toronto. They administered CTP-A to 31 patients with HCC and SBRT to 10 patients with intrahepatic cholangiocarcinomas. The individualised dose prescription was based on the volume of liver irradiated and the estimated risk of liver toxicity, using the NTCP model. The median dose was 36.0 Gy, with a range of 24.0-54.0 Gy administered over 6 fractions. Within three months following SBRT, there were no reports of RILD or treatment-related grade 4/5 toxicities. Five individuals, or 12% of the total, had liver enzymes grade. Within three months following SBRT, seven patients (five with HCC and two with IHC) experienced a drop in liver function from CTP-A to CTP-B. Survival rates for patients with HCC were 11.7 months (95% CI, 9.2-21.6 months) and for those with IHC, it was 15.0 months (95% CI, 6.5-29.0 months). After one year, the LC survival rate was 65% while the OS survival rate was 48%. The majority of the 20 patients with HCC were CTP Class A, with an average size of 3.8 cm. Choi et al. administered 50 Gy in five to ten portions [27, 28]. With LC rates of 80% and OS rates of 70% after one year, respectively, they did not disclose any

cases of severe poisoning. No toxicities of grade C3 were reported during the treatment, and it was well-tolerated. Afterwards, Kwon et al. found that 72 percent of patients had a partial or full response with just one grade 1 liver damage out of 42 patients with CTP class A and B. The patients had a median volume of 15.4 cc and a median dosage of 36 Gy in three fractions. Multivariate research revealed that a tumour volume less than 32 cc was linked to better survival. Univariate analysis revealed significant initial in-field response, in-field advancement, and Child-Pugh score; however, multivariate analysis did not reveal any such significance. Patients with inoperable HCC with diameters [10 cm] who had SBRT as a salvage treatment following TACE failure were the subjects of a dose escalation trial published by Seo et al. (2010). The doses of SBRT were given in three fractions ranging from 33 to 57 Gy for tumours less than 300 cc and 40 to 44 Gy in four parts for tumours between 301 and 500 cc, according to the tumour volume. Only four patients had CPC-B, while thirty-four had CPC-A. Fifteen months was the median duration of follow-up. The results at three months indicated a local response of 63.1% and a progressing illness of 7.9%. Finally, 22 out of 38 patients experienced some kind of progression; the most prevalent of them was regional failure. Rates of overall survival at one, two, and three years were 68.4%, 61.4 %, and 42.1 %, respectively. A dose of C42 Gy divided into three portions was identified as an independent predictor of overall survival on multivariate analysis. We designed a phase I-II trial to examine SBRT's function in HCC patients at Indiana University Simon Cancer Centre (IUSCC). There were 17 individuals with 25 lesions who participated in the phase I dose escalation study. No dose-limiting toxicity occurred when the dosage was increased from 36 to 48 Gy in three portions for CTP-A patients. Grade 3 hepatic toxicity occurred in two patients with CTP-B illness at the 42 Gy (14 Gy/fraction) dose, according to Primary Liver Cancer 171. After one patient developed increasing liver failure, the protocol was changed to allow future CTP-B patients to receive a regimen of five fractions beginning at 40 Gy (8 Gy/fraction). Despite the lack of DLT, four more patients were enrolled; one of them passed away from unrelated causes following an unfinished SBRT course. Only the CTP score ($p = 0.03$) was associated with more than one grade 3 or severe liver damage or death within six months. A liver transplant was performed on six patients. With a median FU of 24 months (10-42 months) and LC/stabilization of the illness of 100%, ten patients are alive and well without progression. The overall survival rate was estimated to be 75% after one year and 60% after two years using the Kaplan-Meier method. With promising early local control and survival rates, our phase I trial showed that SBRT is a well-tolerated treatment for appropriately selected patients with HCC. The accrual period for a confirmatory phase II trial is now open. Eligible patients with CTP-B will get 8 Gy 9/5 fractions, while those with CTP-A will receive 16 Gy 9/3 fractions (48 Gy total dosage) in the present phase II experiment. Including 60 patients with CTP class A and B liver cirrhosis, Andolino et al. (2011) from Indiana University presented the biggest series to date of HCC treated with SBRT. Our study adds to the existing body of evidence supporting the safety of SBRT for HCC, since previously reported studies have shown that only 13% of patients with a CTP score B7 had an elevation of less than one grade in hematologic/hepatic dysfunction. The correlation between pre-treatment CTP score and toxicity development ($p = 0.035$) and the occurrence of an increase in \1 grade in hematologic/hepatic dysfunction ($p = 0.008$) was significant. Our results raise concerns about the safety of SBRT for patients with a CTP score of 8. As part of a previous phase I dose escalation research, two of the eight patients with a score of C8 who suffered progressive liver failure did so after receiving a dosage of 42 Gy, with 14 Gy each fraction. We no longer employ this fractionation technique for patients with CTP class B cirrhosis because it was later determined to be harmful for them. However, it is recommended that only patients who are currently on the transplant waiting list have SBRT for a CTP score of C8. Presently, we are only accepting patients with one to three lesions, a maximum tumour diameter of B6 cm, and a CTP class A or B score of B7 for patients who are not on the transplant waiting list. By censoring patients during transplantation, we were able to obtain a 2-year LC rate of 90%, but median LC has not been reached yet. Rates of 2-year LC obtained with percutaneous ethanol injection (70-85%), radio frequency ablation (85-98%) and transarterial chemo-embolization (60-70%), respectively. With half of the lesions in this series being 3 cm in size, our SBRT results look even more promising, especially when the rates of local control attained with radio-frequency ablation dropped to about 80% or lower for these lesions. Time to progression (TTP) was three years for the non-transplanted group and four years for the overall cohort, which is equally noteworthy and maybe more clinically significant. These rates surpass the quoted rate for similarly sized tumours 10-27 months after trans arterial chemoembolization or radioembolization, and they are equivalent to those obtained with surgical resection and percutaneous ablation. It is still unclear how this liver-directed therapy may affect overall survival compared to others. Comparisons of overall survival cannot be done due

