





Review

“Primum Non Nocere” in Interventional Oncology for Liver Cancer: How to Reduce the Risk for Complications?

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Abstract: Interventional oncology represents a relatively new clinical discipline based upon minimally invasive therapies applicable to almost every human organ and disease. Over the last several decades, rapidly evolving research developments have introduced a newer generation of treatment devices, reagents, and image-guidance systems to expand the armamentarium of interventional oncology across a wide spectrum of disease sites, offering potential cure, control, or palliative care for many types of cancer patients. Due to the widespread use of locoregional procedures, a comprehensive review of the methodologic and technical considerations to optimize patient selection with the aim of performing a safe procedure is mandatory. This article summarizes the expert discussion and report from the Mediterranean Interventional Oncology Live Congress (MIOLive 2020) held in Rome, Italy, integrating evidence-reported literature and experience-based perceptions as a means for providing guidance on prudent ways to reduce complications. The aim of the paper is to provide an updated guiding tool not only to residents and fellows but also to colleagues approaching locoregional treatments.

Keywords: cancer; locoregional treatment; ablation; chemoembolization; radioembolization; safety; complications

1. Introduction

The Latin aphorism “primum non nocere”, meaning “first, do no harm”, most often attributed to Hippocrates of Kos himself, is one of the principal precepts guiding all medical interventions. However, as wisely underlined by Sokol, even if a literal reading of the expression would lead clinicians to do nothing at all, a more applicable formulation should be “primum non plus nocere quam succurrere”, that is “first do no net harm”. For achieving this aim, clinicians must balance their primary obligation to benefit the patient against their obligation not to cause harm [1]. It is from this perspective that this concept must be strictly applied in interventional oncology, a relatively new clinical discipline based on minimally invasive therapies treating almost every human organ and solid cancer type. Over the last several decades, rapidly evolving research developments have introduced a newer generation of treatment devices, reagents, and image-guidance systems to expand the armamentarium of interventional oncology across a wide spectrum of disease sites (e.g., liver, lung, renal, and bone) offering potential cure, control, or palliative care for many types of cancer patients [2–5].

The adaptation of interventional radiology procedures to target and treat cancer exemplifies a new generation of promising treatment options beyond traditional surgery, chemo- and radiation therapy. However, a main current issue relates to the lack of clear indications as to the optimal therapy in some clinical situations. This mandates a comprehensive review of the methodologic and technical considerations to optimize patient selection with the aim of performing a safe procedure.

This article summarizes the expert discussion and report from the Mediterranean Interventional Oncology Live Congress (MIOLive 2020) that was held in Rome, Italy, integrating evidence-reported literature and experience-based perceptions, providing guidance as to prudent ways to achieve reducing complications, particularly for the most commonly treated organ, the liver. All attempts have been made to make the information easy to access by using a point-by-point format. Our goal is to assist not only residents and fellows who are training in interventional radiology, but also practicing colleagues who are gaining greater familiarity with percutaneous or intra-arterial treatments.

2. How to Reduce the Risk for Complications in Interventional Oncology

Reduced complication rates can be achieved by both applying general concepts common to all interventional procedures as well as considering several treatment-specific issues. These aspects can be grouped in four categories related to: (1) a multidisciplinary approach; (2) patient selection, (3) treatment planning, and (4) knowledge of predisposing factors for complications, as well as clinical factors affecting treatment efficacy.

2.1. Patient-Based Multidisciplinary Approach

The first potential opportunity to pursue the principle of minimizing complications is by maximally sharing information and decisions following a patient-based multidisciplinary approach. Multi-Disciplinary Teams (MDT) are an alliance of all medical and healthcare professionals related to a specific disease, whose approach to cancer care is guided by their willingness to agree on evidence-based clinical decisions and to coordinate the delivery of care at all stages of the process, enriched by in turn encouraging patients to take an active role in their care [6]. By means of a shared patient-centered perspective based on evidence, MDTs are intended to improve therapeutic management and treatment protocols aiming to obtain improvement in patient clinical outcomes [7]. Multidisciplinary evaluation takes into consideration the clinical specificities beyond tumor burden, such as comorbidities, compliance to treatment, general performance status, and history of the disease in order to select the best approach for the individual patient following the principles of the prescription of a treatment plan tailored

