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The Essential Handbook for Liver Brachytherapy:

Techniques, protocols, and workflow

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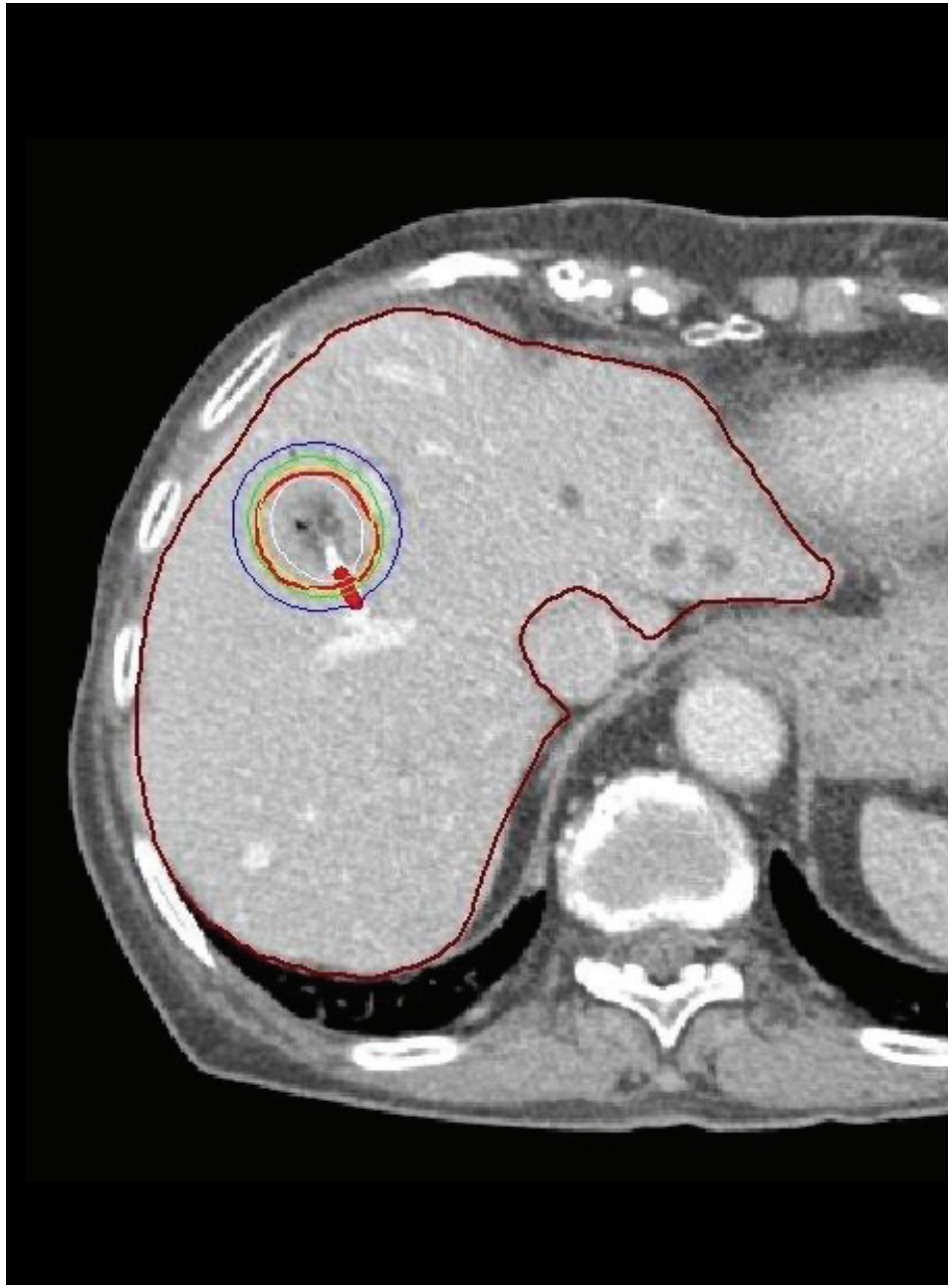

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1. Summary

With interstitial HDR liver brachytherapy, excellent local control rates of >90% at 12 months can be achieved for various entities with prescription doses of 15-25 Gy (depending on histology) in a single session. In contrast to stereotactic body radiation therapy (SBRT), liver brachytherapy allows the application of higher doses to the tumour while sparing surrounding organs at risk. Unlike thermal procedures, tumour size is not a limitation with brachytherapy, nor is central location (heat sink effect). Moreover, exposure of adjacent organs at risk can be determined during treatment planning, and dose constraints for OARs can be met to avoid normal tissue toxicities. Therefore, the available evidence suggests that this minimally invasive treatment option is particularly beneficial in the treatment of large liver tumours, multiple lesions, or tumours in central location.