to the population's heterogeneity, particularly in regards to the degree of liver cirrhosis and the presence or absence of significant comorbidities [29]. Therefore, official phase II/III investigations are necessary before any comparisons can be established. Last but not least, SBRT deserves more attention as a possible alternative in the treatment of HCC B6 cm since it is a noninvasive, safe, and effective technology. Assuming the patient satisfies the requirements, SBRT is currently regarded as the principal bridge to transplant treatment at IUSCC. Andolino et al. (2011) and Cárdenes et al. (2010) both state that it is seriously contemplated as a first-line definitive treatment for one to three lesions up to 6 cm in size, in cases when transplantation is not a possibility.

Selecting Patients

Patients should be reviewed in a multidisciplinary conference including radiation oncology, surgery, interventional radiology, and a member of the transplant services after appropriate evaluations of staging, hepatic function, and performance status have been conducted. The goal of this conference is to determine which patients can be safely resected and which should be added to the transplant list. Patients with a well-compensated liver function status and a CTP score of 7 or below are typically considered for SBRT. Liver function declines significantly after SBRT for patients with scores of 8 or above. Patients with less than three lesions measuring up to 5 or 6 cm have been underserved in the majority of institutional trials. But in a study published by Seo et al. (2010), SBRT was used as salvage treatment following TACE in 38 patients with tumours up to 10 cm. Tumour volumes varied from 11 to 464 ml (median, 40.5 ml), and SBRT dosages (33-57 Gy in three or four fractions) were administered accordingly. Overall survival at two years was 61.4% and local progression-free survival was 66.4%. A total of 63% of the locals responded three months following SBRT. In sixteen percent of cases, liver function was found to have decreased. Technical aspects should be considered with the aforementioned factors when choosing patients for SBRT. Factors that raise the risk of poisoning include close proximity to the stomach, small intestine, or large intestine. Also, in our opinion, uncontrolled ascites is not a good candidate for SBRT since it makes it very difficult to have a consistent daily setup and administer treatments accurately .

