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Short Communication Open Access

Physiologic and Functional Imaging for Tumor Response Assessment Following Transarterial Chemoembolization of Hepatic Malignancy: Imaging Biomarkers Should Reflect the Therapeutic Mechanism of Action

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Short Communication

Transarterial Chemoembolization (TACE) is the infusion of Chemotherapy, in combination with an embolic particle, into the arterial vasculature supplying a hepatic tumor, under angiographic visualization and guidance. This is now a well-established treatment of choice for nonresectable or non-ablatable primary hepatic malignancy which is also used extensively for non-resectable hepatic metastases. Currently, TACE is recommended as first line treatment for patients with stage B (Barcelona Clinic Liver Cancer staging) HCC [1]. In 2002 Initial randomized prospective controlled studies by Llovet and Lo demonstrated statistically significant survival benefits [2,3], setting the stage for the development of the rapidly evolving catheter directed intra-arterial tumor therapies and the field of "Interventional Oncology". Innumerable papers have been written demonstrating efficacy and a number of Meta analyses including the most recent by Lencioni showed 1, 2, 3 and 5 year survival rates of 70%, 52%, 40%, and 32% respectively [4]. The first iteration of these therapies included the mixture of one or multiple chemotherapeutics; Doxorubicin, Cisplatin and Mitomycin in an emulsion with Lipiodol, iodinated oil plus an embolic such as gelfoam, polyvinyl alcohol or spherical embolic particles to occlude the tumor vasculature. Subsequent iterations of the treatment included the development of a number of doxorubicin eluting embolic beads with varying sizes ranging from 40 to 500 microns. Subsequent studies suggested that smaller embolic beads in the range of 100 to 300 microns are more efficacious than 300 to 500 microns beads [5].

The mechanism of action for TACE is not entirely understood. That is to say, it is not well known how much of the efficacy is related to the high intratumoral accumulation of the cytotoxic chemotherapeutic, the embolic effect, causing terminal vessel ischemia and necrosis, or a synergistic effect. In fact, treatment of liver tumors by 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" [6]. Maluccio demonstrated that "bland embolization" the use of the embolic bead without chemotherapeutic, was efficacious showing 1, 2 and 3 year survival rates of to 84%, 66%, and 51%, respectively in patients without extrahepatic disease or portal vein involvement. Interestingly, when performing efficacious bland embolization smaller particles were used such as 50 micron PVA or a 40-100 microns embolic particle to block terminal, arteriolar/capillary vessels [7]. A number of drug eluting beads have been developed with properties aimed at causing more complete and "deeper" vascular embolization. For example, the Hepasphere drug eluting bead is more deformable, better filing the intratumoral intra-vascular space (Merit Medical Systems, Inc. South Jordan, Utah) [8].

It is important to understand hepatic and tumor vascular anatomy and physiology to further elucidate the mechanisms of action of TACE, optimize the therapy, predict and better assess therapeutic response. Hepatocellular carcinoma and hepatic metastases receive their blood supply from segmental or subsegmental hepatic artery while normal liver receives its blood supply largely from the portal vein. It is generally true that tumors are "hypervascular". It is this hypervascularity that is responsible for hepatocellular carcinoma contrast enhancement and washout imaging characteristics on arterial, venous and delayed phases of enhancement on contrast enhanced CT and MRI used for the Liver Imaging Reporting and Data System (LI-RADS) "LIRADS 5" determination of malignancy [9]. It is also this overall tumor hypervasularity which creates a "sump effect" such that the tumor preferentially accumulates the chemoembolic rather than the adjacent liver during TACE. The delivery of the therapeutic, subsequent intratumoral distribution and ultimate efficacy is directly related to tumor perfusion, vascular permeability, and interstitial transit. The blood supply to HCC is one of the main factors affecting the efficacy of TACE treatment. Grossly, increased blood supply to the HCC is associated with greater accumulation of the chemoembolic with improved efficacy, whereas reduced initial perfusion to the tumor results in small therapeutic deposition in the treated lesions [10]. However, intratumoral vascular perfusion is known to be heterogeneous [11]. Within the tumor there are areas of relative high micro-vascular density, perfusion, and hypoperfused areas such as necrotic zones [12,13], accounting for the enhancement patterns seen on contrast enhanced imaging [14].

To be most efficacious, the intra-arterially delivered chemotherapeutic must homogeneously distribute throughout the tumor and the embolic must occlude the intratumoral microvasculature to a high enough degree so as to cause tumor ischemia and necrosis. Ideally the tumor supplying segmental arteries are not embolized and the liver adjacent to the tumor is spared of the chemotherapeutic and embolic ischemic injury. Imaging, used for guidance and early response assessment, should depict this relevant vascular physiology. During the procedure, the infused chemoembolic mixed with lipiodol and or contrast is seen angiographically. Angiographic imaging endpoints such as near stasis, or taking 8 cardiac cycles for the contrast to clear from the vascularity supplying the tumor, loss of tumor hypervascularization or "pruning" of the tumor supplying vascularity, crudely assess the extent of embolization. Under-embolization may lead to inadequately treated tumor [15] while over-embolization may increase liver toxicity and the risk of accelerating liver failure due to their increased baseline liver dysfunction [16]. A descriptive angiographic grading system "subjective angiographic chemoembolization endpoint (SACE)" has

