DISCUSSION

DISCUSSION

Treatment of liver tumors by means of arterial embolization was initially proposed in the late 1970s, with the goal of controlling symptoms and local tumor growth by cutting off the tumor blood supply[136,137]. Series from the late 1970s and early 1980s[138,139] highlighted the use of intra-arterial infusion of chemotherapeutic drugs directly into the liver for primary and metastatic liver tumors, and from this, the addition of chemotherapy to arterial embolization was popularized.[140-141] Chemoembolization emerged as standard of care for unresectable hepatocellular carcinoma (HCC). Drug-eluting beads, polyvinyl alcohol–based microspheres that can be loaded with various types of chemotherapeutic agents; have more recently been developed in effort to Improve the pharmacokinetic profile of the chemotherapeutic agents administered[142,143]. Overcoming the short comings of the techniques of external beam radiation, radio-embolization has separately emerged over the past decade[144].

TACE

In our study, conventional TACE was done for twenty two patients with different primary sites hepatic metastasis ….the most common primaries were colo-rectal, and neuro-endocrine primaries, other primaries were gastric and ovarian primaries. Conventional TACE procedure was done in twenty two patients; ,complete response was noted in one patient, partial response was noted in seventeen patients progressive course was noted in three patients and one patient died before assessment of the lesions response .

Transarterial chemoembolization for metastatic disease has been explored. In 1998, Tellez et al[145] reported findings on 30 patients with metastatic colorectal cancer treated with transarterial chemoembolization after failing standard of care chemotherapy. The authors concluded that transarterial chemoembolization is a feasible treatment modality for patients with colorectal metastasis to the liver who have experienced failure of systemic therapies[145].

Hepatic Metastases from Colorectal cancer: In 2006, Geschwind et al[146] demonstrated that transarterial chemoembolization can prolong survival of patients with colorectal metastases.As in our study ,most of the patients in that cohort had previously been treated with systemic chemotherapy. A significant limitation in our study is lack of survival data after one year, no calculations for three and five years survival rates (either progression free survival or overall survival rate data) were done in this study unlike Geshwind et al[146] study and many studies concerning with the same field.

Albert et al[147] retrospectively evaluated 121 patients with metastatic colorectal carcinoma. Indication for treatment was most commonly failure of systemic chemotherapy to control unresectable liver-dominant disease. A limitation of this study was its pure retrospective design[147], unlike our study and most other studies with prospective design.

Vogl et al[148] prospectively evaluated 463 patients with unresectable liver metastases of colorectal cancer that had previously not responded to systemic chemotherapy. The indication for chemoembolization of liver metastases in patients with colorectal cancer was primarily palliative,similar to this study .TACE was applied for six patients with CRLM in this study ,all showing partial response.

Neuro endocrine Tumors with hepatic Metastases: In our study ten patients with NETLM were subjected to TACE. Neuroendocrine tumors (NETs) with hepatic metastasis

are uncommon in the general population, yet are a common indication for chemoembolization. Although the existing literature consists mainly of small retrospective reports, studies support the use of chemoembolization as a palliative treatment[149]. Dong et al[149] retrospectively analyzed 123 patients with unresectable NETs with hepatic metastases. Overall 3-, 5- and 10-year survivals were 59, 36, and 20%. ,the survival rate were not calculated in this study due to short study follow up period lasting only for one year ,not allowing for calculations of 3 and 5 years survival rates, our study was mainly indicated for symptomatic relief to overcome the carciniod syndrome symptoms ,not only palliative indications.

Chemoembolization Procedure

Chemoembolization was utilized for primary and liver-dominant metastatic disease because the hepatic artery supplies nearly 100% of blood supply to malignant tumors of the liver, embolization renders the tumor tissue ischemic. There is no consensus on the best **chemoembolization** protocol; the procedure varies widely between centers, with different drugs (doxorubicin, mitomycin, cisplatin, mixtures and bead use), embolic agents, doses, and schedules used. Response rates vary and evidence of a survival benefit is low, generally due to embolization therapies being utilized at a late stage.