Simulation

A stereotactic imaging frame with a coordinate system based on fixed fiducials enables isocenter set-up during therapy using specified coordinates, and patients should be simulated in this frame. Some examples of FDA-approved immobilisation devices are the Leibinger frame, the Elekta frame, and the Novalis brain lab ExacTrac system. Implanted fiducials are an alternate to using a stereotactic frame. Nevertheless, the patient runs the risk of more complications because this is an intrusive operation. Patients undergoing thin needle liver biopsy who have HCC run the risk of bleeding and needle track seeding because these tumours are typically very vascularized. It is unclear if this risk remains constant when fiducials are placed inside the tumour or close to it. We do not support the fiducial placement at our facility since it could endanger potential OLT patients. During the simulation, it is recommended to use fluoroscopy or 4D CT to examine the excursion of the right dome of the diaphragm, which is the upper part of the liver. This will help estimate the liver's motion and establish the necessary expansion for differentiating the Planning Target Volume (PTV) from the Gross Tumour Volume (GTV). Active Breathing Control (ABC) and diaphragmatic control devices should ideally be evaluated for patient suitability. Diaphragmatic and breathing control devices are not necessary for the treatment of patients with severe lung illness or those who are unable to tolerate them. Their internal target volume (ITV) will be bigger, though, because they need more room to accommodate intra-fractional organ movement caused by breathing. Volumetric CT scans with intravenous contrast enhancement, using 2-3 mm slices, should be performed either during the simulation or very nearby in a separate diagnostic CT machine. While using the stereotactic frame, ensure that the patient is in the treatment position and that the ABC or diaphragmatic control device is attached. Obtaining a triphasic CT scan when the patient is in the treatment position is crucial, as HCC is more clearly seen during the arterial phase of the examination. It is recommended that the CT scan covers the entire liver and extends below the kidneys. So, it's best to scan all the way down to the iliac crests, starting at the carina. If a patient has a lesion in the caudate lobe or the peripheral-medial liver, it is recommended that they take oral GI contrast to make the stomach and duodenum visible.

Volume Objectives Defining

When determining treatment volumes, it is important to refer to the ICRU Reports 50 (1993) and 62 (1999) for the definitions of GTV, CTV, PTV, and organs at risk (OAR). The GTV or GTVs may not be continuous, but they include all known gross diseases found by the planning CT, diagnostic triphasic CT and/or MRI, as well as clinical information. The CTV and GTV should be almost identical when using SBRT to treat HCC. The ITV considers the target lesion's internal movement, which is mainly caused by the patient's breathing. Respiratory gating, breath holds, and compression devices can help reduce this. While visualising with fluoroscopic guidance or 4D CT, our team at Indiana University tries to limit the diaphragmatic excursion to 1 cm in the cranio-caudal region using a compression device attached to the stereotactic frame. The PTV considers the patient's breathing motion (ITV) and treatment setup uncertainty. Accuracy in the liver can be attained within a range of 1.8 to 5 mm. Hence, 2–5 mm around the ITV is typically the range of most common PTV values. A 5 mm axial and 10 mm craniocaudale expansion PTV surrounds the GTV here at Indiana University. The margins will have to be widened to accommodate the possibility that breathing control is not possible.

Therapy Routines

Hotspots within the PTV are preferred over conventional radiotherapy because they may be able to circumvent the greater radio-resistance of the hypoxic tumour cells that are more concentrated in the tumor's core, thereby delivering more therapeutic benefit. As there is less room for beam penumbra at the target edge and a quick dose falloff, doses are typically prescribed at a lower isodose line (usually 80%) that covers the PTV's surface. This helps spare neighbouring organs that could be at risk. Utilising intensity modulation to provide a parabolic beam entrance profile and a number of highly conformal beams—five to ten in number—in a non-coplanar arrangement helps achieve a sharp dose falloff outside the PTV, which is an important consideration when planning SBRT for the liver. Either the field-in-field method or electronic compensation can achieve the parabolic entrance profile. Better setup precision and treatment delivery can also be achieved with the help of image-guided radiation therapy (IGRT).