been described in which reduction of antegrade arterial flow and tumor blush, reflecting intra-tumoral micro-vasculature, is graded [17,18]. SACE level III is correlated with improved survival over SACE level IV. SACE level IV may inadvertently promote tumor progression or else accelerate liver failure by inducing ischemia of normal liver tissues. Cone Beam CT, obtained with rotational angiography, prior to and immediately following TACE can demonstrate the tumor vascular supply and intratumoral distribution of the chemoembolic [19]. These approaches are subjective and provide predominantly anatomic information. However, the actual change in tumor perfusion is not determined.

Response assessment and imaging endpoints

The most important endpoint in cancer treatment is overall survival. Nonetheless, tumor response and time to progression are commonly used, imaging based, surrogate "imaging endpoints" or "biomarkers" for assessment of efficacy [20]. The sequence of tumor response involves devascularization, tissue ischemia and tumor necrosis with later resultant reduction in tumor diameter. The reduction in overall tumor size may take at least a month to be seen with usual CT or MRI, anatomic imaging, while devascularization and reduced perfusion, occurs immediately. The resulting tumor necrosis is not necessarily accompanied by tumor shrinkage even when response occurs. In fact, some tumors clearly respond to treatment but show no remarkable changes in size on anatomic morphometric based CT or MR imaging [21].

Current usual anatomic imaging endpoints including Response Criteria in Solid Tumors (RECIST), in which single long axis linear measurements are made across the tumor, are not adequate for assessment following locoregional therapy [22,23]. Since there is tumor necrosis, seen as non-enhancing tumor well before reduction in size, Modified RECIST or European Association for the study of Live (EASL) criteria are recommended for response assessment in which the change in percent remaining enhancing tumor is measured [24]. These response assessment criteria are usually applied at follow up imaging at 4 to 6 weeks post procedure and then every three months. However, meaningful and persistent changes in tumor perfusion occur at the time of the TACE procedure.

Vascular physiology can be studied using dynamic contrast enhanced (DCE) imaging, in which multiple images are obtained as contrast is infused over time to generate a time density curve. Measures of tumor perfusion have been correlated with angiogenesis and tumor micro vessel density [25,26]. High perfusion values indirectly suggest a high rate of angiogenesis and micro vessel density within the tumor. Seven parameters are commonly obtained from the time density curve. Area under curve (AUC), width, washes in and means transit time being indicative of intratumoral perfusion. From this the parenchymal blood volume can also be calculated. Furthermore, arrival time and time to peak are indicative of vascularity supplying the tumor and vascular density. There have been a number of studies demonstrating the use of dynamic contrast enhanced CT and MRI following TACE, aimed at evaluating changes in tumor perfusion. Recently contrast enhanced ultrasound, cone beam CT, and perfusion angiography have been used to assess vascular indices such as perfusion or "parenchymal blood volume" during the TACE procedure.

Computed tomography

Computed Tomography Perfusion Imaging (CTPI) or DCE CT measurements include hepatic arterial perfusion (HAP), hepatic portal perfusion (HPP), total liver perfusion (TLP), hepatic arterial perfusion index (HAPI), hepatic portal perfusion index (HPPI), blood volume (BV) and mean transit time (MTT) [27]. Changes in the CT perfusion parameters of viable tumors correlated with responses of HCC to TACE. Furthermore, increased tumor perfusion, seen on pre-TACE CTPI was associated with the increased deposition of lipiodol Chemoembolic mixture, and vice versa [28].

C-arm CT

C-arm CT is a feature of current flat panel angio suites. In this method, the flat panel of the C-arm used for usual angiography is acting like a rotational CT detector around the patient and the obtained data are reconstructed to provide a CT view. There has been much use of this approach to best evaluate the tumor and its blood supply during TACE and improve guidance during catheter positioning [29]. A number of investigators have recently developed C-arm CT based "blood volume" (BV) measurements and generate intra-procedural BV maps which have been shown to correlate with conventional CT perfusion imaging [30]. It was suggested that remaining perfused areas on BV maps corresponded to worse procedural efficacy. Vogel using a similar approach, demonstrated that tumor "parenchymal blood volume" (PBV) decreases with TACE and tumors with low initial PBV have low local response rates whereas those with high initial tumor BV showed better response to TACE [10].