2. Introduction

The use of high-dose rate interstitial brachytherapy (HDR-BT) is frequently limited to gynecological and prostate cancers in many centers globally, as HDR-BT to other anatomical sites such as head-and-neck, esophagus, lung, and liver is challenging. In the liver, commonly used non-surgical local ablative therapies are stereotactic body radiotherapy (SBRT), radiofrequency ablation (RFA), microwave ablation, or cryoablation. Of these, RFA is the most widely used method[1].

Following the percutaneous insertion of HDR-BT applicators, computerized treatment planning enables the delivery of ablative radiation doses to the tumor while predicting the dose exposure of organs-at-risk (OAR). In contrast, most of the aforementioned ablation techniques do not allow for such detailed treatment planning or the ability to predict both tumor ablation and potential toxicity in OARs.

Brachytherapy can also overcome the anatomical and size limitations of RFA. Centrally situated tumors near the hilum and adjacent to great vessels are a limitation for RFA for the so-called "cooling effect."[1] In contrast to RFA, there is no size limitation and multiple lesions can be treated simultaneously with HDR-BT if dosimetric constraints of the liver can be achieved[1–2]. The reported local control (LC) rate of HDR-BT liver is equivalent to RFA for metastatic tumors that are < 4cm.[2] In addition, HDR-BT can be safely applied in larger lesions with good local control rates.

Specifically, hepatocellular carcinoma (HCC) is an extremely radiosensitive tumor, for which a single-fraction dose of 15 Gy is sufficient to achieve LC and hence reduces the risk of radiation-induced liver disease (RILD) in the already cirrhotic liver, due to the lower dose used and the steep dose fall-off compared to liver SBRT.[3]

With the use of flexible plastic applicators in HDR-BT, most liver lesions can be targeted with relative ease. Motion management is also of little concern in HDR-BT liver, unlike in SBRT, as the in-situ applicators move with respiration. Moreover, very high central tumor doses in HDR-BT are likely to be beneficial in overcoming hypoxia-induced radio-resistance.

Recent ESMO guidelines have incorporated HDR-BT liver as one of the treatment modalities for liver-directed therapy in primary HCC and colorectal cancer liver metastasis.[4–5] The literature is still growing regarding the use of HDIRBT for other metastatic tumors to the liver. While there is a steep learning curve, HDR-BT liver is generally a simple and safe procedure that can be performed under percutaneous local anesthesia and minimal sedation with ultrasonography or CT guidance, which are readily available in most radiotherapy departments.

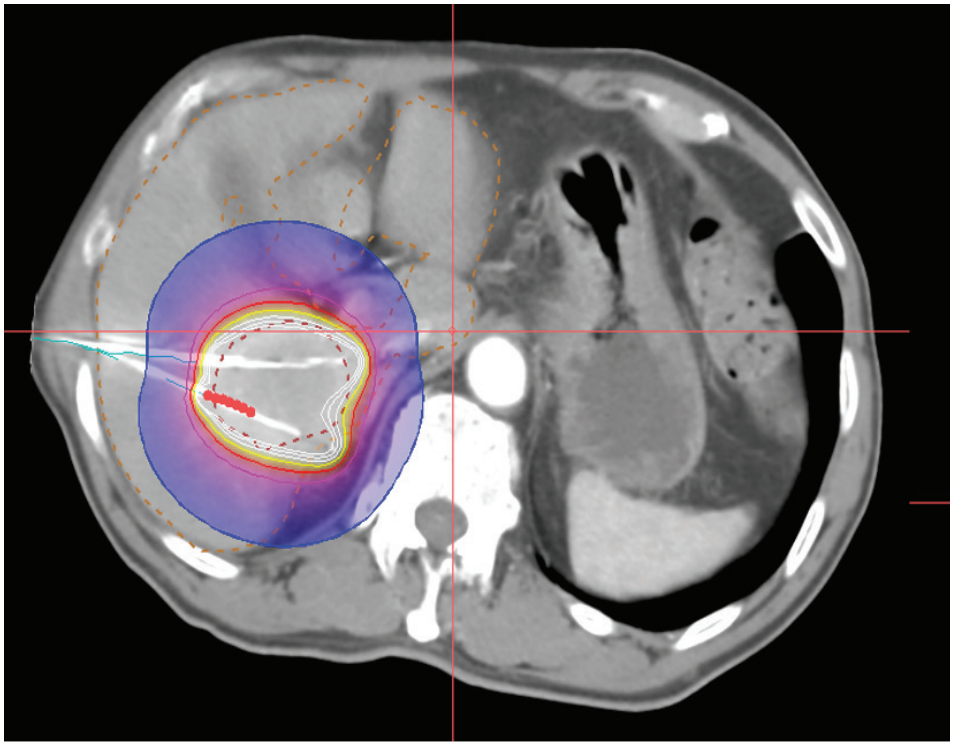

Figure 1. Axial CT image of liver brachytherapy for metastatic lesion of colorectal carcinoma to segment VI of the liver.

3. Indications and patient selection criteria

Patients should be discussed in an interdisciplinary tumor board and deemed amenable for local ablative treatment with HDR-BT. Patients with primary liver malignancy or oligometastatic diseases of the liver who are not suitable or have refused surgery can be considered for liver HDR-BT.