as precision medicine. It has been clearly demonstrated that patients have better results in terms of treatment efficacy and overall survival or disease-free survival if single cases are preliminarily discussed by MDT when compared to direct referral [8–10]. It is imperative to underscore that interdisciplinarity in oncology implies a synergistic application of medical therapy concepts with a focus on prolongation of survival and prevention of tumor progression. Then, locoregional therapies should be applied in order to achieve local tumor control, relief of tumor-related symptoms, and maintenance of quality of life (QoL). Furthermore, an MDT-managed treatment strategy needs to be maintained for the entire duration of a patient's management, to allow the refinement of treatment strategies according to the response to a selected treatment and to the evaluation of the eventual need for integration of ablative and intra-arterial treatments [11–13].

2.2. *Select the Right Therapeutic Option for the Right Patient at the Right Time*

The second point is based on an accurate selection of the proper therapeutic option from the wide array of available modalities, based upon a thorough knowledge of all exclusion criteria and procedural risks.

2.2.1. Ablation

Regarding liver tumors, ablation has a key role in the treatment of hepatocellular carcinoma (HCC) at its very early stages even as a first-line therapy replacing surgery in the case of a single tumor smaller than 2 cm; it is also an alternative to surgical resection or liver transplantation in early-stage patients with 2–3 nodules up to 3 cm, in whom the decision to perform surgery is questionable due to tumor-related factors, such as size and location, and patient-related factors, such as hepatic functional reserve, severity of portal hypertension, and extrahepatic co-morbidities [14]. For colorectal liver metastasis, the European Society for Medical Oncology (ESMO) guidelines include ablation in the toolbox of instruments for local treatment of oligometastatic disease [15]. In oligometastatic patients with unresectable liver disease, ablation may be performed in association with chemotherapy and, eventually, surgery. In patients affected by intrahepatic cholangiocarcinoma as well as neuroendocrine liver metastasis, locoregional treatments are potentially therapeutic options to cure and/or improve outcomes in unresectable patients with limited disease [16,17]. Therefore, ablation by definition can be considered a less invasive therapeutic approach, since it can be applied when other options, most of all surgery, are at high risk, as well as in unfit patients.

To increase the efficacy of ablation, new devices and techniques have been developed, such as expandable multi-tined devices, internally cooled electrodes, multipolar ablation using bipolar electrodes, microwave ablation (MWA), cryoablation, and reversible and irreversible electroporation [2]. Most of these new options try to overcome radiofrequency ablation (RFA) limitations, mainly represented by potential thermal issue of vital adjacent structures, heat sink effect if lesions are adjacent to major vessels, and tissue dependence. In detail, MWA implicates reaching fast a high temperature, thus reducing the heat sink effect, even in the absence of a reliable end point to set the amount of energy deposition. Cryoablation allows an easy monitoring of ice ball progression, decreasing the risk of thermal injuries to vital structures, even if it is supported by limited scientific evidence. Electroporation poses a limited risk of thermal injury to neighboring critical structures and is also insensitive to the heat sink effect but it is limited by the need of general anesthesia and preliminary clinical data [18].

Furthermore, in the last years, a multimodality approach has also emerged, combining percutaneous ablation with intra-arterial procedures, extending the clinical indication and application of the percutaneous approach. In detail, based on a literature review, a combined treatment seems to be a safe and effective option in the treatment of patients with early/intermediate HCC when surgical resection is not feasible. Furthermore, this approach provides better results than RFA and transarterial chemoembolization (TACE) alone for the treatment of large HCC, defined as those exceeding 3 cm in size. It can also expand the indication for RFA to previously contraindicated “complex cases”, with increased risk of thermal ablation-related complications due to tumor location, or to “complex patients” at a high bleeding risk [19].

These treatment modalities for HCC were also applied for metastatic hepatic tumors, expanding the potential curative role of the percutaneous approach.

Moreover, RFA could also be performed alone or in combination with liver resection using a laparoscopic approach or during open surgery [18,20]. Recently, it has been observed that the combination of RFA and immunotherapy could allow achieving better outcomes in comparison to the RFA alone, in terms of improving survival rates and avoiding recurrence, for lesions larger than 3 cm in size. The association between RFA and immunomodulators induces a synergistic anticancer immune response as observed in pre-clinical studies, which seems quite promising for the future of oncological treatment [21].