In this study; Chemoembolization was performed according to our standard protocol, which included selective catheterization of the feeding artery or lobar catheterization according to the distribution of the tumor burden followed by infusion of a solution containing 10 mg of cisplatin (20 ml vial) , 10 mg of mitomycin C and 50 mg of doxorubicin (Adriamycin; Pharmacia & Upjohn, Kalamazoo, Mich), and in a 1:1 or 2:1 mixture of iodized oil (Lipiodol; Guerbert) until all of the solution was injected or until stasis was achieved. The infusion was followed by injection of 150–250 μmol/L of polyvinyl alcohol particles (Ivalon; International Therapeutic) or 300–500 μmol/L of trisacryl gelatin microspheres (Embospheres; Biosphere Medical) to slow arterial inflow and prevent washout of the chemotherapeutic agent.

Several variations of this technique have been demonstrated throughout the world; **no standard protocol has been uniformly adopted.** Centers have differed in the characteristics of the patients treated, the choice of the embolizing agent used, the choice and/or dose of the anticancer agents used, embolization end-points, and the schedule and/or interval of retreatment[150].

There are many different protocols used in different centers; Roche et al.[151] and Kress et al[152] have used doxorubicin as the chemotherapeutic agent with lipiodol, gel foam, and iodinated contrast, whereas Dominguez et al. used streptozocin in an emulsion with lipiodol and a gelatin sponge[153].

Drougas et al[154] preferred to give the patients 5 days of 5 FU (5 Fluorouracil) followed by TACE with a combination of drugs including Adriamycin, Cisplatin, Mitomycin C, and PVA particles.

In a phase II study conducted by Diamandidou et al, microencapsulated cisplatin was used, prepared by emulsifying PVA and cisplatin. It was then mixed with contrast to cause chemoembolization[155].

Ho et al. showed in their study, which 46 patients with carcinoid (n = 31) and islet cell (n = 15) tumors underwent hepatic artery chemoembolization using chemotherapy mixture of 50mg cisplatin, 20mg doxorubicin, and 10mg mitomycin-C mixed with 10 ml

of ethiodized oil followed by particle embolization with 300–500-_m polyvinyl alcohol particles or gelfoam powder, that the mean overall survival time for the entire group was 1273±185 days, with insignificant difference detected for both tumor subgroups, and the progression-free survival times for the carcinoid and islet cell tumor subgroups also were similar ($p = 0.72$).

They also concluded that the presence of extrahepatic metastasis or an unresected primary tumor should not limit the use of hepatic artery chemoembolization[156].

Chemo-embolization with drug eluting beads (DEB TACE)

DEB-TACE was done to four patients in our study .DEB-TACE represents a relatively new mechanism of enhancing the delivery of potent anticancer agents to the site of the tumor. The concept of drug-eluting beads is to load polyvinyl alcohol–based microspheres with various types of chemotherapeutic agents and deliver them intraarterially in a manner similar to that of conventional chemoembolization. The unique properties of these beads allow for fixed dosing and the ability to release the anticancer agents in a sustained and controlled manner. Significant reductions of peak plasma concentrations have been observed with drug-eluting beads when compared with conventional chemoembolization, suggesting that a greater amount of the anticancer agent is being sequestered by the tumor versus distributing in the systemic circulation[157]. This may result in a more pronounced tumor response, while diminishing the systemic bioavailability of the agent.

A comparison of plasma doxorubicin concentrations after therapy with drug-eluting microspheres as opposed to standard TACE therapy demonstrated that the peak drug concentration as well as the area under the curve is significantly lower after therapy with drug-eluting microspheres than after standard TACE therapy[158]. This finding implies a lesser potential for systemic toxic effects with the use of drug-eluting microspheres than with standard TACE therapy.

The first prospective study in the United States in which drug-eluting beads were used for the treatment of patients with unresectable HCC was published in 2009. Twenty patients underwent 34 treatment sessions. RECIST and EASL response rates at 1 month were 10% and 60%, respectively. The remainder had stable disease. The authors concluded that chemoembolization with drug-eluting beads is safe and effective in achieving local tumor control in patients with unresectable HCC[159].

Drug-eluting beads loaded with irinotecan are being investigated for the treatment of patients with colorectal hepatic metastases[160]. Most recently, Martin et al[161] published results from a multicenter study of metastatic colorectal cancer patients who received drug-eluting beads with irinotecan after failing systemic chemotherapy, their study included 55 patients with liver dominant metastatic colon cancer. After failure of other therapies, these patients underwent DEB chemoembolization with irinotecan DEBs. Median follow-up for this patient cohort was 18 months. There were no deaths at 30 days post-procedure. The 12-month response rates were 40%, with 15% (n=8) showing complete response and 25% (n = 14) showing partial response. They concluded that this treatment was safe and effective in this subset of cancer patients[161]. Although DEB-TACE was done to four patients only in our study, our 12 months response rate was 50% (one patient showed complete response, one patient showed partial response and two patients showed progressive course, approaching the fore mentioned study, there were no 30 days post – procedure deaths.