The patient selection criteria for HDR-BT liver are [6]:

1. Child-Pugh score < 8 points; Platelet counts > 80,000, PT < 1.5x, PTT < 50 seconds
2. No gross ascites (minimal ascites is acceptable)
3. No chemotherapy 2–3 weeks pre- and post-brachytherapy (or longer for targeted therapies depending on pharmacokinetics)

Relative contraindications include liver cirrhosis and Child-Pugh-stage B or higher (because of a considerably higher risk of severe bleeding and catheter dislocation rather than concerns regarding post-interventional liver function). Ascites is a technical contraindication, although though it may be drained before the procedure, as it indicates either advanced liver cirrhosis, peritoneal carcinomatosis, or cardiac comorbidity, questioning the benefit of HDR-BT procedure given the guarded prognosis.

Patients with biliodigestive anastomosis appear to have an increased risk of post-interventional infection and abscess formation and might require prophylactic antibiotics. Serious attention should also be given to patients receiving oral or subcutaneous anticoagulation due to the increased risk of severe bleeding.

Patient management and preparation

Patients are admitted to the ward one day before the intervention to prepare for the procedure. Baseline blood investigations include full blood count, liver function, renal profile, and coagulation profile, in addition to blood grouping and cross-matching.

Informed consent is obtained from the patient after a detailed explanation of HDR-BT risk-benefit and expected clinical outcome. Radiological imaging, such as an MRI of the liver with hepatocyte-specific contrast media (Primovist®) or multiphase CT scan is repeated as indicated.

Patients on anticoagulation treatment should have their treatment interrupted or bridged according to contemporary guidelines (e.g. Society of Interventional Radiology consensus guidelines). However, if needed, acetylsalicylic acid may be continued in patients who are taking it as a secondary prophylaxis.

The patient needs to be fasted overnight or at least for eight hours before the intervention. Because interstitial brachytherapy is typically performed under local anesthesia and conscious sedation [e.g. midazolam (0.5 mg up to 2.5 mg - stepwise), patient-specific] and fentanyl [50-75 µg up to 200 µg (stepwise), patient-specific], premedication with antiemetics (e.g., ondansetron 8 mg i.v. and dexamethasone 8 mg i.v.) prior to catheter insertion is recommended especially if it is a large tumor or prolonged treatment time is to be expected. If prolonged treatment time is expected, a Foley catheter may be inserted to enhance patient comfort. Vitals signs (blood pressure, heart rate, oxygen saturation and ECG) are monitored during the entire procedure. The patient will be on nasal prong oxygen if conscious sedation is used.

The patient is positioned carefully to ensure the best possible access to the tumor. Moldable vacuum bags or other positioning devices are an option for patient positioning on the CT couch for patient comfort and to provide access to the planned needle insertion site. The positioning devices reduce the chance of catheter movement/dislocation when transporting the patient—after catheter insertion—to the brachytherapy suite. The supine position is usually chosen with both arms extended above the head. The patient must remain in this position for the duration of the treatment until BT catheter removal. Sometimes, the patient is also placed in the prone position if a posterior approach is preferred due to the tumor position.

Beside patient comfort, special attention must be given to the length of the puncture tract and the vicinity to possible structures or organs-at-risk (e.g. arteries, ribs, bowel, lung) when deciding on the puncture site and approach. When the patient is in supine position, the interventional radiologist usually stands on the patient's right side. Tubings for intravenous access extend to the back of the CT gantry, which enable adjustment of the analgesia even during the intervention.

There are different techniques to perform liver implants. The two commonly used techniques are the direct puncture method and the Seldinger technique, which is frequently used by interventional radiologists and allows a catheter-in-catheter technique.

4. Material/surgical equipment

If the Seldinger technique is chosen for catheter placement (usually under fluoroscopy-CT guidance), required materials include:

- Sterile swabs
- Scalpel
- Hollow puncture needle (e.g. 17-gauge needles PerkuCess, Pflugbeil, Zorneding Germany)
- Stiff guide-wire (e.g. Amplatz Super Stiff 1cm tip, Boston Scientific, Boston, USA)
- Angiography sheath (e.g. 25cm 6F Radiofocus Introducer II, Terumo™, Tokyo, Japan)
- Brachytherapy catheters (e.g. Primed Halberstadt Medizintechnik GmbH, Halberstadt, Germany)
- Suture material to secure the sheath to the skin
- Sterile solution for prepping the procedural site

It is important to use hydrophilic-coated sheaths for easy insertion and reduced discomfort during skin and liver capsule puncture. After the HDR-BT is delivered, the required materials during catheter removal are small pieces of gelatine foam (e.g. Spongostan standard, Johnson & Johnson Medical). The gelatine foam is cut into small pieces and rolled to be inserted through each angiography sheath during removal, sealing the puncture tract to prevent bleeding.

