Computed tomography-guided iodine-125 brachytherapy for unresectable hepatocellular carcinoma

ABSTRACT

Purpose: This study aimed to retrospectively assess the outcome of interstitial iodine-125 brachytherapy for unresectable hepatocellular carcinoma (HCC).

Materials and Methods: Between February 2013 and March 2019, 57 patients with 108 unresectable HCC lesions treated with computed tomography (CT)-guided iodine-125 seed brachytherapy were retrospectively analyzed. The primary endpoint was overall survival (OS). The secondary endpoints included local tumor control and progression-free survival (PFS). Potential factors associated with OS were assessed.

Results: The mean follow-up duration was 24.3 ± 15.6 months (median, 20.5 months; range, 3.9–66.8 months). The median OS time was 23.6 months (95% confidence interval [CI], 18.4–28.8 months). The 1-, 2-, and 3-year actuarial OS rates were 80.0%, 46.1%, and 24.3%, respectively. The median PFS time was 12 months (95% CI, 9.9–14.5 months). The 1- and 2-year actuarial PFS rates were 50% and 20.1%, respectively. Local progression was noted in 11 (11.3%) of 108 lesions with mean local control time of 20.5 ± 8.8 months. The 1- and 2-year local control rates were 96.5% and 88.8%, respectively. Barcelona clinic liver cancer stage and Child–Pugh score were independent risk factors affecting the prognosis (hazard ratio [HR] = 0.330 [95% CI, 0.128–0.853] and HR = 0.303 [95% CI, 0.151–0.610], respectively). Hepatic artery pseudoaneurysm was found in 1 (1.8%) patient with lesion located in the porta hepatis. No other major complications developed during follow-up.

Conclusion: CT-guided iodine-125 brachytherapy may be an effective and safe alternative with promising survival and increased local control rate in unresectable HCC treatment.

KEY WORDS: Brachytherapy, iodine-125, unresectable hepatocellular carcinoma

INTRODUCTION

Hepatocellular carcinoma (HCC) ranks third among the leading causes of cancer-related death worldwide.[1] The incidence and mortality of HCC increased recently according to the statistics of the National Cancer Center.[2] Nowadays, surgical resection was the first-line treatment for HCC with 5-year survival rates of up to 51%.[3] However, a majority of patients are ineligible for resection due to advanced tumor stage, poor liver function, diffuse lesions, and comorbidity.[4] As the only potentially curative method, liver transplantation is restricted by the shortage of grafts and Milan criteria.[5] Radiofrequency ablation (RFA) is the advocated therapy for HCC lesions < 3 cm in size with confirmed effectiveness.[3] The application of this method is limited by many factors, such as tumor location, size, and vascularization.[6] Complete ablation is potentially prohibited in tumors > 5 cm in size, adjacent to large blood vessels, and close to vital organs.[7] Transarterial chemoembolization (TACE) was proved to be an effective method for unresectable HCC.[8] However, the survival was not satisfied in patients with Barcelona clinic liver cancer (BCLC) Stage B (16–16.9 months) and C (6–10.7 months) treated with this palliative method.[9,10] Recently, iodine-125 seeds have been widely used in many types of tumors, and its efficacy has been confirmed by several randomized studies.[11-13] With a 1.7-cm tissue half-value layer, this low-energy radioactive seed was safe for the...
surrounding critical tissue. In contrast, the effect of iodine-125 was not restricted by portal vein tumor thrombus, tumor size, or heat sink effect of surrounding vessels.\textsuperscript{14} However, there were limited studies related to iodine-125 brachytherapy for HCC.\textsuperscript{15,16} Our study investigates the therapeutic effect and prognostic factor of iodine-125 seed in treating unresectable HCC in 57 patients with long-term follow-up in two medical centers.