Y^{90} radio-embolization

Radio-embolization was done in only one patient in this study, with extensive CRLM; Unfortunately ,radio-embolization study was limited in our study, only done for one patient with extensive CRLM ,the patient died before assessment of the procedure response ,limitations of the technique included its high cost , as There are two absolute contraindications to microsphere-based 90Y treatment: exaggerated hepatopulmonary shunting, and reflux into the arteries that supply the gastro duodenal region, extra –effort is needed to make sure delivery of the microspheres to the target .

The role of radio-embolization in metastatic disease has been studied, Gray et al[162] published findings of randomized clinical trial of 74 patients that was conducted to assess whether a single injection of Y^{90} in combination with intrahepatic FUDR could increase the tumor response rate, time to disease progression in the liver, and survival when compared with FUDR alone. Patients with unresectable colon cancer treated with Y^{90} and hepatic artery chemotherapy exhibited longer time to progression[162].

Van Hazel et al[163] reported findings from a randomized study in 21 patients (11patients received Y^{90} plus 5-fluorouracil)/leucovorin), 10 patients received 5-fluorouracil/ leucovorin alone). The authors concluded that the administration of Y^{90} along with a standard chemotherapeutic regimen significantly increased treatment-related response, when compared with chemotherapy alone, such conclusion was agreed by many other authors[164-166].

In our study, trans-arterial approaches were applied on twenty seven patients, twenty two patients were subjected to conventional TACE, four patients were subjected to TACE with drug eluting beads, and one patient was subjected to radio-embolization, there are other trans-arterial approaches not done in this study, like trans-arterial embolization (TAE) and hepatic arterial chemo infusion.

Trans-arterial embolization (TAE)

Trans-arterial embolization was not applied in this study, we thought that adding chemotherapeutic agents (whether conventional TACE, or DEB TACE) will add beneficial effect in the management of the LM.

In case of hepatic trans arterial embolization (TAE), there have been different protocols used with the intent to create tumor ischemia by embolizing the hepatic arterial branches supplying the tumor.Permanent embolic agents such as cyanoacrylate (histoacryl) have been effectively used by Loewe et al. in conjunction with lipiodol to create complete embolization of the tumor feeding artery[167].

In other studies, embolization has been performed using gel foam particles, with or without lipiodol[168]. Moertel et al. performed hepatic artery embolization followed by systemic chemotherapy, which they found to be useful[169]. Permanent embolic particles like PVA (Polyvinyl alcohol) foam and microspheres have been used by Gupta et al[170].

Intra-arterial chemo infusion

The principle of chemo infusion has been studied most extensively in patients with colorectal cancer and unresectable liver metastases. Since 1987, findings of at least 10 prospective clinical trials[171] comparing systemic treatment versus chemo infusion therapy have been published. These trials have consistently shown higher response rates for chemoinfusion (42%–62%) versus intra-venous chemotherapy (9%–21%).

Multiple agents such 5-fluorouracil (5-FU), mitomycin,cisplatin, and doxorubicin have been infused, but 5-fluoro-2′-deoxyuridine (floxuridine, FUDR) has been the chemotherapeutic agent most frequently studied. FUDR has a 95% hepatic extraction when continuously infused in the hepatic artery, resulting in a 16-fold higher concentration in liver metastasis compared with venous administration[172].

The recent emergence of molecularly targeted monoclonal antibody therapies[173], with proven efficacy in metastatic colorectal cancer, provides a significant improvement in the outcomes for patients, but also presenting challenges for clinicians in selecting the most appropriate combination of therapy for their patients.

Local thermal ablation techniques

In this study, local thermal ablation techniques were used for twenty three patients, RFA was used in seventeen patients, and MWA was used in six patients, collectively: complete response was obtained in seventeen patients; partial response was obtained in five patients, and one patient died before assessment of the response.

RFA

In this study; Equipment used for RFA was Rita medical system^{R} (Mountain view, Calif), the device consists of electrical generator, needle electrode, ground pads. the device made by Rita medical system^{R} has a 15 Gauge needle with four to eight retractable curved prongs .The radiofrequency generator was operated at 460k HZ at a power setting of 50-200 W ,achieving a final temperature of about 60 degrees C.

