

TRANSCATHETER ARTERIAL CHEMOEMBOLIZATION

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Liver Lesion Treatment Options

Surgery:

- Resection
- Transplantation

Chemical Ablation:

- Ethanol (Percutaneous Alcohol Injection, PEI)
- Acetic Acid

Thermal:

- Cryosurgery
- Radiofrequency Ablation (RFA)
- Microwave
- Laser
- High intensity ultrasound

Chemotherapy:

- Systemic
- Hepatic artery infusion (HAI)
- Transcatheter Arterial chemoembolization (TACE)

Bland Embolization

- TACE minus the C

Combination Therapy:

- TACE + PEI
- TACE + RFA

Transcatheter Arterial Chemoembolization (TACE):

Historically, systemic chemotherapy has had both a poor response rate for hepatoma and colorectal metastasis (20 – 40 %) as well as a poor survival benefit.

Advantages of TACE over systemic chemotherapy:

Delivery of the drug is quicker.

Selective catheterization can deliver a higher dose and greater uptake of chemotherapy.

TACE can achieve a tumor drug concentration of 10 – 25 times > IV infusion alone.

It also prolongs the dwell time or exposure of the tumor cells (as long as a month) to the chemotherapy agent by delaying the washout.

It causes less morbidity by reducing the systemic effects of chemotherapy

Embolization deprives the tumor of essential nutrients by causing ischemia.

Nilsson first attempted surgical dearterialization of liver tumors in 1966 by ligating the proper hepatic artery. Survival was not increased by ligation alone. The problem was with the formation of collaterals. Collaterals have been shown to develop as early as 4 hours after ligation and can be fully developed in four days.

Subsequently in 1977, Yamada first performed TACE using mitomycin C or Adriamycin and Gelfoam for unresectable HCC.

1987 Takayasu used Adriamycin and lipiodol followed by gelfoam for HCC.

The strategy to perform TACE is based on the fact that the normal liver receives 75% of blood flow (50%) of oxygen supply from the portal vein and 25% of blood flow (50%) oxygen from the hepatic artery.

Hepatic tumors on the other hand receive 90% of oxygen from the hepatic artery.

Basically, tumor angiogenesis is derived mainly from the hepatic artery.

50% of all liver tumors are hypervascular but even the hypovascular tumors receive 90% of their blood supply from the hepatic artery.

Blocking portal flow causes an increase in arterial flow but the reverse is not true. So hepatic arterial occlusion does not result in compensatory portal flow to the tumor.

There are, however, several caveats that should be noted. Small tumors, the periphery of larger tumors and well - differentiated tumors are commonly supplied predominantly by the portal vein.

Additionally, blood flow through a tumor is not always uniform and the center is commonly less perfused than the periphery. The presence of AV shunting may also impede local therapy.

Indications for TACE:

Unresectable HCC

Multinodular HCC

Unresectable metastasis

 Neuroendocrine tumors

 Colorectal metastasis

 Other metastasis

 Ocular melanoma gastric sarcoma, and thyroid. These have fatal liver metastasis despite a resectable primary tumor.

Reduce tumor bulk in patients who are borderline resectable

Post resection recurrence

Reduce progression of disease while awaiting a liver transplant

Shrink a large unresectable lesion causing local symptoms

Adjuvant therapy

TACE + RFA

TACE + PEI is better than PEI alone followed by TACE alone followed by supportive care.

It is important to remember that TACE is a palliative procedure.

The effectiveness of TACE has been and is controversial.

Early non-randomized studies suggested a definite survival benefit. Most studies showed a 3 - fold increase in median survival. Later, 3-6 randomized studies suggested that this was not the case. It appears that these randomized studies may have been flawed. They included heterogeneous patients with heterogeneous tumors making conclusions questionable. Additionally the studies were multicenter collaborations with a small number of patients and few patients in each arm. One of the studies had 61% liver failure after the first chemoembolization and also had to eliminate 10% of patients because of hepatic artery occlusion.

The problem is that various institutions differ in the type, dose and combination of chemotherapeutic agent as well as the type of embolic material, amount of liver embolized and end points of therapy. Follow up and retreatment protocols also differ.

The dissenters believe that the effects on the liver from chemoembolization counteract the benefits and don't add to survival. They believe chemoembolization is no better than supportive care.