MATERIALS AND METHODS

Patients and tumors

A total of 88 patients were treated with computed tomography (CT)-guided iodine-125 seed brachytherapy in three medical centers between January 2013 and March 2019. Thirty-one of 88 patients were lost to follow-up. The remaining 57 patients with 108 unresectable HCC lesions with detailed follow-up information were retrospectively analyzed. The diagnosis of HCC was based on imaging criteria and histopathology assessment. The inclusion of patients was decided by a consensus of the institutional multidisciplinary tumor board after other potential therapeutic methods were discussed. Patients were eligible if they met the following criteria: (1) largest tumor diameter <7 cm and tumor number <5, (2) liver function grade of Child–Pugh A or B, (3) total serum bilirubin level <5 mg/dL, (4) platelet count >50 × 10^4/L, (5) prothrombin time ratio >50%, and (6) Eastern Cooperative Oncology Group performance status ≤2. The exclusion criteria were as follows: (1) largest tumor diameter >7 cm or tumor number >5, (2) liver function grade of Child–Pugh C, (3) dyscrasia and multiple organ dysfunction or failure, and (4) refractory coagulation dysfunction. All patients provided written informed consent before the procedure. This retrospective study was approved by the institutional review board. All procedures conformed to the ethical standards of the institutional research committee and 1964 Declaration of Helsinki. Baseline characteristics of the patients and tumors are summarized in Table 1.

Procedure

Iodine-125 seed

We used the iodine-125 seeds (Chinese Jaco Pharmaceuticals Co., Ltd., Ningbo, China) with an activity of 0.6 mCi and half-life of 59.6 days. Low-dose γ-ray (5% of 35 keV) was continuously released to damage the DNA of the target tumor with a 1.7-cm tissue half-value layer. About 93%–97% of the seed energy was delivered into the tumor after decaying for 8–10 months.

Preoperative planning

Abdominal contrast-enhanced CT images were acquired using a gemstone energy spectrum CT (General Electric Medical System, Milwaukee, WI) <7 days before the procedure. The DICOM format images were imported into the radioactive seed implantation treatment planning system (TPS) (Beijing University of Aeronautics and Astronautics, Beijing, China). The planning target volume (PTV) of each HCC lesions was carefully delineated in every slice. PTV was defined as the margin of gross target volume expanded 5 mm outward. A dose-volume histogram was generated by the TPS with a prescribed matched peripheral dose (MPD) of 110–160 Gy. The seed number and isodose curves were calculated. The dose distribution of the target tumor and risk organs was demonstrated. The implantation position and approach were also planned according to the location of the target tumor. The preoperative planning was simultaneously conducted by a specialist medical physicist and radiologist.

Computed tomography-guided iodine-125 brachytherapy

All procedures of seed implantation were performed by the interventional radiologists who have engaged in CT-guided iodine-125 brachytherapy for >10 years. Four hours of ambrosia was required before the procedure, which was accomplished under intravenous anesthesia using dexmedetomidine combined with local anesthesia using lidocaine. Vacuum cushion was applied to fix the appropriate position according to the preoperative plan. The location of tumor was identified by CT before the procedure. The puncture sites were marked on the skin, which were consistent with the plan. Moreover, 18-G needles (Hakko Co., Ltd., Chikuma, Japan) were inserted into the tumor and pushed forward until the tips reached the distal margin of the tumor. This process should be completed step-by-step to keep the puncture approach in line with the plan. Needles were retracted, and the seeds were implanted after all needles were located in the proper position according to the plan. The distance

Table 1: Baseline patient characteristics

| Patient characteristics | Data (%) |
|-------------------------|----------|
| Total                    | 57       |
| Sex                      |          |
| Male                     | 36 (63.2) |
| Female                   | 21 (36.8) |
| Age                      |          |
| Mean age                 | 58.8±12.4 |
| Median age               | 57       |
| Age range                | 30–85    |
| Unifocal disease         | 24 (42.1) |
| Multifocal disease       | 33 (57.9) |
| Liver disease            |          |
| Liver cirrhosis          | 57       |
| Hepatitis B virus        | 48 (84.2) |
| Hepatitis C virus        | 1 (1.8)   |
| Alcoholic cirrhosis      | 8 (14)    |
| Child-Pugh classification|          |
| Child-Pugh A             | 30 (52.6) |
| Child-Pugh B             | 27 (47.4) |
| BCLC A                   | 20 (35.1) |
| BCLC B                   | 37 (64.9) |
| Tumors                   |          |
| Mean size of the largest tumor, mm (range) | 44.7±16.9 (16-69) |
| Previous therapy         |          |
| Chemoembolization         | 45 (78.9) |
| Microwave ablation       | 20 (35.1) |
| Radiofrequency ablation  | 15 (26.3) |
| Hepatic resection        | 10 (17.5) |
| External beam radiotherapy | 3 (5.3) |