2.2.2. Chemoembolization

Unlike ablation that induces the precise destruction of liver tumors with limited damage to surrounding hepatic parenchyma, TACE does not allow for a precise destruction of liver tumors. Rather, TACE, even when employing super-selective techniques, allows for a degree of “shotgun” imprecision, targeting a broader area of the liver, which contains both the tumor and healthy tissue [3,22–24]. Thus, when considering patients eligible for TACE, a fine equilibrium between liver function and tumor volume requiring treatment must be weighed in order to treat efficiently, minimizing the potential harm to the patient. This is especially true when considering patients with chronic hepatic disease (CHD), which is frequently associated with HCC. Balancing the liver functional reserve and the non-tumoral liver volume that needs treatment is essential for patient selection and for achieving the best result in terms of local tumor control and patient’s survival benefit, avoiding unnecessary or obvious harm [3,25].

The guidelines of the European Association for the Study of the Liver–European Organisation for Research and Treatment of Cancer recommend TACE as a first-line treatment for asymptomatic patients with preserved liver function who have multinodular lesions but show no evidence of vascular invasion or extrahepatic spread (intermediate stage, or stage B in the Barcelona Clinic Liver Cancer (BCLC) staging system) [26,27]. TACE is also an appropriate palliative treatment for patients who require curative treatment but are not suitable for surgery or percutaneous ablation [28].

Chemoembolization can be performed using the conventional technique (cTACE, a two-stage treatment with a drug mixed to lipiodol followed by embolic material) or using calibrated microspheres loaded with a drug (drug-eluted microspheres (DEM)-TACE). Indications and contraindications for DEM-TACE are similar to those for c-TACE, even if DEM-TACE is considered a better option than c-TACE for patients with more advanced disease or cardiac failure and for those expected to experience severe post-embolic toxicity [29].

In the last years, new degradable beads have emerged with the possibility to overcome TACE contraindications. In detail, TACE based on degradable starch microspheres (Embocept) allows the temporary occlusion of the smaller arterial vessels, so improving the overall therapeutic effectiveness by reducing the immediate wash-out of the cytostatic agent and decreasing the risk of systemic toxicity and post-embolic syndrome. These advantages allow the safe use of this procedure also in locally advanced cases, as a second-line option in patients dismissed or ineligible for systemic options [30]. Due to a 3D cross-linking reaction, degradable beads can be mixed with a range of drugs, with indication also for secondary liver tumors and in palliative setting, also combined with systemic options, increasing drug concentration in the liver and reducing systemic toxicity and procedural adverse events [31].

2.2.3. Radioembolization

Transarterial radioembolization (TARE) is a catheter-directed procedure that has been used mainly for palliation and more recently for curative purposes, with increasing frequency in the case of unresectable locally advanced primary tumors or liver-only/dominant metastatic disease. TARE is based upon the intra-arterial delivery of beta emitter Yttrium-90 (Yt-90)-embedded microspheres to achieve local therapeutic doses in the target area, with a minimal systemic effect of radiation. There are two commercially available Yt-90 preparations—glass and resin. Although both have shown

to be safe and effective, they differ in terms of size, specific gravity, and activity per microsphere [4]. Holmium-166 (Ho-166) is a more recently described alternative to Yt-90 as a beta emitter. Ho-166 also emits gamma radiation, and Holmium itself is paramagnetic; these properties allow dosimetry through quantitative analysis of scintigraphic and Magnetic Resonance (MR) images [32].

TARE has shown promising results, with a safe profile; however, it is still not recommended as the standard of therapy for HCC. Nevertheless, given that TACE has its own limitations in the treatment of the subgroups of patients with large-size HCC (>5 cm) and/or portal vein neoplastic thrombosis (PVT), TARE is a reliable alternative therapy for these patients [33,34]. Indeed, the most common indication for TARE in patients with HCC is PVT. In patients with HCC, TARE can be also used as a bridge to transplantation to maintain or even reduce the size of the tumor burden while maintaining patients on the waiting list [35]. Additionally, TARE has been used to induce hypertrophy of untreated hemi-liver as an alternative to portal vein embolization prior to surgery [36,37].