For the direct puncture technique, 6F sharp Elekta ProGuide catheters [Nucletron, Elekta AB, Sweden (240 mm and 294 mm)], rigid steel obturators, 2.0 nylon sutures, 6F Elekta ComfortCath buttons for fixation, sterile ruler, local analgesia and surgical dye/marker are used.

5. Preplanning

Before catheter placement, it may be useful to generate a pre-plan to assess the optimal catheter position for full dose coverage and OAR sparing. Based on available diagnostic 3D imaging, the planning target volume (PTV) and OARs are delineated. Thereafter, the number and geographical placement of catheters can be estimated in close collaboration between the medical physicist and the radiation oncologist or interventional radiologist. In principle, the catheters should be arranged in parallel, as this configuration provides a good and reproducible dose coverage of the PTV. However, practical aspects need to be considered, as the proposed catheter trajectories must be practically accessible and avoid OARs. With experience after a learning period, pre-planning can be omitted in standard cases but will remain helpful in complex targets.

6. Catheter placement

6.1 Seldinger technique

The catheters should be implanted for liver interventions by a trained radiation oncologist or interventional radiologist. The intervention is always conducted under sterile conditions. The catheters are usually implanted under CT fluoroscopic guidance. However, some centers also have the possibility to perform the procedure in an open MRI, which requires MR-compatible material. Ultrasound-guided implantation is rarely used nowadays; however, it is a perfect option if the staff has the required experience. However, simulation CT or MRI imaging is still required for treatment planning purpose.

The interstitial placement of the brachytherapy catheters is usually performed under analgosedation with local anesthesia, or rarely under general anesthesia. Before the procedure, a CT scan without contrast in the region of interest is usually acquired for intervention planning purposes, and then the brachytherapy catheters are inserted into the tumor under CT fluoroscopy.

When using the Seldinger technique, a guide wire is inserted into the puncture needle core before the needle is removed, and thereafter a long hydrophilic angiography sheath is inserted under the guide wire guidance. Subsequently, brachytherapy catheters are placed into the angiography sheaths after removal of the guidewire. The brachytherapy catheter is sealed at the tip and has a millimeter scale, which is needed for correct positioning of the brachytherapy catheter within the angiography sheath.

The brachytherapy catheter is then marked with steristrips for correct catheter numbering and to define the final position within the angiography sheath, which is sutured to the patient's skin for fixation. It is important that the brachytherapy catheter is always inserted at a depth that is at least equal to or exceeds the length of the angiography sheath within the liver, as the angiography sheath is radiopaque. The exact position of the brachytherapy catheter tip would not be visible on CT imaging for catheter reconstruction if it is located anywhere within the angiography sheath. The number of catheters depends on the size and shape of the tumor. Irregularly shaped and larger tumors require more catheters to adequately cover the target with the prescribed dose and to ensure good sparing of healthy liver tissue and adjacent OARs.

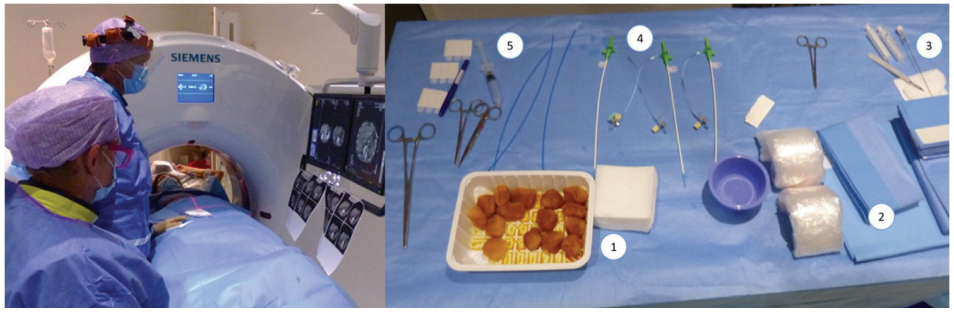

Figure 2. An example of the setup (left) and material (right) used for CT-guided catheter implantation using the Seldinger technique. Exemplar materials used for implant: 1) sterile swaps and compresses, 2) sterile draping material, 3) scalpel and hollow puncture needle, 4) numbered angiography sheaths, and 5) brachytherapy catheters.

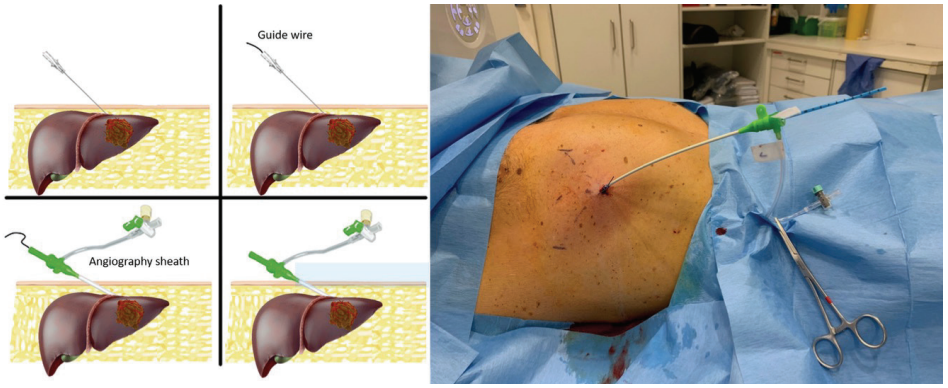

Figure 3. Schematic workflow of the catheter placement using the Seldinger technique (left) and image of the final implant (right). The blue brachytherapy catheter can be seen inside the green/white angiography sheath. The transfer tube of the afterloader (not included in the image) will be connected directly to the blue brachytherapy catheter.