The technique varies with different authors; Elvin et al. followed a protocol where they were able to achieve an average final temperature in the tumor of 65±8.2 degrees C which was delivered at 72±19W[174]. Gillams et al., on the other hand, have used the saline perfused electrodes predominantly with a single or cluster of three internally cooled electrodes[175].

In this study RFA was used in lesions smaller than three cm in maximal diameter, RFA has been used for lesions larger than 3 cm with multiple applicators in the same sitting[176]. Henn et al. have treated up to 12 lesions in a single sitting under mild diazepam with CT guidance; the maximum tumor size they ablated was 7.1cm[176]. Elvin et al. have successfully treated tumors up to 7 cm in size[174].

Liver abscess occurred in only one patient in this study, drained by pigtail catheter insertion, five patient developed post procedure right hypochondrial pain, Complications associated with radiofrequency ablation have been generally related to the electrode application, such as pneumothorax and neuritis at the site of skin entry. Liver abscess have also been reported, as well as infrequent subdiaphragmatic hematomas. Major complications are rare and have been reported in 5% or less cases; death is extremely rare. Skin burn at site of skin pads in the case of a unipolar electrode system has also been reported. Post-ablation transient elevation of liver enzymes AST and ALT has been documented by most authors, but seem to return back to normal within few days[174-176], that was also noted in our study .

MWA

In this study MWA was done in six patients , in this study MWA ablation was used for management of lesions close to major hepatic vesssels to avoid the heat sink effect faced when using RFA technique. Five patients showed complete response while one patient showed

partial reponse. Microwave has many theoretical advantages over current technologies: microwave energy has the potential to produce **faster** heating over **a larger volume of** tissue with **less susceptibility to heat sink** effects; can be effective in **tissues with high impedance such as lung** or **charred, desiccated tissue**; is capable of generating very high temperatures, often in excess of 100° C; is highly conducive; and does not require grounding pads or other ancillary components[177-178].

The liver is a vascular solid organ with an abundance of large vessels creating the potential for heat sink effects. Microwaves appear to be more able to overcome perfusion and large heat sinks than other heat based ablation modalities[179-182]. Microwave energy has been shown to ablate tissue up to and around large hepatic vessels measuring up to 10 mm and creates larger zones of ablation in high perfusion areas[179,183]. High perfusion rates in hepatic vessels greater than 3 mm limits the effectiveness of radiofrequency ablation, and has been shown to be an independent predictor of incomplete tumor destruction[184].

The decreased susceptibility to vascular cooling has been studied and confirmed in preclinical studies. In agreement with our study, Awad et al demonstrated large and consistent zones of ablation in shorter times than would normally be seen with radiofrequency ablation and proximity to hepatic vasculature and inflow did not significantly change ablation zone size or shape with microwave ablation[182].

In addition, preclinical data has suggested that microwaves, particularly with the use of multiple applicators, **may be effective in the treatment of larger tumors (> 3cm)**[177,185-187], overcoming our study size limit. Tumors over three cm have historically been problematic for radiofrequency ablation, with a significantly increased risk of local tumor progression[188]. However, the larger ablation zones possible with microwave ablation could potentially make these tumors more consistently treatable. For example, Brace et al demonstrated ablation zones with mean diameters up to 6.5 cm using three 17-gauge microwave antennas spaced 3 cm apart in an *in vivo* porcine model[177]. Strickland et al used variable times and power outputs ranging from 36 to 200 W in an *in vivo* porcine liver model and demonstrated ablation zones ranging from 3 to 6 cm in diameter produced very rapidly, i.e. within three minutes[186] , yet in our study we were stuck to the three cm size limit.

Early clinical studies have suggested microwaves are effective in the treatment of colorectal hepatic metastatic disease[189,190]. Shibata et al prospectively randomized 30 patients with multiple metastatic colorectal tumors to microwave ablation or surgical resection and identified no significant difference between the 1, 2 and 3 year survival rates, with less blood loss in the microwave group[190]. Ogata et al treated 102 unresectable colorectal metastatic lesions, with a high local control rate of 95% over median follow up of 33 months[191], our results are relatively close to Ogata et al study ,complete response was noted in 83.3% of our cases over follow up period of about 12 months.