Prospective randomized clinical trials (RCT) have been conducted to assess the efficacy and safety of TARE in those patients. The SARAH and SIRveNIB multi-center RCTs compared the efficacy and safety of sorafenib (a multi-kinase inhibitor which is the standard systemic therapy for advanced HCC) to those of TARE using Yt-90 resin microspheres in patients with unresectable HCC and failed to demonstrate the superiority of TARE over sorafenib as regards overall survival (OS) [38,39]. However, these studies reported significantly better tolerability and local tumor control in patients treated with TARE in comparison to those administered sorafenib. Additionally, the SARAH trial reported better QoL scores for TARE-treated patients compared to those treated with sorafenib, an important aspect of oncologic decision-making [40]. The Soramic Trial Palliative Cohort, a multi-center, multi-nation RCT that compared the efficacy and safety of a combination of sorafenib and TARE using Yt-90 resin microspheres to those of sorafenib alone in patients with unresectable HCC, reported that the combination of sorafenib and TARE did not demonstrate a significant improvement in OS [41]. Although the safety and toxicity profiles were similar between groups, subgroup analyses suggested a possible clinical benefit of TARE plus sorafenib for non-cirrhotic patients, patients with non-alcoholic etiology of liver disease, and younger patients.

Looking at metastatic liver disease, SIRFLOX was a multi-center RCT aimed to assess the efficacy and safety of adding TARE with Y-90 resin microspheres to chemotherapy based on fluorouracil, leucovorin, and oxaliplatin (FOLFOX) for the treatment of patients with liver-only/dominant metastatic colorectal cancer (mCRC) as a first-line treatment [41]. Although the study showed no benefit of adding TARE to FOLFOX for progression free survival (PFS) at any site, the combination of TARE and FOLFOX improved median PFS in the liver by 7.9 months, with a 31% risk reduction for disease progression. Moreover, the REsect study demonstrated that adding TARE to chemotherapy significantly increased the number of patients with colorectal metastases who became amenable to resection at follow-up [42,43]. TARE has also shown to be effective and safe, with promising results in patients with unresectable, chemorefractory intrahepatic cholangiocarcinoma and metastatic neuroendocrine and breast cancer metastasis [44–47].

2.3. Perform Proper Treatment Planning and Define Correct Procedural Technique

2.3.1. Ablation

When performing an ablative treatment, selection of proper imaging guidance is mandatory. The target to treat should be visualized under the guidance of ultrasound (US) and/or computed tomography (CT) based upon location and conspicuity, and treatment can also be performed with videolaparoscopic (VSL) and/or robotic approaches. In addition, guidance and monitoring can be improved by means of stereotactic guidance systems, which represent a useful aid to improve accuracy especially in difficult locations and/or when complex multiple treatments are needed, combining the possibility of complete ablation of the tumor with the preservation of delicate surrounding structures and minimizing destruction of healthy tissue [2].

When considering potential complications, technical aspects, usually related to the target tumor location, must also be evaluated. As an example, direct applicator insertion into superficial nodules with a subcapsular location or invasive tumoral pattern can cause needle track seeding in up to 2.5% of patients (range 0–12.5%) if ablation followed diagnostic biopsy [48]. Thus, direct puncture should be avoided, and transhepatic paths or a “no touch of the tumor” technique should be used to avoid tumoral seeding [2]. Peribiliary nodules are another difficult challenge, especially when adjacent to the main biliary ducts. To protect the biliary system, a modulated ablation technique and/or duct cooling can be performed. Cooling can be accomplished intraoperatively, percutaneously, or by an endoscopic nasobiliary drainage tube [49]. Nodules in close proximity to gut and gallbladder can be approached with hydrodissection or gas dissection in order to separate the gallbladder from the heated zone and to reduce complications. Solutions of non-conductive 5% dextrose in water (5% DW) for RFA and of 0.9% NaCl for MWA should be used and can be mixed with an iodinated contrast medium to improve visualization [50]. Self-limited morbidity is noted in most patients after ablation of nodules adjacent to the gallbladder, most often attributed to a mild iatrogenic cholecystitis [51]. To reduce this complication, the ablation zone can be reconfigured by offsetting the applicator from the center of the tumor [52]. A combined angio/percutaneous approach is advisable in case of centrally located intermediate-size tumors due to the high probability of transverse arterial vessels reaching the tumor [53]. In the last years, to improve the placement of the ablation needle in the tumor and an adequate treatment planning, a stereotactic image guidance has been proposed, allowing a better coverage of a tumor with necrosis, with an accurate safety margin of at least 5 to 10 mm, reducing the risk of residual disease or local tumor progression and influencing survival prognosis [54]. Stereotactic ablation could also allow the treatment of complex lesions in difficult-to-reach location with low complication rate, also facilitating complicated access routes [55].