6.2 Direct puncture technique

Another method, favored by some radiation oncologists, is the direct puncture technique. This technique, however, does not allow sealing of the puncture tract foam after catheter removal. Furthermore, if a catheter position correction is required, this instance, the direct puncture technique has a higher trauma risk compared to a needle rearrangement in the Seldinger Technique.

A trained interventional radiologist or radiation oncologist performs the procedure under aseptic conditions. An initial CT scan is performed to identify the liver tumor and plan the puncture tract. The skin puncture site at the corresponding intercostal space is identified based on CT guidance and local anesthesia is administered. Local anesthesia is infused at the skin up to the liver capsule and a small skin incision is made with a sharp scalpel. Areas of high subcutaneous fat are avoided to reduce the risk of catheter displacement in obese patients.

A sharp tip 6F needle (Elekta AB, Sweden) is inserted into a fixation button, and the button is adjusted to the estimated insertion depth. Then, the brachytherapy catheter with the button at the estimated depth is inserted through the skin incision, passing through the intercostal space and liver capsule directly into the tumor. When a non-planar insertion is performed (especially for lesions in segment 7/8), multiple short-range scans or CT fluoroscopy are used to ease the non-planar maneuvering. The number and position of the applicators are based on the tumor size and geography. If it is deemed safe, the brachytherapy catheters are advanced up to 5 mm beyond the tumor to account for respiratory motion and catheter offset. Applicators are secured to the skin with a button and skin suture.

7. Treatment planning

After catheter placement, a CT simulation scan is performed, preferably with a contrast agent. The CT images are then transferred to the treatment planning system. A slice thickness of 2 mm is preferable to achieve exact target volume delineation and catheter reconstruction.

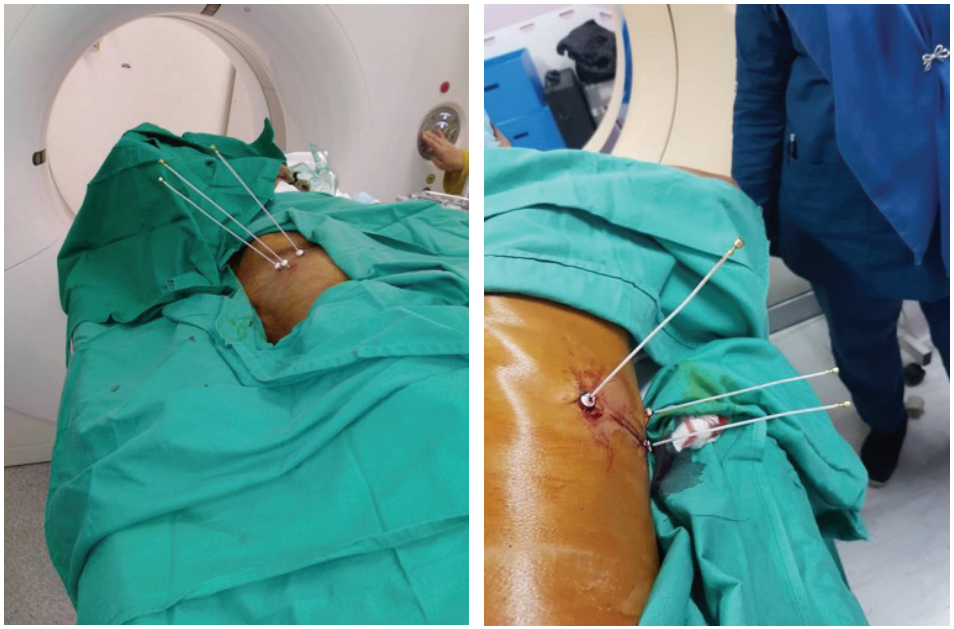

Figure 4–5. Direct technique post-insertion

Target delineation includes the gross tumor volume (GTV) with an additional margin of 0-5 mm for the generation of the clinical target volume (CTV), depending on the visualization quality of the GTV. The GTV is contoured using additional pre-treatment diagnostic imaging (CT with IV contrast, liver-specific MRI with hepatocyte-specific contrast, or PET-CT). Since no relative movement between the target and the applicator is expected, no additional margin is added to generate the PTV (CTV = PTV). Adjacent OARs, such as healthy liver, main biliary tract/duct, heart, esophagus, stomach, duodenum, colon, and small intestines are delineated.