Most authors **report shorter ablation times** in the liver with microwave ablation than with radiofrequency ablation, frequently less than 10 minutes, and many ranging from 2 to 5 minutes depending on number of applicators, lesion size and power output. From a practical standpoint, decreased time needed for microwave ablation translates to more efficient use of equipment and personnel and decreased time for patients under general anesthesia, which is routinely used for ablation at our institution. In addition, the speed of treatment gives microwaves an advantage for treating multiple lesions during one ablation session[192].

Currently available microwave systems continue to face technical limitations, and this has prevented the potential of microwave from being realized in the clinic . Major limitations include underpowered systems, shaft heating, large diameter probes, long and relatively thin ablation zones. Similarly, there is still some unpredictability to the size and shape of the zone of ablation which may be related to technical factors[189-192].

Complications and side effects

In this study, abdominal pain, nausea, vomiting, and fever (i.e., post-embolization syndrome) were common, almost in every patient subjected to trans arterial approaches, liver abscess occurred in only one patient in this study subjected to RFA, and drained by pigtail catheter insertion .Complications seen vary in literature, With Touzios et al, a high 30 day mortality of 5.6% and a morbidity of 28% have been reported[193], compared to our study there is 48% early post procedure morbidity rate ,mainly post embolization syndrome, while other authors have zero percent in early post-procedure mortality. Morbidity in literature includes liver abscess, noted in only one patient in our study other morbidities includes transient hepatorenal failure (which, if not corrected urgently, can be fatal), pleural effusion, sepsis, bowel ischemia requiring surgery, septicemia requiring antibiotic therapy and prolonging hospital stay, and hepatic infarction. Other less morbid adverse reaction includes post-embolization syndrome, which is seen in most of the patients, some reports putting the figure at 80–90%. It also includes a fever that subsides in a couple of days, leukocytosis, abdominal pain sometimes requiring morphine, and a transient increase in liver enzymes predominantly transaminases and LDH which generally comes down within a few days to 2–3 weeks. Increased bilirubin levels have also been noted. In addition, moderate elevation of alkaline phosphatase have also been noticed. The best possible way to reduce post embolization syndrome is to keep the patient well hydrated and in supportive care [193], post procedure medications were used in our study to overcome the expected post embolization syndrome symptoms.

Response parameters

In this study, we used mainly three types of response; Morphological response has been calculated by measuring the size of the lesions before and after 4–6 weeks of completion of therapy, with doing a comparison on long term follow up.

Evaluation by RECIST citeria was used in this study:

Complete Response (CR): Disappearance of all target lesions.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the base line sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study

EASL criteria (response represented by a lack of enhancement in the tumor, a finding indicative of necrosis) was also used, very useful indicator of tumor response.

In this study, objective response, meaning partial and complete response (over all response) was about 86% after one month post procedure, reaching 64 % at the end of follow up period.

According to Vogl TJ, et al: objective response, meaning partial and complete response in the case of TAE has been around 37–74%, going as high as 95% when stable disease is added to the figure. The time periods vary between 3 and 88 months. With respect to TACE, the objective response was between 35% and 74% of patients, going up to 98% when stable disease was also added. Time periods have been between 6 and 63 months[194].

Biological response

There are multiple biological tumor markers depending upon the site of the primary tumor and the tumor secretions. Carcino-embryonic antigen was the most important tumor marker for CRLM, for NET: Urinary 5 HIAA is an important metabolic product of serotonin synthesis. Other tumor markers include Chromgranin A, serum serotonin, serum, gastrin, insulin, dopamine, and neuro specific enolase.

Serum levels of tumor biomarkers also are assessed at follow-up evaluations, with a reduction in serum values representing a positive tumor response. Increase in serum biomarker values are more difficult to interpret after treatment; they may be due to tumor lysis or to extrahepatic disease progression.

Reduced survival rates were noted with increased tumor markers. In agreement with this study, many authors evaluated the effective clinical response to therapy by assessing the amount of reduction of the tumor markers[194].

Symptomatic response

In this study; the symptomatic response to therapy has been used as a parameter, this was mainly appreciable in NETLM. The significant improvement in carcinoid syndrome symptoms (flushing, bronchospasm, diarrhea) was significant following our procedure, other metastatic liver symptoms (right hypochondrial pain, right hypochondrial heaviness, dyspnea) were partially improved in our study. According to Vogl TJ, et al study[194]; TAE is generally associated with 64% of patients to have symptomatic improvement for a period varying between 1 and 18 months. TACE is associated with symptomatic response around 53% of patients for a period of 10–55 months, this was best applicable in this study in NETLM cases (20%). Surgery is associated with a symptomatic response of 90–95% of patients for a mean duration of 19.5 months[194].