Magnetic resonance imaging (MRI)

Functional imaging also includes diffusion MR imaging which measures free, non-intracellular water, as an increase in Apparent Diffusion Coefficient (ADC), indicating the degree of tumor viability and necrosis (free water) at the cellular level. Diffusion and DCE MR imaging parameters are significantly altered after TACE [31]. Specifically, free water (ADC) increases and enhancement decreases. Interestingly, patients who demonstrated ≥ 65% decrease in enhancement had significantly improved overall survival compared to non-responders ($p<0.005$) [32]. While not readily available, a hybrid procedural angiography and MRI suite allowed the development of an innovative approach "transcatheter intraarterial perfusion (TRIP) MR imaging" in which gadolinium MRI contrast is injected through the angiographic catheter being used for the TACE procedure immediately prior to and following TACE. Lewandowski compared TACE angiographic endpoints to TRIP imaging. Interestingly, subjective angiographic chemoembolization endpoint (SACE) did not correlate with quantitative perfusion reduction, as determined with TRIP MR imaging [18,33].

Contrast enhanced ultrasound

Contrast Enhanced Ultrasound (CEUS) has been used for years to improve tumor visualization. SonoVue™ (Bracco, Milan, Italy) is the most widely used contrast agent in Europe and consists of microbubbles containing an inert gas (sulfur hexafluoride) encapsulated by a phospholipid shell, marketed as Lumason™ (Bracco, Milan, Italy) in the United States. These contrast agents are strictly intravascular, due to their size being slightly smaller than erythrocytes, unlike CT and MRI contrast agents which diffuse out of the intravascular space to the interstitium. Thus, perfusion but not

permeability can be assessed with CEUS. CEUS has been shown to have better temporal resolution than with contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) [34].

Early studies evaluating the use of intravenous contrast enhanced ultrasound for response assessment following TACE demonstrated the capacity to be similar to MRI and CT using criteria similar to mRECIST. However, it was suggested CEUS imaging determined response at 2 or more days after transarterial chemoembolization and may be predictive of tumor outcome that required 3 months to be reliably detected with computed tomography and magnetic resonance imaging [35]. Subsequently, quantitative DCE CEUS was developed with applications for the evaluation of TACE response investigated. Frampas demonstrated that a decrease in the AUC of more than 40% at one month, predicted non-progression and may be a potential early surrogate marker of tumor response one month after TACE [36]. Kaufman also found CEUS and volume perfusion computed tomography, performed one day after TACE and could be used to predict response demonstrated on MRI performed 2 and 4 months following TACE, using mRECIST response criteria. Hepatic perfusion index (HPI), arterial liver perfusion (ALP), blood flow (BF), and blood volume (BV) were measured with Volume Perfusion CT (VPCT). Peak intensity (PI), time-to-peak (TTP), and regional blood flow (RBF) were measured with CEUS. For responders, reduction in HPI, ALP, BV, and BF at day 1 post TACE proved significant ($P<0.001$). For non-responders, the change in all VPCT parameters proved non-significant. A cutoff of 40% reduction in HPI and a reduction in ALP of >29.6%, in BV of >41.4%, or in BF of >53.1% was indicative of response demonstrated on CT two months later. For responders only, changes in PI ($P<0.001$), TTP ($P<0.01$), and BF ($P<0.01$) proved significant whereas for non-responders, all CEUS parameters proved non-significant [37].

Intra-arterial (IA) CEUS was then introduced in which the microbubble contrast agent is injected directly into the artery during catheter-based arteriography, allowing more selective evaluation of arterial supply to the tumor [38]. Lekht also demonstrated the utility of intra-procedural intra-arterial CEUS to help visualize the tumor and its arterial supply without additional iodinated contrast or angiography related x ray exposure [39]. Uller also showed time intensity curves (TIC), generated with Intra-arterial and intravenous CEUS during DEB TACE could be used to measure a reduction of vascularization which correlated with subsequent tumor response [40].

Perfusion angiography

Recently, the capacity to perform intra-procedural 2D perfusion angiography has been introduced providing real time high temporal and spatial resolution tumor imaging [41-43]. In this manner the reduction of antegrade blood flow and tumor blush could be quantified. The application of color-coded DSA (ccDSA) enables the interventionists to extract physiologic information directly from conventional 2D-DSA series within seconds. The contrast-bolus geometry (maximum opacification) of each pixel from injection is color-coded and displayed in a single composite image. In similar manner as DCE MRI and CT, time intensity curves can be generated from a region of interest (ROI) and quantitative physiologic metrics such as AUC, can be assessed in real time during the TACE procedure. Thus, intra-arterial angiography is being facilitated as functional imaging to assess the treatment outcome during the TACE procedure. Recently, Wang J demonstrated a perfusion reduction either as AUCnorm or CI-Peaknorm ranging from 30% to 40% was associated with SACE level III and a reduction ranging from 60% to 70% was equivalent to SACE level IV. SACE level III was associated with a better subsequent clinical response than a higher perfusion reduction (SACE level IV) [42]. It is possible that these early objective measures of perfusion can be used as immediate response assessment, predicting subsequent clinical response [43].

In conclusion, morphometric anatomic measurements have limitations for the assessment of tumor response following TACE. Functional and physiologic perfusion imaging allows assessment of the mechanism of action of TACE, and could replace currently utilized anatomic morphometric imaging to provide earliest response assessment. Furthermore, some of these approaches can be used for intra-procedural guidance, demonstrating the need for additional embolization at the time of the TACE procedure.

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