The next step is the reconstruction of the catheters in the treatment planning system (TPS), which can be done before target structure and OAR delineation. Each catheter must be correctly identified and the first dwell position in each catheter tip must be marked in the TPS. After catheter reconstruction,

all reconstructed catheters should be checked for plausibility, i.e., via visual inspection of a 3D rendering of the catheters. It may be helpful to have a schematic drawing of how the catheters exit through the patient's skin. In addition, if catheter insertion is performed using the Seldinger technique, the excess end of the brachytherapy catheter from the angiography sheath outside the patient should be measured as a second validation. Using this information, the internal excess of the brachytherapy catheter can be calculated and checked against the manual catheter reconstruction (distance of the end of the angiography sheath to the (radiopaque) tip of the brachytherapy catheter on the CT images). The angiography sheath can be identified with great reliability as it is radio-opaque.

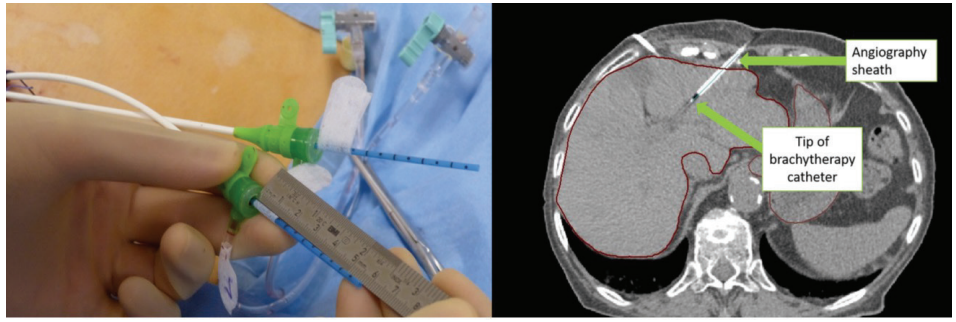

Figure 6. The excess end of the brachytherapy catheter to the angiography sheath outside the patient can be measured with a sterile ruler as a second validation and used to validate the internal excess of the brachytherapy catheter.

An alternative to marking the first dwell position is the use of a reference mark with a known offset. This catheter reference point is commonly identified by the radiopaque marker within the tip of the brachytherapy catheter, or alternatively, CT markers inserted into the brachytherapy catheter prior to planning CT can be used. Usually, 2 mm dwell position spacing is used for liver HDR brachytherapy.

Dose optimization is performed either manually or via semiautomatic inverse dose optimization (e.g. HIPO, IPSA, hybrid inverse planning and optimization, Elekta AB, Sweden) or a combination of both. It is advisable to generate a first version of the plan via automated dose planning and then proceed with manual fine adjustment of dwell times. When optimizing the dose, as a first step, the aim should be to achieve full coverage of the PTV with the prescribed dose. Following that, optimal sparing of OARs will be attempted. Compared to other entities, dose distribution in liver brachytherapy plans is usually inhomogeneous with very high central doses. While it is possible to increase the dose homogeneity by inserting numerous catheters, depending on the volume of the treated lesion and due to the potential risk of procedural complications during the catheter placement, only a limited number of catheters is usually inserted compared to other anatomic sites (e.g. breast, prostate). The trade-off between the loss of full dose coverage and treatment efficacy or the acceptance of possible higher risks for side effects is a complex clinical judgment for each case. However, as a general rule, OAR sparing has higher priority over full dose coverage. The puncture tract is frequently irradiated with ~5 Gy at catheter surface up to the patient's skin to avoid seedling along the puncture tract (tract irradiation).

8. Dose prescription and reporting

The dose prescription aim is for the prescribed dose to encompass 100% of the PTV volume. The D100%, D95% and D90% are usually reported. The prescribed dose is histology-driven. For serial OARs, mostly maximum point dose constraints are used, while for parallel organs (e.g., liver, kidney), volumetric constraints are usually applied.

