Computed Tomographic appearance of liver lesions treated with locoregional interventional radiology therapies

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Learning objectives

The purpose of this educational exhibit is to describe the Computed Tomographic (CT) appearance of malignant liver lesions treated with transcatheter arterial embolization and/or percutaneous ablation therapies (including hepatocellular carcinoma, colon cancer metastasis and neuroendocrine tumours metastasis).
Background

The development of transarterial and percutaneous locorregional techniques opened new frontiers for patients with primary and secondary hepatic malignancies and not eligible for hepatic surgery. The anticancer effect of these approaches relies on the selective delivery of chemotherapeutic agents, blockage of arterial supply with particles or tumour ablation by means of energy waves.

A. TRANSARTERIAL AND PERCUTANEOUS TECHNIQUES DESCRIPTION

1. Transcatheter Arterial Chemoembolization (TACE) (1-3) (Fig.1)

TACE can in turn be subdivided into:

• **TACE (cTACE)** that consists of an infusion of a mixture of chemotherapeutic agents, with or without lipiodol (an iodized oil derived from poppy seeds), followed by or coadministered with an embolic agent (either gelfoam or particles) in order to deliver a local and sustained dose of drug direct to the tumour; Lipiodol acts as a carrier of chemotherapeutic agents, which are released slowly and increases retention of chemotherapy agents within the tumour, providing longer exposures and selectively persists in the neovascuclature and extravascular spaces of liver tumours for weeks/months (due to the absence of functioning hepatic lymphatics and Kupffer cells in these lesions).

• TACE with drug-eluting beads (**DEB-TACE**) or with polyvinyl alcohol-based microspheres (**DEM-TACE**) loaded with various types of chemotherapeutic agents, that have recently been developed in order to improve the pharmacokinetic profile of the chemotherapeutic drugs.

Advantages:

§ Local and targeted drug delivery à Minimizes systemic drug bioavailability.

§ Tumour-feeding artery embolization à Prevents washout of the drug at the tumour site and induces ischemic necrosis.
**Possible adverse effects:**

- "Post-embolization syndrome": fever, nausea/vomiting and pain, occurs within the first 72 hours after embolization.
- Formation of liver abscess in the necrotic tumour and bile duct injury.
- Periprocedure mortality (rate ~2.5% in 30-days)
- Vascular complications
- Myocardial infarction
- Contrast material-induced nephropathy
- Toxicities related to non-target embolization include: Cholecystitis; Pancreatitis; Hepatic decompensation

2. **Bland transcatheter arterial embolization (TAE)** (4,5)

No chemotherapeutic agent is delivered.

The anticancer effect of embolization is based only on terminal arterial blockade and subsequent tumour ischemia.

**Draw-backs:**

Some studies have demonstrated that hypoxic change alone can lead to tumour progression by inhibiting apoptosis and stimulating angiogenesis, therefore implying the need for adjuvant chemotherapy.

3. **Percutaneous ablation with a thermal energy source**

3.1 **Radiofrequency Ablation (RF)** (6-8) (Fig.2)

Relies on alternating electrical current flow to generate heat via ionic friction in tissues: achieving sustained temperatures of at least 60°C.

The energy generated by RF ablation induces coagulative necrosis of the tumour producing a safety ring in the peritumoural tissue, which might eliminate small-undetected satellites.

RF current is able to pass through tissue however it is not a perfect conductor and causes resistive heating.

The target tumour should not exceed 3 cm to achieve best rates of complete ablation.
Thermal ablation of lesions adjacent to hepatic vessels is not harmful because flowing blood usually protects the vascular wall from thermal injury.

**Draw-backs:**

The main cause of ablation failure is perfusion-mediated convective heat transfer à "heat-sink effect" à only sublethal temperatures are achieved.

As tumour size increases à increased blood flowà bigger heat loss à the effectiveness of RF is reduced.

This thermal attenuation in perivenous lesions is venous size-dependent à predictable to occur more frequently near veins # 3 mm in diameter.

RF ablation capability is therefore limited in lesions >3 cm and in high-perfused areas.

3.2 Microwave Ablation (MW) (9) (Fig.3)

MW ablation is a special form of dielectric heating: an electromagnetic field forces water molecules in the tissue to oscillate what causes heating.

Coagulative necrosis causes cellular death and destroys tissue in the treatment area, resulting in reduction of tumour size.

The major distinction between MW and RF heating is that MW heating occurs in a volume around the applicator antenna, while RF heating is limited to areas of high current density.