The problem is that many of these patients (specifically those with HCC) have 2 diseases. One is tumor and the other is chronic liver disease (for HCC). Half of the patients die from liver disease so treating the tumor may be futile.

Some of the randomized studies, which claim chemoembolization doesn't work, arbitrarily set up a protocol of embolization every 8 to 12 weeks. However, if a regimen of repetition based on tumor response and patient tolerance (necessity and underlying labs) is performed better survival and fewer complications have been shown.

Additionally, more selective injections, tailoring the dose to size and extent of tumor as well as making the protocol patient specific, decreases the negative effect of chemoembolization and improves survival according to U of Hong Kong. Using TACE in this manner can definitely improve quality of life and survival. For example, patients claim improved appetite a feeling of well being without the side effects of systemic chemotherapy.

Also, it appears that survival and quality of life may directly correlate with the vascularity or the tumor. Reports of HCC and neuroendocrine chemoembolization have shown improved survival and quality of life. Some colorectal metastasis (typically

hypovascular) have also shown a good response and this may be related to the fact that some have greater vascularity.

The Japanese literature suggests a difference when TACE is performed selectively / subselectively vs. non-selective. They also don't repeat the procedure if there is a morphologic response whereas the randomized studies noted above continued repeatedly and may have led to decreased liver function.

Focal HCC has been shown to have less recurrence than multinodular.

Lesion size, number, location, bilobality and alpha fetal protein did not have anything to do with survival.

Portal vein involvement does not preclude increased survival.

Another controversy is whether the chemo portion of chemoembolization adds anything. There is no definite evidence that the chemo portion of chemoembolization adds anything to survival.

Yoshikawa et al showed that the addition of Lipiodol yields a better response rate than just the drug alone. One-year survival was also improved.

Chemotherapy was felt to contribute to post procedure morbidity.

Chang et al reported that the addition of cisplatin to gelfoam and Lipiodol did not add to survival and survival in the control group (no cisplatin) was the same. The only difference was more vomiting post procedure with cisplatin.

A recent meta-analysis (2002) included 2,466 patients from 18 randomized controlled studies. Their results showed that TACE significantly reduced the overall 2-year mortality when compared with no therapy. In addition, they found that embolization without a chemotherapeutic agent (TAE) had less mortality than TACE. This suggested that the addition of chemotherapy may not only be of no use but may actually be detrimental by exacerbating liver failure. Also, success is better in patients with Child class A and B as opposed to C. Essentially TACE is not for everyone. The procedure, its dose and its repetitions must be individual to the patient.

Basic components include:

Iodized oil (Ethiodol, Lipiodol) (iodized poppy seed oil)

Chemotherapeutic agents

 Doxorubicin (Europe)

 Cisplatin, doxorubicin, mitomycin C (CAM) (US)

 Cisplatin alone

Embolic agent

 Ivalon (PVA, polyvinyl alcohol alcohol) (150-250 ug size)

 Gelfoam (1 -2 mm particles)

 Thrombus

 Degradable starch microspheres (Spherex)

 Coils

Useful chemotherapeutic agents:

Cisplatin, (Platinol)

Cisplatin alone has been used at 2mg/kg body weight at a total dose of 100-150 mg for HCC, metastatic colorectal, metastatic ocular melanoma and neuroendocrine tumors.

Doxorubicin (Adriamycin)

Doxorubicin doses range from 20 –100mg and it should be tapered to the patient's liver function and lessened if mixed with other drugs.

Mitomycin C

The standard dose is 10-20 mg as a single agent.

Other

Neocarzinostatin (SMANCS), Vincristine, Gemcitabine (Gemsar) Streptozotocin

When agents are mixed it is typical to reduce the individual dose by 1/2 to 1/3.

Embolic agents:

The most commonly used agents are:

Gelfoam sponge (1-3 mm pledgets) absorbable sponge derived from gelatin

PVA (150-250 um) Polyvinyl Alcohol basically plastic

Lipiodol (iodinized poppy seed oil)

Permanent embolic agents such as coils are not suggested as they may enhance collateralization and preclude later cannulation of the vessels for reembolization.

Theoretically, devascularizing the tumor will enhance necrosis. Embolic agents delay chemotherapy washout and induce hypoxia. Hypoxia may upset cellular pumps and permit increased uptake of chemotherapeutic agents.