The Tolerance of Organ Doses

The typical tissue limits established for conventionalally fractionated radiation cannot be used because of the ablative dose levels. We currently know very little, but more and more, about the usual tissue tolerances for ablative radiation doses. Possible organ separation methods include using parallel and serial tissues. The capacity to maintain physiological function despite total organ ablation is a hallmark of compartmentalised, parallel tissues. Some examples are the kidneys, liver, and lungs. Here, dosage restrictions are highly case-specific with respect to volume. However, the spinal cord, ribs, and gastrointestinal tract are all examples of serial organs that work in a chain; ablating only one part of this chain could result in the complete loss of physiologic capability of the organ. There is a belief that patients with HCCs, in contrast to those with liver metastases, have a lower threshold for inducing symptomatic liver damage since they often have underlying liver disease. Hence, when treating HCC, it is prudent to exercise more caution with doses that do not affect normal liver tissue than when dealing with metastatic hepatic lesions. Based on our published experience at Indiana University with patients who have CTP-A liver cirrhosis, we recommend limiting the dose to B10 Gy (3.3 Gy/fxn) for one-third of the uninvolved liver and C500 cc of uninvolved liver to \7 Gy (2.3 Gy/fxn). A patient with CTP-B cirrhosis can only get B18 Gy (3.6 Gy/fxn) to one-third of their uninvolved liver, and C500 cc of their uninvolved liver should receive \12 Gy (2.4 Gy/fxn). A high CTP score is associated with radiation-induced liver damage. Only 12% of patients with a CTP score of B7 had an increase of \1 grade of hematologic or hepatic toxicity, according to our examination of 60 patients treated up to 2009. Additionally, unless they are on the transplant waiting list, patients with a CTP score of 8 or above may not be safe candidates for SBRT, according to our experience. Out of the eight patients whose CTP scores were 8 or above, two of those four individuals died, and four more went on to develop liver failure. According to Son et al. (2010), total liver volume receiving [18 Gy] was the sole dosimetric measure that was found to be significantly associated to grade C2 liver toxicity on multivariate analysis. The danger of liver dysfunction worsening increased dramatically if the volume of liver receiving 18 Gy was less than 800 cc. Consequently, the main sources for OAR tolerance dose recommendations are institutional knowledge, toxicity data, and radiobiological models .

Maintain Contact

In order to evaluate toxicity and response to treatment, patients undergoing SBRT for HCC should be monitored frequently both during and after the course of treatment. Fatigue, nausea, and vomiting are all symptoms of the expected toxicity, but they should go away over the course of a few months to a few days. When it comes to side effects, RILD is the worst part of this treatment. Hence, it is highly advised to undergo clinical and laboratory examination before each SBRT session, again one month after therapy ends, and every three months thereafter. When it comes to monitoring treated liver tumours, the preferred imaging modalities are multiphase MRI or tri phasic CT scans, which are similar to surveillance. Currently, there is a lack of data about the use of FDG-PET or post-SBRT follow-up. Additionally, PET is not suitable for HCC surveillance on its own, so it cannot be advised without multiphase CT or MRI. Consistent risk of new tumours necessitates that patients get follow-up scans at least once every three months, ideally more frequently than surveillance for high-risk individuals. To better search for changes in normal liver that may suggest new tumours and to make direct comparisons to pre-treatment scans, it is ideal to employ the same modality as early monitoring. Three distinct responses to SBRT for liver lesions have been well-described; all three probably reflect the same sort of response that evolves with time. Radiologic correlates of response for HCC are severely understudied. For a long time, the Response Evaluation Criteria in Solid Tumours (RECIST) was the gold standard for grading response in clinical studies. The European Association for the Study of the Liver (EASL) has advocated for the use of non-enhanced regions by spiral CT to detect tumour necrosis since 2001 as the gold standard for evaluating local response. When it comes to determining the efficacy of local treatments, a new study compared the RECIST and EASL standards for concordance. It found that RECIST failed to detect all full responses and underrated the severity of partial tumour responses. A study assessing the efficacy of SBRT in 26 patients diagnosed with HCC was published not long ago by Price et al. from Indiana University. Participants in the phase I-II trial were all patients at Indiana University who did not meet the criteria to have surgery. Prior to, during, and after SBRT, all patients underwent imaging at intervals of one to three months. We followed up with patients for an average of thirteen months. At 12 months, four patients (CR), fifteen (PR), and seven (SD) had achieved a complete response (CR) according to RECIST. Marginal progression to the treated area was observed in one patient with SD. A total of 73% of people were able to respond favourably (CR + PR). At 12 months, 18 out of 26 patients did not have C50% augmentation according to EASL criteria. Out of the 18 patients, 13 showed no improvement at all, and 5 showed no improvement at all but a 50% level. Estimates of 1- and 2-year survival using Kaplan-Meier methods were 77% and 60%, correspondingly. The authors found that SBRT is a successful treatment for HCC patients, with a best response rate (CR + PR) of 73% overall. following evaluate the response of HCC following SBRT in the first 6 to 12 months, a surrogate for ablation, such as reduced vascularity or nonenhancement on imaging, may be more informative than size reduction, supporting EASL criteria. Then, after 24 patients at Indiana University underwent liver SBRT and OLT, Zook et al. evaluated the radiological and pathological connection in relation to 33 lesions that were compatible with HCC. Publication Pending indicates that RECIST criteria had higher specificity and positive predictive value when it came to predicting a CR, whereas EASL criteria outperformed both RECIST and WHO criteria when it came to forecasting whether a disease would develop or remain stable.