BCLC=Barcelona clinic liver cancer
between the seeds was usually 1 cm or in compliance with the plan. Repeat CT was performed to check for possible complications. The image was imported into the TPS to verify the dose distribution. An appropriate number of seeds were implanted to ensure the quality of brachytherapy if a cold area was detected [Figure 1].

**Radiation protection**

Patients who received iodine-125 brachytherapy were recommended to wear lead-containing radiation protection pad for 6 months. Patients need to keep a distance of >75 cm from the population, especially from vulnerable groups, such as pregnant women and children.\(^{[17,18]}\)

**Follow-up and study endpoints**

Contrast-enhanced CT or magnetic resonance imaging (MRI) was performed 1 month after the procedure and then every 3 months to assess the therapeutic effectiveness of brachytherapy. Liver function and alpha-fetoprotein were also examined.

Local tumor control (LTC) was defined based on the Response Evaluation Criteria in Solid Tumors. LTC referred to the proportion of tumors treated with iodine-125 brachytherapy and achieved complete response (CR), partial response (PR), and stable disease (SD).\(^{[19]}\) Progression-free survival (PFS) was defined as the absence of new intrahepatic or extrahepatic lesion, local progression, or death. Time from the date of seed implantation to last follow-up or death was defined as overall survival (OS). Adverse events were assessed based on the guidelines of the Society of Interventional Radiology.\(^{[20]}\) Radiation-induced liver disease (RILD) was characterized by increased alkaline phosphatase levels accompanied by ascites or total bilirubin level >51 \(\mu\)mol/L and ascites without tumor progression or obstructive jaundice 1 or 2 months after brachytherapy.

**Statistical analysis**

Data analysis was performed using SPSS (version 24; SPSS, Chicago, IL, USA). Continuous variables were expressed as mean ± standard deviation. Data of abnormal distribution are presented as median and interquartile range (IQR) (25%–75%). OS, LTC, and PFS probabilities were calculated using the Kaplan–Meier method. Potential factors associated with OS were assessed using Cox proportional hazards regression model. Statistical significance was defined as \(P < 0.05\). Stratified and analyzed study variables were stage of liver cancer (BCLC A or B), age (≤60 or >60 years), liver function grade (Child–Pugh A or B), largest tumor diameter (<5 or ≥5 cm), and tumor pattern (single or multifocal tumor).

**RESULTS**

**Seed implantation and dosimetry description**

Seven (8.8%) of 57 patients underwent a second seed implantation session to match the requirements of dosimetry when the cold area was detected based on postoperative dose verification. The other 50 (91.2%) patients underwent a single brachytherapy session. The actuarial median MPD was 130 Gy (range, 110–160 Gy). The seed activity was 0.6 mCi. Among 108 tumors, the diameters of 34 lesions were >5 cm, and the other 64 lesions had a diameter <5 cm. The mean diameter of 108 lesions was 40.9 ± 16.3 mm. The actuarial PTV was 51.4 mL (IQR, 12.1–112.1), and 45 seeds were implanted (IQR, 16–70). The actuarial dose 90 (D90, minimum absorbed dose at 90% target volume) was 131.6 Gy (IQR, 123.9–139.9).