Authors have used the embolic agents in a variety of ways. Some use the embolic agents before or during the administration of chemotherapy. Others deliver it afterwards. One group mixes the PVA with the chemotherapy and Lipiodol prior to delivery.

Some also differ on the endpoint of embolization. One option is to embolize until the flow is slow versus embolizing until the artery is completely occluded.

A recent abstract of a study comparing embolic agents was performed using PVA mixed with the chemo-oil mixture and PVA or Gelfoam after the chemo-oil mixture. When PVA is delivered as part of the slurry both the amount of chemoembolization mixture delivered and arterial patency were reduced. Embolizing later with either Gelfoam or

PVA yielded a greater delivery volume of chemotherapy agent to the liver and had better arterial patency on follow up. Gelfoam and PVA did not differ.

The primary objective is to promote revascularization in order to prevent small collateral formation that eventually precludes reembolization.

Ethiodol (same as Lipiodol different labs):

Iodized poppy seed oil (an ethyl ester of the fatty acid of poppy seed oil containing 37 - 39% iodine by weight).

It is normally removed by the reticuloendothelial (RES) cells of the liver, lung, spleen and bone marrow.

Normal liver usually removes Lipiodol in 1 to 30 days.

RES cells are missing in hepatic tumors.

Theoretically Lipiodol acts as a carrier for the chemotherapeutic agent.

The mechanism of Lipiodol is thought to be due to one or more of the following:

Neovascularity or tumor-produced cytokines may enhance uptake in and around tumors. Surface tension, viscosity and electrostatic charge may cause it to adhere to the tumor microvasculature.

Lipiodol may enter tumor microvasculature, it's endothelial lining the extracellular space or in the tumor cell itself.

Once taken up by tumor cells it permits direct cellular exposure and death.

It occludes presinusoid arteriportal shunts prolonging exposure to the tumor.

Dose:

.2ml/kg is generally considered a safe dose.

A typical generalized TACE dose is 10 - 20 ml. Otherwise it may exceed the RES and embolize the lung and spleen.

Alternatively, for tumors < 5 cm the number of ml. administered is slightly larger than the maximum diameter of the tumor. For tumors > 5 cm the number of ml. delivered is equal to the maximum diameter of the tumor.

When delivering up to 15ml of Lipiodol some may get into portal vein but it stays by the tumor. If > 15 ml is given, it may enter portal vein not supplying tumor. It gets through small arteriportal communications in the sinusoids that occur when exposed to Lipiodol.

Arterial delivery of Lipiodol has been shown to enter the portal vein.

There are 3 different sites of communication.

Transinusoidal

Vaso vasrum (trans vassal)

Venous plexus (peribiliary arterial plexus) of the bile duct

Lipiodol is also effective in predicting necrosis. If there is a greater amount and homogeneity of Lipiodol uptake in a tumor nodule, this correlates with a better embolization response and necrosis.

Peripheral nonhomogeneous Lipiodol uptake suggests incomplete response.
There is greater local recurrence when uptake is heterogeneous

Ethiodol chemotherapy mixture is an emulsion, which tends to separate and must be mixed constantly. We use a 3 way stopcock and 2, 50 cc syringes for the delivery.

Chemoembolization Regimens:

The usual mixture is made by dissolving the chemotherapeutic agent in a solution of nonionic water-soluble contrast and saline then mixed with twice the volume of Lipiodol. The solution of contrast and saline are adjusted to yield the same specific gravity of Lipiodol in order to stabilize the emulsion.

The solution must be constantly mixed to prevent separation.

Some of the reported regimens include:

1. Lipiodol, Gelfoam
2. Doxorubicin, Lipiodol, Gelfoam
3. 5-FU, mitomycin-C, Lipiodol and Gelfoam
4. Cisplatin, doxorubicin, mitomycin-C (CAM) and Gelfoam.
CAM = Cisplatin (Platinol) 100 – 150 mg, Doxorubicin (Adramycin) 50 mg, and Mitomycin-C (Mutamycin) 10 mg dissolved in 10 cc radiographic contrast and emulsified with 10 cc iodized oil.
5. CAM, iodized oil and PVA
6. Lipiodol 10 cc + Cisplatin 10 mg + Iodinated contrast 10 cc

Contraindications of TACE:

Contraindications are patient specific and the procedure should be tailored to the patient's clinical status, prognosis, type of tumor and potential for liver transplantation.