Advances in assessing response to therapy and future promises

Follow-up imaging is typically performed 4–6 weeks after therapy, while maximum imaging response is often seen 3–4months after therapy. Evaluation of treatment efficacy for all therapies has been traditionally performed with radiologic measurement of tumor size as proposed by the RECIST guidelines[195,196]. RECIST guidelines rely on anatomic criteria for the evaluation of tumor response. However, the accuracy and completeness of these guidelines have been challenged several times. The expert panel of the Barcelona 2000 EASL conference emphasized that tumor necrosis following treatment with loco-regional liver directed therapies may not be paralleled by a reduction in tumor diameter and recommended that estimations of tumor response should account for necrosis, which can readily be estimated by the area of non enhancement at contrast enhanced CT or MR

imaging[197]. Furthermore, the panel stressed that tumor diameter measurements should reflect the area of viable tumor, rather than the overall diameter.

More recently, the WHO and RECIST guidelines have been also challenged by new forms of targeted therapies that do not result in tumor size changes that qualify as complete or partial response, but lead to intratumoral functional changes and cellular necrosis that can be measured at functional imaging (diffusion-weighted MR imaging, dynamic contrast- enhanced MR imaging, PET, and single photon emission computed tomography)[150]. Since transcatheter-based therapies and local thermal ablation techniques are targeted therapies that may lead to both anatomic and functional intratumoral changes, it is essential that future imaging evaluation of tumor response routinely incorporates both anatomic and functional information of the tumor burden. Finally, a recent study has been published combining both size and necrosis criteria for assessing response to loco-regional therapies, with pathology explants serving as the standard, and the authors concluded that the optimal method of response assessment must include the early findings of necrosis(EASL) and the time-dependent changes in size (RECIST guidelines)[198].

The size alone may not be a reliable criterion for assessing the response of a tumor to regional therapies, because necrosis, edema, and hemorrhage may cause an initial increase in the size of a tumor that is responding to therapy[199]. Instead, to accurately determine the tumor response, the tumor size should be assessed in conjunction with the presence and extent of tumor necrosis. Response to therapy may be assessed early after treatment by using the combined criteria of size and necrosis depicted at CT. Necrosis may be defined as a lack of enhancement (a change in attenuation by less than 10 HU) after the administration of contrast material at CT[199,200].

PET may help identify disease response at 1-month follow-up by depicting a decrease in the uptake of FDG by the tumor. Although PET is of limited use for the detection of small new lesions, the use of combined PET/CT may mitigate this limitation, Miller FH, et al demonstrated that a combination of size and necrosis criteria may be more accurate than size criteria alone for defining tumor response at imaging in patients with hepatic metastases from colorectal cancer[201]. FDG uptake by the tumor at PET may be a very useful indicator of tumor response. In fact, a combination of the criteria of tumor size and necrosis at CT with correlative FDG uptake at PET may be most accurate for determining the response of metastatic disease[201]. In addition, early studies with diffusion-weighted MR imaging demonstrated a post treatment increase in the apparent diffusion coefficient of tumors, a finding consistent with treatment-induced cell death both after therapeutic embolization with Y^{90}-bearing microspheres and after standard TACE therapy[202,203].

In this study, response assessment in solid tumors is established with imaging by using tumor size in accordance with response Evaluation criteria in solid Tumors (RECIST) guidelines[204,205]. Also tumor enhancement has been used as an indicator of treatment response as recommended by the European Association for the Study of Liver disease[206], and decrease in tumor enhancement has been shown to enable prediction of favorable response of HCC and LM to TACE[207-209].

Functional changes, on the other hand, occur prior to alterations in tumor size[210], and functional biomarkers—particularly diffusion-weighted (DW) and contrast material–enhanced magnetic resonance (MR) imaging has the potential to enable earlier indication of response to treatment. On the other hand, DW MR imaging can yield functional

information at a cellular level by measuring water diffusion values within a neoplasm and DW MR Imaging has been used to monitor treatment response and evaluate prognostic value after loco-regional therapy in patients with hepatocellular carcinoma, as well as in those with hepatic metastases of colorectal cancer, leiomyosarcoma, neuroendocrine cancer, ocular melanoma, and breast cancer[207,211,212].