**Follow-up and complications**

The mean follow-up duration was 24 ± 12.9 months (range, 3.2–60 months; median, 24 months). Eleven (19.3%) patients were alive during the last follow-up. Hepatic artery pseudoaneurysm was noted in one (1.8%) patient with the

---

**Figure 1:** Images from an 85-year-old man with hepatocellular carcinoma. The patient was previously treated with transarterial chemoembolization. (a) Contrast-enhanced computed tomography showed a lesion located in liver segment VI with partial lipiodol deposition. The lesion was adjacent to the hepatic flexure of the colon. (b) Preoperative dose-volume histogram was generated by the treatment planning system. (c) Moreover, 18-G needles were inserted into the tumor. (d) Seeds were implanted. (e) Postoperative dose-volume histogram demonstrated a qualified dose distribution. (f) Contrast-enhanced computed tomography after 2 years showed that complete response was achieved.
lesion located in the porta hepatis 3 days after the procedure. The patient was aged 58 years and had abdominal pain and melena after the procedure. The diagnosis was confirmed by contrast-enhanced CT and hepatic artery angiography. The pseudoaneurysm was located at the branch of the right hepatic artery. A microcatheter was inserted into the feeding artery, and embolization with coils was performed to prevent bleeding. This patient recovered well after the procedure. No other major complications developed during the follow-up. No procedure-related deaths were reported. No hepatic infection and RILD were observed. No needle tract metastases were diagnosed.

**Local tumor control and disease progression**

Local progression was found in 11 (11.3%) of 108 lesions with a mean local control time of 21.5 ± 7.5 months. Of the other 97 (89.8%) lesions, CR, PR, and SD were observed in 21 (19.4%), 53 (49.1%), and 23 (21.3%) lesions, respectively, during the follow-up. Generally, the 1- and 2-year local control rates were 97.8% and 89.8%, respectively [Figure 2]. Five (45.4%) of 11 cases of local progression were observed in tumors >5 cm in size. The other 6 (54.6%) cases of local progression were found in tumors <5 cm in size. Percutaneous ethanol injection was performed in 4 of 11 patients with local progression. Repeated iodine-125 brachytherapy was performed in the other 3 patients with local progression. Persistent LTC was achieved in these 7 patients during follow-up. Another 4 patients were treated with sorafenib for concurrent systemic progression. The median PFS time was 14.2 ± 2.3 months (95% confidence interval (CI), 9.7–18.7 months). The 1- and 2-year actuarial PFS rates were 55.9 and 26.8%, respectively [Figure 3]. Forty-seven (82.5%) of 57 patients developed intrahepatic or extrahepatic metastases during the follow-up.

**Overall survival and prognostic factors**

The median OS time was 23.6 months (95% CI, 18.4–28.8 months). The 1-, 2-, and 3-year actuarial OS rates were 80.0%, 46.1%, and 24.3%, respectively [Figure 4]. The analysis of prognostic factors related to OS is presented in Table 2. OS was not influenced by age or tumor pattern. The largest lesion diameter showed no statistically significant effect on OS after iodine-125 brachytherapy [Figure 5]. BCLC and Child–Pugh classification were shown to be independent factors affecting OS. Patients with BCLC A stage and Child–Pugh A liver function achieved better prognosis [Figures 6 and 7].

**DISCUSSION**

The treatment of unresectable HCC, which has a poor prognosis, remains challenging. In this present study, the data on CT-guided iodine-125 brachytherapy in 57 patients with 108 tumors were reviewed. The promising results of this present study demonstrated that CT-guided iodine-125 brachytherapy was an effective and safe palliative therapeutic strategy in the treatment of unresectable HCC.
There were several studies that focused on brachytherapy for the treatment of intrahepatic malignancy, including \(^{192}\)Ir and \(^{90}\)Y for HCC and metastatic liver tumors.\(^{22-26}\) However, there is limited literature on the application of iodine-125 seed implantation in unresectable HCC. Nag et al. reported their experience with iodine-125 brachytherapy in 64 patients with intrahepatic malignant tumors, but the tumor types were metastatic tumors and cholangiocarcinoma. The implantation methods used consisted of intraoperative ultrasound-guided volume implantation and planar surface implantation.\(^{27}\) Other studies, referring to iodine-125 seed implanted to the liver masses reported by Martinez-Monge et al., Armstrong et al., and Donath et al., also focused on metastatic liver tumors.\(^{28-30}\) In a small cohort reported by Lin et al., 23 patients with 65 HCC lesions were treated with MRI-guided iodine-125 brachytherapy. They achieved a local control rate of 84.5% and a 1-year survival rate of 95.7%.\(^{31}\) To the best of our knowledge, our cohort of 57 patients with HCC represents one of the largest series of iodine-125 interstitial implantation in the treatment of unresectable HCC.