Significant or active extra hepatic neoplastic disease
Hepatic encephalopathy

Clinically apparent jaundice – bilirubin > 2.0 mg/dl

Poor liver function

Child class C

> 50% tumor replacement of liver

Aspartate transaminase (AST) > 100 iu/l

Elevated lactate dehydrogenase (LDH) > 425 iu/l

Total bilirubin > 2 mg/dl (this may be the most important)

1/3 of patients with LDH > 425, > 50% liver involvement, bilirubin > 2 and AST > 100 die within 1 month from liver failure.

Biliary obstruction – even if bilirubin normal this area susceptible to biliary necrosis.

Portal venous flow compromise

TACE can be performed with portal branch thrombosis as long as collateral hepatopetal flow is demonstrated and bilirubin is normal. If thrombosis is present it is wise to limit the volume of area embolized. Complications are increased in patients with portal hypertension and portal vein occlusion. TACE is not advised in patients with hepatofugal flow.

Uncorrectable bleeding disorder

Especially from varices as portal vein pressure increases after TACE.

Large AV shunting

Potentially these can be occluded and TACE performed

Pneumobilia or cholangitis may be a relative contraindication as it indicates contamination of bile ducts.

Complications :

Overall complications ~ 20 - 25%

Serious complications ~ 5 – 7%

Overall 30 day mortality (usually from liver failure or infection) ~ 4 % (0-10%)

The risk of post procedure mortality is increased with the number of treatments, the addition of a chemotherapy agent, treatment of patients with portal vein thrombosis and non-selective embolization.

Post embolization syndrome:

It is the most common complication seen in 20 – 80% of patients. It is usually self-limiting. It most commonly lasts 1 – 3 days but may continue for a week.

Post embolization syndrome consists of:

Fever

Pain (RUQ, back, chest)

Nausea, and vomiting

Leukocytosis.

Adynamic ileus can also occur.

Hepatic insufficiency or infarction:

Acute Progressive Hepatic Insufficiency (APHI) It is reported in ~ 2-13% but depending on the definition it has been reported in 2-60% in some cases.

Many believe APHI is defined as:

A new onset of ascites, encephalopathy and increased serum bilirubin > 2 mg/dl or doubling of the bilirubin or greater than 3 second increase in PTT after TACE from pre TACE levels.

There is a wide disparity but most insufficiency returns to baseline within 1 week. Commonly liver enzymes demonstrate a transient rise peaking at 24 – 36 hours and returning to baseline after 5 - 7 days.

Good numbers to remember are:

Incidence of APHI is 13%.

Irreversible APHI (mortality) is seen in a small percentage around 2%.

Non-target embolization to the gut:

Liver abscess:

Cholecystitis, gall bladder perforation:

Periprocedural cardiac events:

Renal insufficiency:

Pulmonary oil embolism:

Gastrointestinal bleeding:

Hypertensive crisis in neuroendocrine tumors:

Formation of multiple intrahepatic aneurysms:

These occur rarely and usually measure 1-6 mm in diameter. They resolve spontaneously and no cases of rupture have been reported.

Tumor lysis syndrome:

Post TACE the patient can get hypercoagulable (increased fibrinogen) followed by fibrinolysis with a decrease in platelets and in the worst-case scenario DIC. It may be accompanied by a drop in HCT and an elevation in creatinine.

Bile duct injury:

Incomplete embolization:

Success:

Success is measured by a change in tumor markers as well as a radiographic response.

A positive radiographic response is defined as tumor necrosis or $\geq 25\%$ decrease in tumor size.

Complete response is the absence of enhanced tumoral areas reflecting complete tumoral necrosis.

Partial response is defined as $\geq 50\%$ reduction in the product of 2 perpendicular diameter measurements through the tumor.

Minor response is $\geq 25\%$ - 50% reduction in the product of 2 perpendicular diameter measurements through the tumor.

Stable disease is $\leq 25\%$ reduction or increase in the lesion size.

Progressive disease is $\geq 25\%$ increase in lesion size.

CT may underestimate the amount of necrosis especially when Lipiodol is present.