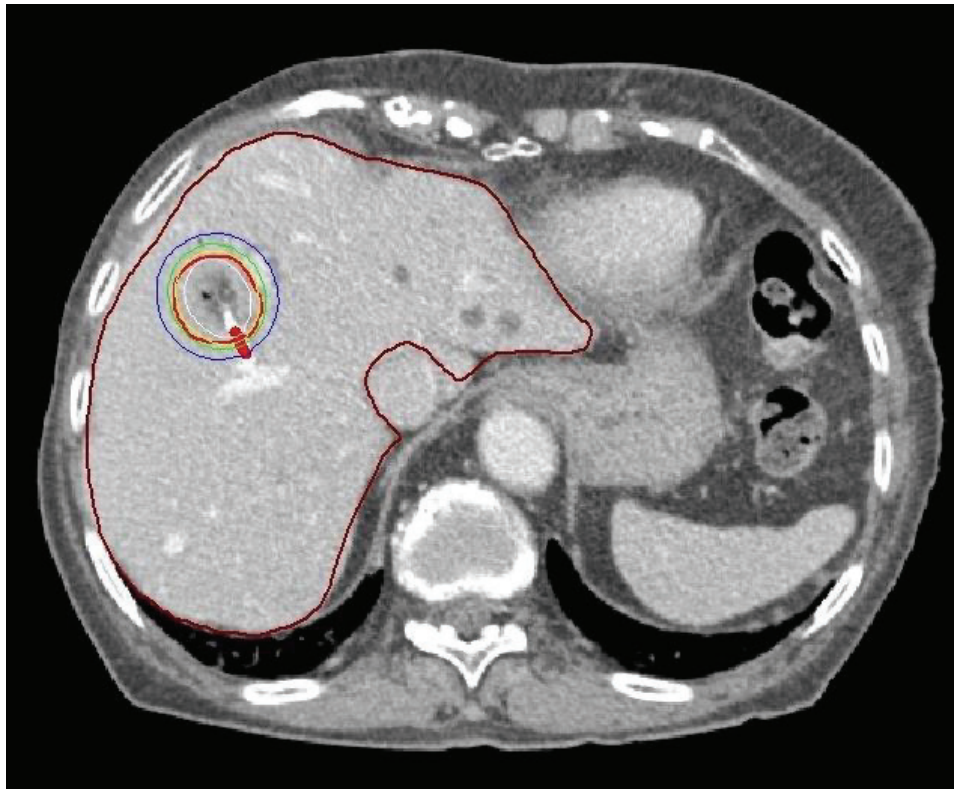

Figure 7. Axial CT image of liver brachytherapy in the Seldinger technique for a metastatic lesion of pancreatic cancer in segment VIII of the liver. Green isodose: 20 Gy.

Dose constraints

Organ	DVH value	Dose [Gy]
BT	1.5	2.1
Bowel	D1ccm	12
	D0.1ccm	15
Colon	D1ccm	12
	D0.1ccm	15
Stomach	D1ccm	12
	D0.1ccm	15
Esophagus	D1ccm	12
	D0.1ccm	15
Myelon	D1ccm	10
	D0.1ccm	12
Liver hilum	D1ccm	18
	D0.1ccm	20
Skin	D1ccm	10
Healthy liver tissue	<33% liver volume	10Gy (2/3 of liver <10Gy)
	<66% liver volume	5Gy (1/3 of liver <5Gy)

Table 1.

9. Treatment delivery

After approval of the treatment plan and transfer to the afterloader software, the transfer tubes are connected to the afterloader and the dose is delivered to the tumor. The integrity of the data transfer must be validated for each plan, and plausibility checks (e.g. patient name, plan code, radiation time) should be performed. All relevant parameters of the treatment plan must be cross-checked with the ones at the afterloader, i.e., the current source activity or overall irradiation time. The duration of irradiation is determined by the size of the target volume, the number of catheters, the prescribed dose, and the source activity (diminishing with time due to radioactive decay); typically, it is between 10 and 60 minutes.

The departmental emergency procedure must be in place for each different brachytherapy technique. An advantage of the Seldinger technique is that, with the catheter-in-catheter technique, the emergency procedure is easy to handle as the brachytherapy catheters can be quickly removed from the angiography sheaths.

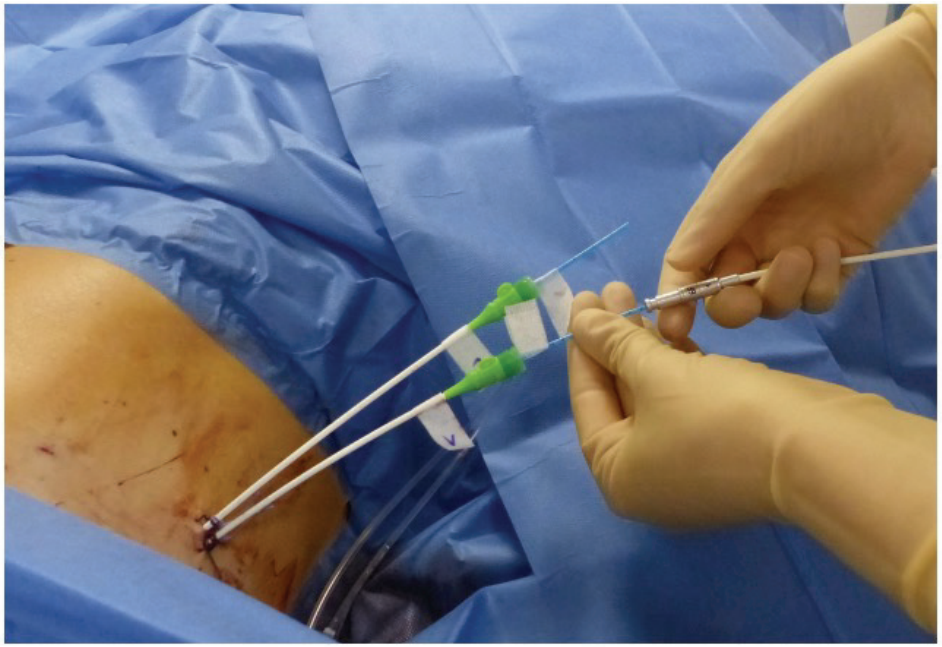

Figure 7. Connection of the transfer tubes to the brachytherapy catheters prior to dose delivery for the Seldinger technique.