Example of a Case

A 69-year-old male with a medical history of liver cirrhosis caused by nonalcoholic steatohepatitis (NASH) presented with nausea, vomiting, and abdominal pain. An ultrasound revealed a 4.1 9 4.3 9 4 cm mass in the left lobe of the liver, located in segment 2. Arterial enhancement on a dual-phase CT scan revealed the lesion. He had a slightly increased AFP. Hepatocellular carcinoma was confirmed by a biopsy conducted at an external institution. He was sent to radiation oncology to pursue stereotactic body radiation therapy (SBRT) after his case was deemed unsuitable for surgery at a multidisciplinary liver tumour conference owing to his cardiac comorbidity. A 7 was his Child Pugh score. With the heart dose in mind, the protocol was devised so that he would get four thousand cGy divided into five 800 cGy fractions administered to the 80% isodose line covering the PTV. There was an effort to preserve 500 cc of liver at 12 Gy and one-third of the liver at 18 Gy. In addition, 15 Gy should be administered to two-thirds of the right kidney and one-third of the left kidney. Heart dose was capped at 400 cGy per fraction, while cord dose was kept below 18 Gy. One to three times weekly, he would receive treatment. To identify possible liver toxicity, a full battery of clinical, biochemical, and haematological tests were run before each portion. The patient had a good response to treatment, and after only one month, his CT scan revealed a similarly sized lesion with some hypo-attenuation in the centre. It is indicative of a treatment's efficacy. By the third month, the hypodense area had grown in size, but its

borders were less clear and the lesion as a whole was much less enhancing in the arterial phase. All of these changes were predicted and point to a positive reaction to treatment. Six months after treatment, hyperemia with a central hypodense still showed up in the treated area. A region of hypodensity was seen after one year and two years after treatment began, but the area of hyperemia in the treatment area slowly faded away over the next three years. as well as three years. Although it is not always the case, this hypodense area without arterial-contrast enhancement is frequently observed in hepatocellular carcinoma cases following SBRT. As a result of the treatment, the liver often shows signs of hyperemia in the treated area, which gradually fades with time.

CONCLUSION

The use of radiation in the treatment of primary HCC is rapidly becoming standard practice. While there is still much mystery surrounding the ideal sequencing, radiotherapy's precise role, and volume, the presence or absence of portal venous tumour invasion, liver function, and patient performance status are all important considerations in the multidisciplinary decision-making process. Possible directions for research into SBRT's function in HCC therapy include : The Function of Sorafenib in Combination with SBRT. Function of adjuvant Sorafenib following SBRT. Exploring the early response of normal liver parenchyma and tumour tissues to SBRT in a more comprehensive manner. Liver toxicity and tumour response predictors 5. Results of SBRT over time for HCC treatment

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