**Advantages:**

à Faster heating and higher temperatures provided by microwave energy;
à Larger coagulation volumes;
à Less susceptibility to the "heat-sink" effect;
à Achieves complete ablation in lesions up to 5 cm;

4. Percutaneous Ethanol injection (PEI) (10,11) (Fig.4)

Ethanol is a strong protein coagulant and a permanent embolic material.
PEI causes dehydration and necrosis of tumour cells accompanied by small vessel thrombosis, leading to tumour ischemia and destruction. The addition of PEI to TACE failed to prove a clear benefit in terms of survival and local recurrence. Although the size of the tumour necrosis is larger in patients treated with both procedures.

**Draw-backs:**

- It can also injure normal liver tissue and vessels.
- Limited necrosis in tumours larger than 3 cm, because of the incomplete ethanol infiltration in the whole tumoral tissue.
- Often requires repeated injections on separate days for completion of a treatment.

5. **Cryoablation (12,13)**

Destruction of tissues by rapid freezing with resultant cell death due to ice crystallization, desiccation, ischemia, and reperfusion injury during thawing. Cryoablation has mainly been applied at open or laparoscopic surgery, percutaneous cryoablation is now emerging. Causes less pain than radiofrequency ablation.

**Draw-backs:**

- Certain complications, including thrombocytopenia, haemorrhage and cryoshock, are more common in cryoablation than other ablative modalities

6. **Irreversible electroporation (IRE) (14)**

Nonthermal form of tissue ablation using high-voltage electrical current to induce pores in the lipid bilayer of cells, resulting in cell death. Preclinical studies suggest that IRE may have advantages over conventional forms of thermal tumour ablation including no heat sink effect and preservation of the acellular elements of tissue, resulting in less unwanted collateral damage.

**B. SPECIFIC INDICATIONS**

1. **Hepatocellular carcinoma (HCC) (15-21)**
1.1 TACE

TACE is the current standard of care for patients presenting with multinodular HCC and relatively preserved liver function, with no cancer-related symptoms, and with no evidence of vascular invasion or extrahepatic spread.

Experimental and clinical studies have shown that the use of drug eluting beads loaded with doxorubicin (DEBDOX) has a safe pharmacokinetic profile with lower systemic drug exposure.

According to the 2012 European Association for the Study of the Liver (EASL) and the European Organisation for Research and Treatment of Cancer (EORTC) joint Clinical Practice Guidelines for the management of HCC (EASL-EORTC CPGs):

- TACE is recommended for patients with BCLC stage B, multinodular asymptomatic tumours without vascular invasion or extra-hepatic spread (evidence 1iiA; recommendation 1A)
- Chemoembolization is discouraged in patients with decompensated liver disease, advanced liver dysfunction, macroscopic invasion or extrahepatic spread (evidence 1iiA; recommendation 1B)
- The use of drug-eluting beads has shown similar response rates than gelfoam-lipiodol particles associated with less systemic adverse events (evidence 1D; recommendation 2B)
- Bland embolization is generally not recommended
- Selective intra-arterial chemotherapy or lipiodolization (without embolization) are not recommended for the management of HCC (evidence 2A; recommendation 2B)
- These guidelines also recommend neo-adjuvant treatment pre-transplant if the waiting list time is > 6 months to prevent dropouts due to tumour progression (evidence 2D; recommendation 2B)

However, some other published works claim that TACE and TAE might be equally effective for HCC management and that the lack of standardization of embolization therapies worldwide may be responsible for varying results (22-24).

1.2 LOCAL ABLATION

Local ablation with RF or percutaneous ethanol injection is considered the standard of care for patients with BCLC 0-A tumours not suitable for surgery (recommendation 1B)
RF ablation is recommended in most instances as the main ablative therapy in tumours < 5 cm due to a significantly better control of the disease **(recommendation 1A)**. Other ablative therapies, such as MW or cryoablation, are still under investigation. Ethanol injection is recommended in cases where RF ablation is not technically feasible (around 10-15%). In tumours <2 cm, BCLC 0, both techniques achieve complete responses in more than 90% of cases with good long-term outcome.***(evidence 1iA; recommendation 1C)***

1.3 COMBINATION TACE AND RF (25-27)

The combination of ablative and intra-arterial treatments seems to improve both tumour response rates and survival in patients with intermediate-size lesions:

§ In a prospective two-arm study comparing TACE + RF with RF alone for small lesions (HCC #3 cm) à no benefit of combination therapy

§ Studies investigating the efficacy of combination TACE + RF for larger lesions à higher rate of complete response and survival benefit

The exact size range is not well defined, but certainly for the addition of TACE to be beneficial the lesion must be 3 cm or larger.