In this present review, iodine-125 was employed in 108 HCC tumors. The 1- and 2-year local control rates were 97.8 and 89.8%, respectively. This result is satisfactory, considering that the mean diameter of the 108 lesions was \(40.9 \pm 16.3\) mm, and multifocal lesions were noted in 57.9% of 57 patients. Moreover, iodine-125 brachytherapy also demonstrated effectiveness in treating large tumors (diameter \(\geq 5\) cm) based on the results of our cohort, in which local tumor progression developed only in 5 (14.7%) of 34 lesions with diameters \(>5\) cm, and the prognostic factor analysis showed that the largest lesion diameter was not an independent risk factor influencing survival. The same results were reported by earlier studies using high-dose-rate brachytherapy.\(^{23,32,33}\)

Another major finding of this study was that the median OS time (23.6 months) was favorable compared with the data obtained from a meta-analysis, including 55 randomized controlled trials with 5,763 patients, comparing different
liver-directed therapy options for unresectable HCC reported by Katsanos et al., where the estimated median survival time was 18.1 months in TACE and 20.6 months in drug-eluting bead TACE. Furthermore, the assessment of prognostic factor identified that OS was affected by BCLC and Child–Pugh classification but was not influenced by tumor pattern after iodine-125 brachytherapy.

Historically, HCC had a low radiosensitivity, owing to the poor results from inadequate radiation dose delivered to the tumor, and the risk of radiation-related liver toxicity was a cause for concern. However, this notion was proven to be incorrect with the advancement of radiotherapy technology, such as stereotactic conformal radiotherapy, which increased the delivery of radiation dose while reducing the harm to surrounding tissues. Bujold et al. conducted a Phase I and II study using stereotactic body radiotherapy to treat 102 patients diagnosed with unresectable HCC. The median radiotherapy dose was 36 Gy. The 1-year local control rate was 87%, while the median OS time was 17 months.

Iodine-125 brachytherapy is one of the methods of precision radiotherapy, which demonstrates favorable effectiveness in the treatment of several kinds of malignant carcinomas, such as prostate cancer, lung cancer, pancreatic carcinoma, secondary adrenal carcinoma, and lymph node metastatic carcinoma. Under image guidance, iodine-125 seeds are directly implanted into the tumor. Owing to the 1.7-cm tissue half-value layer of iodine-125 seeds, the dose absorbed by the surrounding normal tissue falls off sharply; so, critical organs are spared from radiation toxicity. Simultaneously, sufficient dose is produced to kill the tumor cells. In this study, the actuarial median MPD and D90 was 130 Gy and 131.6 Gy, respectively. These results were higher compared with those in stereotactic body radiotherapy. The high local control rate in this study may be attributed to this.

Recently, the multi-mode comprehensive treatment of unresectable HCC combined with TACE and other locoregional treatment methods, such as RFA, and high-dose-rate brachytherapy, was considered superior to TACE alone. In our study, TACE using lobaplatin, which was a third-generation platinum with radiation sensitization, was previously performed in a majority of this cohort. The combination of TACE and iodine-125 brachytherapy may be another reason for the encouraging results of this study.

Special attention should be paid to the management of hilar lesions using iodine-125 brachytherapy for the complicated anatomical structure composed of hepatic artery, portal vein, and bile duct. In this present study, hepatic artery pseudoaneurysm relevant to needle puncture during the procedure was diagnosed in one (1.8%) patient with hilar lesion. The step-by-step techniques of intraoperative contrast enhancement and needle puncture were applied, and these complications were subsequently prevented. No other major complications, such as RILD, which is a serious complication related to liver irradiation and has a rate of up to 18.5% associated with stereotactic body radiotherapy, were noted in this study. These results were consistent with the report by Nag et al. Lin et al. punctured 65 HCC lesions to implant seeds, and no severe complications were observed.