10. Catheter removal

Since both the hepatic metastases, primary liver tumors and liver parenchyma are typically well-perfused, complications may arise from bleeding along the catheter path after removal. When the Seldinger technique is used, it is possible to perform catheter tract embolization by applying gelatine sponge sealing (see above) during stepwise withdrawal of the angiography sheath. In the direct puncture technique, the applicators are withdrawn in a gradual or staggered manner, and pressure is applied to the puncture site with povidone-soaked gauze.

In addition, standardized follow-up is important for early detection of complications (e.g., ultrasound after 1–2 hours), and routine monitoring (non-invasive blood pressure, heart rate, oxygenation, and ECG) should be ensured over the first four hours after applicator removal. Ideally, patient monitoring after catheter removal can be performed in a dedicated and adequately staffed monitoring area. Patients are not brought to the ward prior to ultrasound and stable vital signs for at least 2 hours.

11. Post-treatment management

Patients with a history of biliodigestive anastomosis or following endoscopic papillectomy have an increased risk of developing a liver abscess or cholangitis after HDR-BT. In such cases, peri-interventional antibiotics can be administered (e.g., oral ciprofloxacin 500 mg 1-0-1 for two weeks, or IV antibiotics with piperacillin/tazobactam for 10 days).

RILD (radiation-induced liver disease) is a fatal complication of liver HDR-BT and needs serious attention. RILD usually develops 4–6 weeks after interstitial radiation for extensive volumes, with resulting ascites and impaired liver function. This typically manifests in laboratory changes: increased bilirubin and alkaline phosphatase. It is recommended to limit the exposure of >10 Gy to a maximum of one-third of the liver volume. A liver-protective regimen that specifies enoxaparin, pentoxifylline, and ursodeoxycholic acid has been shown to significantly reduce the rate of RILD over eight weeks following targeted radiotherapy. Patients should be on proton pump inhibitors (PPI) for at least 6–8 weeks if the mucosal area of the stomach has received a substantial dose (>5Gy).

12. Procedural complications and toxicity

Overall, procedural complications that may arise from this minimally invasive intervention should be distinguished from the toxicity of the radiation itself. Severe complications are rare and reported to be less than 1.5% (bleeding, infection, and pain). There is evidence for strong correlation between major bleeding events and advanced liver cirrhosis, usually in patients with hepatocellular carcinoma, or the peri-interventional administration

of low-molecular-weight heparin[7]. If there are signs of hypovolemic shock, internal bleeding must be ruled out by CT, and if active arterial bleeding is detected, immediate intervention is required. The treatment of choice is angiographic embolization with particles or coils. Surgical intervention is rarely needed in liver HDR-BT. Liver abscesses (~2%) may occur more frequently in patients with a history of biliodigestive anastomosis or following endoscopic papillectomy. Usually, they arise with a latency of weeks to months after the intervention and can be clinically silent. Abscess formation can be detected by contrast-enhanced CT, and the treatment of choice is percutaneous drainage with aspiration material sent for culture and appropriate antibiotic treatment. In high-risk cases, applying prophylactic antibiosis might be a treatment option to prevent infection.

Regarding radiation toxicity, adjacent liver parenchyma will be exposed to a significant radiation dose and will suffer focal radiation-induced damage following brachytherapy. Published literature on the tolerance dose of single parenchymal sub-unit of liver parenchyma is around 10 Gy for single-fraction brachytherapy, which usually corresponds to a relatively small volume of radiation-induced liver parenchymal damage around the ablated tumor for the commonly used HDR-BT dose. However, in patients with multiple ablations (sequential or multiple lesions at the same time) and/or in patients with a small functional liver reserve, this radiation-induced liver injury can lead to clinically apparent radiation-induced liver disease (RILD, i.e., liver decompensation). The frequency of RILD after brachytherapy is around 0.5%. To avoid RILD after HDR-BT, a minimum of one-third of the liver should not be exposed to more than 5 Gy (Table 1).

For large, centrally located liver tumors, clinically relevant biliary duct complications are rare and have not been associated with a reduction in overall survival in available studies[8]. The excellent treatability and control rate of central liver tumors is a unique feature of interstitial brachytherapy compared to other local therapeutic procedures, including surgical resection.

13. Follow-up and Imaging

Following treatment completion, patients are eventually followed up at 1 week for a repeat liver function test and a physical examination. Patients will then be evaluated every six weeks with blood tests and three-monthly imaging (CT liver or MRI liver).

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