- **TACE+RF**

  TACE is performed first à diminished regional blood flow to and around the target lesion. When RF is performed the "heat-sink" effect is mitigated resulting in a larger ablation volume.

- **RF+TACE**

  If RF is offered first à after ablation a peripheral hyperaemic rim is present. Secondly during TACE, this increased local vascular supply to peripheral of target lesion improves the deposition of the TACE cocktail, potentially treating undetected satellite lesions, which may cause recurrence.

2. Unresectable liver metastasis in patients with colorectal cancer (28-34)

2.1 TACE with irinotecan-loaded drug-eluting beads (DEBIRI)

Used to treat liver-only or liver-dominant metastatic disease from colorectal cancer. DEBIRI in addition to systemic chemotherapy improve response rates, increased resectability and prolongs hepatic progression-free survival.
3. Unresectable liver metastasis in patients with neuroendocrine tumours (NET) (35-36)

TAE, TACE and RF are the most common therapeutic options, that proven to be effective at palliation of hormonal symptoms of metastatic neuroendocrine tumors (NETs), as well as a means of cytoreduction.

There is still no consensus on which chemotherapeutic agents for TACE are the most efficacious in the treatment of liver metastases from NETs, although Doxorubicin is the most commonly used.

TAE can reduce tumour size and hormone output in liver metastases from NETs, resulting in palliation of symptoms without the use of cytotoxic drugs, resulting in better tolerability. Newly developed locoregional ablative procedures are under evaluation.
Fig. 1: DEB-TACE

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Radiofrequency percutaneous ablation needle that generates a high frequency alternating current.

**Fig. 2: RF**

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Fig. 3: MW

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Fig. 4: PEI

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Findings and procedure details

Anatomic tumour response metrics (RECIST) can be misleading when applied to locoregional therapies in liver lesions.

Tumour swelling and internal necrosis may be responsible for an increase in overall tumour diameter at early follow-up scans, potentially leading to incorrect diagnoses of tumour progression.

Unmasking of small tumour foci as a result of internal necrosis may also simulate the emergence of new tumour lesions and lead to incorrect response evaluation.

Assessment of tumour vascularity with the use of a triple-phase liver CT 2-4 weeks after treatment is recommended to evaluate tumoral response (Fig.5-19)

Modified RECIST criteria should be used to assess response --> tumour vascularity should be considered rather than size.

The American Association for the Study of Liver Diseases (AASLD) adapted the concept of viable tumour: tumoral tissue showing uptake in arterial phase --> modified RECIST assessment (mRECIST).

- **Complete Response:** Disappearance of any intratumoural arterial enhancement in all target lesions.

- **Partial Response:** ≥30% decrease in the sum of diameters of viable (enhancement in the arterial phase) target lesions, taking as reference the baseline sum of the diameters of target lesions.

- **Stable Disease:** Any cases that do not qualify for either partial response or progressive disease.

- **Progression:** ≥20% in the sum of the diameters of viable (enhancing) target lesions, taking as reference the smallest sum of the diameters of viable (enhancing) target lesions recorded since treatment started.

mRECIST has been shown to be associated with survival.
Images for this section:

**Fig. 5:** HCC treated with DEB-DOX.

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55-year-old patient with a 4 cm hypervascular nodule in segment VII, compatible with HCC. Selective arteriography of the celiac trunk revealed an hypervascular nodule supplied by a branch of the right hepatic artery. Three sessions of chemoembolization with doxorubicin loaded beads were performed to achieve complete response.

**Fig. 6:** HCC treated with DEB-DOX

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**Fig. 7:** HCC treated with DEB-DOX.

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Fig. 8: HCC treated with DEB-DOX

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Fig. 9: HCC treated with RF.

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Fig. 10: HCC treated with PEI.

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**Fig. 11:** HCC treated with PEI.

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Fig. 12: HCC treated with MW.

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Fig. 13: CCR metastasis after DEBIRI.

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Fig. 14: CCR metastasis after DEBIRI.

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**Fig. 16:** CCR liver metastasis after MW ablation.

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Fig. 17: CCR liver metastasis after MW ablation.

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Fig. 18: CCR liver metastasis after MW.

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Fig. 19: NET metastasis after TAE.

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**Fig. 15:** CCR metastasis after DEBIRI.

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Conclusion

Transcatheter intraarterial and percutaneous therapies have proved to be valuable tools against primary and metastatic liver malignancies.

The familiarity with these techniques and particularly with post-treatment CT imaging spectrum is essential for an accurate radiological assessment of treatment response by the Radiologist reading the follow-up imaging studies.
References