There are several limitations in this study. First, this is a retrospective study with a small cohort. The inherent selection bias should be taken into account. Second, a small number of patients were followed with contrast-enhanced CT rather than contrast-enhanced MRI, which has little influence on seed artifacts, so they can be used to accurately determine whether the lesion was active. Finally, no control group treated with the standard method, such as TACE, was set to compare the efficacy. For the abovementioned reasons, our results should be cautiously interpreted, and large sample randomized controlled trials with high quality were expected to confirm the reliability.

CONCLUSION

Our study suggests that CT-guided iodine-125 brachytherapy may be an effective and safe method to achieve better local control and prolonged survival for unresectable HCC. Iodine-125 seed implantation can be expected as another alternative locoregional therapeutic method to complement current options. Moreover, the evidence is still insufficient to justify the role of iodine-125 in the treatment of HCC.
Financial support and sponsorship
This work is supported by the Shandong Provincial Natural Science Foundation, China (ZR2018PH033, ZR2018PH032) and the National Natural Science Foundation of China (61671276).

Conflicts of interest
There are no conflicts of interest.

REFERENCES
1. Forner A, Llovet JM, Bruix J. Hepatocellular carcinoma. Lancet 2012;379:1245‑53.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. CA Cancer J Clin 2017;67:7‑30.
3. Jaeck D, Bachellier P, Oussoultzoglou E, Weber JC, Wolf P. Surgical resection of hepatocellular carcinoma. Post‑operative outcome and long‑term results in Europe: An overview. Liver Transpl 2004;10:558‑63.
4. Maluccio M, Covey A. Recent progress in understanding, diagnosing, and treating hepatocellular carcinoma. CA Cancer J Clin 2012;62:394‑9.
5. Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med 1996;334:693‑9.
6. Crocetti L, de Baere T, Lencioni R. Quality improvement guidelines for radiofrequency ablation of liver tumours. Cardiovasc Intervent Radiol 2010;33:11‑7.
7. Curley SA, Izzo F. Radiofrequency ablation of primary and metastatic hepatic malignancies. Int J Clin Oncol 2002;7:72‑81.
8. Llovet JM, Bruix J. Systematic review of randomized trials for unresectable hepatocellular carcinoma: Chemoembolization improves survival. Hepatology 2003;37:429‑42.
9. Vogel A, Cervantes A, Chau I, Daniele B, Llovet J, Meyer T, et al. Hepatocellular carcinoma: ESMO clinical practice guidelines for diagnosis, treatment and follow‑up. Ann Oncol 2018;29:v238‑55.
10. Lo CM, Ngan H, Tso WK, Liu CL, Lam CM, Poon RT, et al. Randomized controlled trial of transarterial transluminal iodized oil chemoembolization for unresectable hepatocellular carcinoma. Hepatology 2002;35:1164‑71.
11. Zhu HD, Guo JH, Huang M, Ji JS, Xu H, Lu J, et al. Irradiation stents vs. conventional metal stents for unresectable malignant biliary obstruction: A multicenter trial. J Hepatol 2018;68:970‑7.
12. Zhang F, Wang J, Guo J, Li Y, Huang X, Guan Z, et al. Chinese expert consensus workshop report: Guideline for permanent iodine‑125 seed implantation of primary and metastatic lung tumors. Thorac Cancer 2019;10:388‑94.
13. Zhu HD, Guo JH, Mao AW, Lv WF, Ji JS, Wang WH, et al. Conventional stents versus stents loaded with (125) iodine seeds for the treatment of unresectable oesophageal cancer: A multicentre, randomised phase 3 trial. Lancet Oncol 2014;15:612‑9.