Limitations of this study:

This study had several limitations:

- The study patient population size was limited; distributed over multiple techniques therefore; further studies with a larger sample size are needed to confirm our results and conclusions.
- Heterogeneous nature of the study populations, different primary sites, different sizes different patterns of the focal hepatic lesions enhancements
- The percentage of persons living at the end of 2, and 5 years after the onset of metastases and the first time interventional therapy (survival rates) was not applied in this study; this is important factor as considered by different authors. Surgery has the longest 5-year survival rate of 70–76%, TACE with rates between 48% and 83%, and TAE is associated with rates between 40 and 54%.
- Methods of response assessment were using RECIST guidelines and European Association for the Study of Liver Disease (EASL) criteria, had been used. These criteria are based on assessment of tumor size and necrosis, with the assumption that a viable tumor maintains its vascularity…., due to their high costs, functional imaging modalities were not used in this study, even health insurance systems are not covering these techniques, future studies using functional imaging techniques (PET CT, DWI, dynamic contrast enhanced MRI study, SPECT) for assessment of the response are required.
- RECIST criteria are based on single longest measurements and are not readily applicable to tumors with rim enhancement. These criteria are also difficult to apply in tumors with multifocal residual enhancement or in tumors in which residual enhancement is eccentrically located in a plane other than the conventional axial plane, assessment of volumetric response may be of adding value in future studies.

SUMMARY

SUMMARY

The aim of this thesis was to assess the role of loco-regional ablation techniques and trans-arterial techniques in the management of liver metastasis and identify the proper indications, contraindications, side effects and benefits of these techniques.

Many anatomical variants were encountered in the course of our study, the most common being the replaced right hepatic artery, arising from the superior mesenteric artery. CTA, Abdominal aortography and superior mesenteric angiography were found to be very useful in many cases.

Our TACE protocol included the use of a combination of chemotherapeutic agents (Mitomycin, Adriamycin, Cisplatin) mixed with iodized oil (ultra fluid lipiodol). Chemoperfusion was then followed by injection of gelfoam sponge particles to achieve complete embolization.

Drug-Eluting Beads (DEBIRI): The use of drug-eluting microspheres in a new variation of the TACE method is designed to improve the precision of drug delivery**.** Drug-eluting microspheres are made of polyvinyl alcohol hydrogel and are biocompatible, hydrophilic, and nonresorbable.

Yttrium-90 (^{90}Y) bearing microspheres act as point sources of radiation that, when delivered via the hepatic artery, are deposited predominantly within tumor tissue.

Equipment used for RFA was Rita medical system ^{R} (Mountain view, Calif), the device consists of electrical generator, needle electrode, ground pad. **The equipment for microwave ablation** consists of a microwave generator and needle electrodes (microtaze , Heiwa ,Osaka, Japan).

In our study, few complications were encountered, the most common being post embolization syndrome.

Due to the relative short time of our study and the heterogeneity of the study population, the survival rates could not be estimated.

Loco-regional interventional techniques proved to be very effective in causing tumor devascularization and shrinkage. In our thesis by the end of follow up period, 59.5 % of the patients showed stable disease, 8.5% showed complete response, 31.9 % had progressive diseases while three patients died before response assessment.

Loco-regional techniques were proved to be very useful in palliating the patients' symptoms and improving their life style. Many patients admitted that they carried a totally normal life after TACE in spite of their deteriorated pre-embolization conditions. Dramatic improvement in patients' conditions and an improved performance status was a very common finding in our study.

Triphasic CT scanning and tumor markers evaluation were the gold standards for pre and post procedure evaluation as well as planning for future sessions. Adequately performed Triphasic CT is crucial for proper management of the patients.

In this study, Response assessment in solid tumors is established with imaging by using tumor size in accordance with Response Evaluation Criteria in Solid Tumors (RECIST) guidelines. Also tumor enhancement has been used as an indicator of treatment response as recommended by the European Association for the Study of Liver Disease (EASL), and decrease in tumor enhancement has been shown to enable prediction of favorable response of LM to our procedure.

Functional changes, on the other hand, occur prior to alterations in tumor size, and functional biomarkers—particularly PET, diffusion-weighted (DW) and dynamic contrast enhanced magnetic resonance (MR) imaging has the potential to enable earlier indication of response to treatment. PET may help identify disease response at 1-month follow-up by depicting a decrease in the uptake of FDG by the tumor.