A new defect in a lesion previously demonstrating homogenous Lipiodol uptake is indicative of tumor recurrence.

To confuse matters, there can be a successful response with HCC and it not be manifested by decrease in size. Instead it is seen as decreased vascularity.

HCC:

Post TACE response rates measured by a decrease in tumor volume size and AFP approximates 60 – 80% with an average duration of 1 year.

A complete necrosis rate of 64% has been reported.

1-year survival – 54 – 88%

2-year survival – 33 - 64%

3-year survival - 18 – 51%

5-year survival – $< 6\%$

Colorectal metastasis:

Morphologic response has been seen in 85%

Morphologic stabilization or regression was seen in 72%

CEA stabilized or regressed in 90%

20% complete regression

1 year survival: 78%

2 year survival 35%

3 year survival 15%

TACE yielded a positive response rate of 53% and a mean survival of 18 months whereas systemic chemotherapy yielded 17% and 11 months respectively.

Neuroendocrine metastasis:

Bland embolization is effective for neuroendocrine tumors.

Reduction in tumor size is 25 – 50%

Embolization can produce symptom-free intervals averaging 1 year in 90-100% of patients (almost 100% complete and partial response).

One author reported the mean duration of symptomatic relief to be 29 months another 6 – 27 months.

Procedure:

Pre-op:

Prior to instituting a protocol utilizing chemotherapeutic agents it is imperative to have an inservice dealing with cytotoxic drugs. Because of the potential deleterious effects of these agents to health care workers and others, there are specific methods for preparation, handling and disposal of equipment used in the delivery of chemotherapy. Specifically for TACE, a chemotherapy compatible stopcock (Ultra line of Medex) is essential as routine stopcocks may melt and cause contamination.

Chest x-ray or Chest CT

Cross sectional abdominal imaging (CT of MR)

Exclude extrahepatic disease and localize the intrahepatic lesion(s) and their effect on local structures. Look at the size, number and location of tumors. Look for portal or hepatic vein involvement as well as bile duct obstruction.

Labs:

Bilirubin
LDH
AST
Creatinine
PTT
INR
AFP
CBC
Platelets

Procedure directed history and physical:

Orders:

NPO

IV for meds and hydration. One author suggests saline hydration at 250 – 300 ml/hr during and 150 ml/hr for 3 hours following the procedure. This is to assist in elimination of cytokines, myoglobin, uric acid, contrast and other products of necrosis.

It is essential to check the patients renal status prior to ordering hydration.

Antibiotics

Pre procedural may intuitively seem beneficial but their effectiveness has not been proven.

Procedure cocktail

Patients tend to experience pain and nausea with embolization. Many regimens have proven effective. We have used 2 drugs with great success.

We administer Zofran (Odansetron) 4 mg. IV prior to the procedure and again just prior to the embolization. Ketorolac (Toradol) 30 mg. is given at the same time as Zofran, once pre procedure and again just prior to the embolization.

Additional conscious sedation and pain relief is administered during the procedure as necessary. Pain medication is commonly required post procedure.

Angiography:

The diagnostic angiogram is tailored to the patients renal status.

Aortogram

To define possible parasitized vessels or non-hepatic arterial supply the tumor.

Superior mesenteric angiogram

This is performed to evaluate variant hepatic anatomy (replaced vessels) as well as portal vein patency, thrombus and direction of flow.

Celiac axis angiogram

For anatomy, especially gastroduodenal, hepatic arteries and R gastric artery.

Selective common hepatic angiogram

This is optional depending upon visualization from other runs. It can evaluate position of cystic arteries, segmental anatomy and the presence of AV shunts. It is important to recognize AV shunting to avoid inadvertent chemoembolization.

Embolization:

Selective placement of the embolization catheter which is dependent on the lesion(s) location and the extent of intended embolization.

Catheter combinations -

4 Fr glide catheter with glide wire combo

4 Fr glide catheter with micro catheter combo
6-7 Fr guide catheter with 4 Fr glide catheter combo
6-7 Fr guide catheter with 4 Fr glide catheter combo and micro catheter

When positioning the catheter try to avoid embolizing the cystic artery if possible. This complication may be overestimated.

Intraarterial lidocaine has been suggested to decrease pain and spasm prior to embolization. It is most effective if given directly before embolization as opposed to afterward or not at all.