14. Huang M, Lin Q, Wang H, Chen J, Bai M, Wang L, et al. Survival benefit of chemoembolization plus iodine125 seed implantation in unresectable hepatocellular carcinoma with PVT: A retrospective matched cohort study. Eur Radiol 2016;26:3428‑36.
15. Peretz T, Neri D, Hilaris B, Manolatos S, Linares L, Harrison L, et al. Treatment of primary unresectable carcinoma of the pancreas with I‑125 implantation. Int J Radiat Oncol Biol Phys 1989;17:931‑5.
16. Zhang FJ, Li CX, Zhang L, Wu PH, Jiao DC, Duan GF. Short‑to mid‑term evaluation of CT‑guided 125I brachytherapy on intra‑hepatic recurrent tumors and/or extra‑hepatic metastases after liver transplantation for hepatocellular carcinoma. Cancer Biol Ther 2009;8:585‑90.
17. Lu J. Radiation protection of 125I seed implantation. J Chin Oncol 2004;10:363‑4.
18. Zhuo SQ, Chen L, Zhang FJ, Zhao M, Zhang L, Liu J, et al. Environmental radiation dose monitor after 125I radioactive seed implantation. Ai Zhou 2007;26:666‑8.
19. Ricke J, Thomann M, Ludewig M, Jungnickel K, Grosser O, Wybranski C, et al. MR‑guided liver tumor ablation employing open high‑field 1.0T MRI for image‑guided brachytherapy. Eur Radiol 2010;20:1985‑93.
20. Goldberg SN, Grassi CJ, Cardella JF, Charboneau JW, Dodd GD 3rd, Dupuy DE, et al. Image‑guided tumor ablation: Standardization of terminology and reporting criteria. J Vasc Interv Radiol 2009;20:5377‑90.
21. Okuda K, Ohtsuki T, Obata H, Tomimatsu M, Okazaki N, Hasegawa H, et al. Natural history of hepatocellular carcinoma and prognosis in relation to treatment. Study of 850 patients. Cancer 1985;56:918‑28.
22. Stubbs RS, Cannan RJ, Mitchell AW. Selective internal radiation therapy with 90Ytrrium microspheres for extensive colorectal liver metastases. J Gastrointest Surg 2001;5:294‑302.
23. Colletti F, Schreiber N, Schnapauff D, Denecke T, Wust P, Schott E, et al. CT‑guided high‑dose‑rate brachytherapy of unresectable hepatocellular carcinoma. Strahlenther Onkol 2015;191:405‑12.
24. Schnapauff D, Tegel BR, Poverski MJ, Colletti F, Hamm B, Gebauer B. Interstitial brachytherapy in combination with previous transarterial embolization in patients with unresectable hepatocellular carcinoma. Anticancer Res 2019;39:1329‑36.
25. Kieszko D, Cisek P, Kordzińska‑Cisek I, Grzybowska‑Sztakowska L. Treatment of hepatic metastases with computed tomography‑guided interstitial brachytherapy. Oncol Lett 2018;15:8717‑22.
26. Mohnike K, Wiemers G, Schwartz F, Seidensticker M, Pech M, Ruehl R, et al. Computed tomography‑guided high‑dose‑rate brachytherapy in hepatocellular carcinoma: Safety, efficacy, and effect on survival. Int J Radiat Oncol Biol Phys 2010;78:172‑9.
27. Nag S, DeHaan M, Scruggs G, Mayr N, Martin EW. Long‑term follow‑up of patients of intrahepatic malignancies treated with iodine‑125 brachytherapy. Int J Radiat Oncol Biol Phys 2006;64:736‑44.
28. Armstrong JG, Anderson LL, Harrison LB. Treatment of liver metastases from colorectal cancer with radioactive implants. Cancer 1994;73:1800‑4.
29. Martinez‑Monge R, Nag S, Nieroda CA, Martin EW. Iodine‑125 brachytherapy in the treatment of colorectal adenocarcinoma metastatic to the liver. Cancer 1999;85:1218‑25.
30. Donath D, Neri D, Turnbull A, Kaufman N, Fortner JG. Brachytherapy in the treatment of solitary colorectal metastases to the liver. J Surg Oncol 1990;44:55‑61.