Lidocaine 30 mg bolus is given intraarterially prior to and if necessary during the procedure. Lidocaine has a blood half-life of approximately 30 minutes.

Remember that the Chemotherapy, Lipiodol and contrast combination represents an emulsion that must be mixed constantly. We use 2, 50 cc syringes attached to a 3-way stopcock that is attached to the delivery catheter.

Also it is imperative to use a chemotherapy compatible stopcock otherwise they can dissolve and cause contamination.

Remember protective garments and appropriate disposal of chemotherapy delivery materials is essential.

Dose is related to size of tumor, vascularity, underlying tumor function and cessation of flow when delivering emulsion.

Infuse chemo mixture gently to avoid reflux.

We typically perform embolization on 1 lobe at a time. We usually choose the lobe with the largest tumor burden. This allows us to assess the clinical response and limit the discomfort and possible morbidity. Patients appear to become less symptomatic and tolerant to additional procedures experiencing less postembolization syndrome.

The patient returns in 4 weeks for repeat embolization. Depending upon the number and location of the tumor and the previous extent of post embolization syndrome we may embolize either the non-embolized or both lobes.

After 4 - 6 weeks we repeat embolization of both lobes. The delay allows liver function to recover.

All of this is dependent on the patient's clinical, radiographic and laboratory response.

Our endpoint for chemoembolization includes:

1. continued progression or no response after 3 treatments

2. absence of vascular access to the tumor(s)
3. complete response
4. tumor(s) is now resectable
5. repeat embolization is precluded by patients liver function

Some repeat the procedure every 8 - 12 weeks until resolution, contraindications to TACE or progressive disease (liver function deterioration).

Currently there is no consensus on how many embolizations are essential.

Most deliver chemotherapy to only one side at a time. Some treat one side completely q 8-12 weeks 2-3 times and then do the other. The lobe with the most disease is most commonly embolized first.

Repeat chemoembolization is performed at 4-week intervals for progressive lesions, new lesions, progressive symptoms and rising AFP. Repeat embolization in HCC is determined by morphologic (radiologic) and tumor marker response (AFP)

Segmental or superselective embolization has been described (specifically in the Japanese literature) where the catheter is placed right at the tumor. Segmental Chemoembolization “overembolization” entails superselective arterial chemoembolization and pushing Lipiodol into the portal vein resulting in segmental infarction of the tumor and the normal parenchyma surrounding it. To do this there have to be only a few tumors and the tumor can be fed by only 1 artery.

Candidates for segmental embolization:

Patients with markedly impaired liver function precluding diffuse embolization.
Lesion with or without daughter nodules limited to a single or a few segments.
Lesions located in the subcapsular part or close to the diaphragm or gallbladder not accessible to other percutaneous therapies.

With the segmental method, post procedure problems and symptoms are rare.

Redistribution technique:

If embolization is difficult because of inaccessible vessels or small collaterals the GDA or accessory hepatic arteries can be permanently embolized to redistribute blood flow towards the tumor and away from non-target organs. Occlusion should be performed proximal to the first bifurcation to allow the best collateral development. Collateral development is instantaneous. One paper showed anywhere from 4 hours to 4 days.

Post Procedure Follow Up:

Most of our patients are discharged after a 23-hour admission. Patients can be discharged when the oral intake is adequate and there is minimal discomfort without need for parenteral medication.

Labs:

Repeat pre operative labs in the initial post embolization period and follow accordingly.

Labs should be repeated and evaluated prior to repeat chemoembolization.

Imaging:

Repeat at 1 month and/or prior to additional treatment.

CT – look at Lipiodol homogeneity. Be aware that Lipiodol may obscure enhancement of residual tumor. A new defect in the Lipiodol pattern can represent recurrent tumor.

CT may also demonstrate a pseudocapsule formation due to inflammatory changes after necrosis. This can be seen as increased thickness of the capsule.

Infarction and atrophy of adjacent segments can also be seen and occur over time.

Contrast MR may be better to evaluate tumor as it is not obscured by retained Lipiodol.

Even though a mass might exist on imaging, success is confirmed by lack of enhancement or hypervascularity. The mass may be present but necrotic.

After Chemoembolization treatments are completed repeat imaging can be performed at 3-month intervals.