31. Lin ZY, Lin J, Lin C, Li YG, Chen SM, Hu JP, et al. 1.5T conventional MR‑guided iodine‑125 interstitial implants for hepatocellular carcinoma: Feasibility and preliminary clinical experience. Eur J Radiol 2012;81:1420‑5.
32. Colletti F, Schnapauff D, Poellinger A, Denecke T, Schott E, Colletti F, et al. Hepatocellular carcinoma: Computed‑tomography‑guided high‑dose‑rate brachytherapy (CT‑HDVRT) ablation of large (> 7 cm) and very large (> 7 cm) tumours. Eur Radiol 2012;22:1101‑9.
33. Tsenis N, Chatzikonstantinou G, Kolatas C, Milikovic N, Baltas D, Chung TL, et al. Hypofractionated accelerated computed tomography‑guided interstitial high‑dose‑rate brachytherapy for liver malignancies. Brachytherapy 2012;11:507‑14.
34. Katsanos K, Kitrou P, Spiliopoulos S, Maroulis I, Petsas T, Karnabatidis D. Comparative effectiveness of different transarterial embolization therapies alone or in combination with local ablative or adjuvant systemic treatments for unresectable hepatocellular carcinoma: A network meta‑analysis of randomized controlled trials. PLoS One 2017;12:e0184397.
35. Wigg AJ, Palumbo K, Wigg DR. Radiotherapy for hepatocellular carcinoma: Systematic review of radiobiology and modeling projections indicate reconsideration of its use. J Gastroenterology 2010;20:1985‑93.
37. Bujold A, Massey CA, Kim JJ, Brierley J, Cho C, Wong RK, et al. Sequential phase I and II trials of stereotactic body radiotherapy for locally advanced hepatocellular carcinoma. J Clin Oncol 2013;31:1631-9.
38. Hurwitz MD, Cormack R, Tempany CM, Kumar S, D’Amico AV. Three-dimensional real-time magnetic resonance-guided interstitial prostate brachytherapy optimizes radiation dose distribution resulting in a favorable acute side effect profile in patients with clinically localized prostate cancer. Tech Urol 2000;6:89-94.
39. Johnson M, Colonias A, Parda D, Trombetta M, Gayou O, Reitz B, et al. Dosimetric and technical aspects of intraoperative I-125 brachytherapy for stage I non-small cell lung cancer. Phys Med Biol 2007;52:1237-45.
40. Hertzanu Y, Ye X. A valuable guideline of radioactive 125I seeds interstitial implantation brachytherapy for pancreatic cancer. J Cancer Res Ther 2018;14:1453-4.
41. He C, Liu Y, Li Y, Yang L, Li YT, Li SL, et al. Efficacy and safety of computed tomography-guided 125I brachytherapy for lymph node metastatic from hepatocellular carcinoma. J Cancer Res Ther 2018;14:754-9.
42. Lin ZY, Yang JY, Chen J, Chen J. Evaluating the effectiveness of computed tomography-guided 125I seed interstitial implantation in patients with secondary adrenal carcinoma. J Cancer Res Ther 2019;15:813-7.
43. Raoul JL, Sangro B, Forner A, Mazzaferro V, Piscaglia F, Bolondi L, et al. Evolving strategies for the management of intermediate-stage hepatocellular carcinoma: Available evidence and expert opinion on the use of transarterial chemoembolization. Cancer Treat Rev 2011;37:212-20.
44. Iezzi R, Pompili M, Posa A, Coppola G, Gasbarrini A, Bonomo L. Combined locoregional treatment of patients with hepatocellular carcinoma: State of the art. World J Gastroenterol 2016;22:1935-42.
45. Candelaria M, Garcia-Arias A, Cetina L, Dueñas-Gonzalez A. Radiosensitizers in cervical cancer. Cisplatin and beyond. Radiat Oncol 2006;1:15.
46. Jung J, Yoon SM, Kim SY, Cho B, Park JH, Kim SS, et al. Radiation-induced liver disease after stereotactic body radiotherapy for small hepatocellular carcinoma: Clinical and dose-volumetric parameters. Radiat Oncol 2013;8:249.