2.3.2. Intra-Arterial Treatments

For intra-arterial treatments such as TACE and TARE, the use of C-arm cone-beam computed tomography (CBCT) is becoming mandatory to overcome the substantial limitations of two-dimensional angiography alone [56]. Specifically, CBCT can help interventional radiologists to visualize small tumors and tumor-feeding arteries, identify occult lesions and the 3D configuration of tortuous hepatic arteries. Furthermore, it can suggest the presence of extrahepatic collateral arteries supplying the tumors, minimize nontarget embolization, and confirm and reassure the operator of the completeness of the administered treatment [57–60].

New generations of microcatheters have also been developed, with the goal of allowing not only a better treatment delivery (i.e., smaller catheter size, preformed tip shape, steerable tip) but also pressure dynamic alterations which are useful to maximize treatment delivery to the tumor (in the case of low-vascular-capacitance tumors) and exposure to the targeted volume, reducing complications and non-target embolization (antireflux microcatheters) [61–63]. These devices can be based upon different mechanisms. An example is the microballoon microcatheter, which allows a flow redistribution and a reduction of non-target embolization, creating a fluid barrier with a unique filter tip or utilizing an expanded tip that collapses under pressure of forward-flowing blood, while also expanding to act as a valve to prevent backflow during the infusion of therapeutic agents.

Intra-Arterial: Chemoembolization

Although interventional radiologists are becoming ever more comfortable with superselective catheterization with microcatheters, and complications from non-target embolization are becoming less problematic, the latter still need to be considered. Avoiding selective contrast administration using high-pressure-pump injections after embolization or eliminating additional “control” angiography near the tumor target can help minimize non-target embolization due to reflux of the embolic material previously delivered. Careful hand injections or control angiography with power injections from a different catheter at a more proximal location are other options. When performing angiography

before TACE, arterio-portal or arterio-hepatic venous fistulas can be seen and, when recognized, should prompt cessation of the procedure, as they can lead to biliary and liver necrosis (arterio-portal fistulas) or systemic distribution of the embolic material (arterio-hepatic vein fistulas) [25]. Another aspect to be considered when performing liver TACE is the dosage of the drug used, as high amounts of the injected drug can increase the risk of bile duct toxicity (ischemic biliopathy), leading to biloma formation, liver infarction, and abscess [3,25,64–66]. Likewise, it is prudent to adjust the dose of the drug to each of the currently available drug-eluting microspheres, as they can have different drug elution and release properties with respect to the liver [67].

It is also mandatory to evaluate the tumor volume and location. In order to avoid liver insufficiency from overtreatment, many physicians use the absolute upper treatment cutoff of >50% of tumor burden with respect to liver volume, while less conservative practitioners use a cutoff of >75% of liver replacement by a tumor. Moreover, large tumors present a higher risk of portal invasion or thrombosis and, thus, of liver infarction. They also frequently may reach the liver capsule, causing an increased risk of rupture and bleeding into the peritoneum. Furthermore, large tumors frequently also need to be treated with higher volumes of embolics and higher dosages of chemotherapy, and this inevitably rises the risk of hepatic failure and severe post-embolization syndrome (PES) [68,69]. Additionally, when considering location, tumors adjacent to the gallbladder may be vascularized by arterial branches of the cystic artery, or reflux of embolic material may reach the gallbladder, leading to cholecystitis. Exophytic and subcapsular tumors may recruit extra-hepatic, systemic arterial feeders, with a higher potential for extra-hepatic non-target embolization. In these situations, bland embolization may be considered instead of TACE [3].

Intra-Arterial: Radioembolization

Careful pretreatment planning and dosimetry play a key role in the avoidance of TARE-related complications. All patients should undergo pretreatment clinical, laboratory, and diagnostic imaging evaluation. Pretreatment screening angiography needs to be performed to assess the hepatic-mesenteric vasculature and to administer Technetium-99m macroaggregated albumin (Tc-99m MAA), which is considered to be a trial surrogate to the Yt-90, into the hepatic artery branch intended for TARE. After Tc-99m MAA administration, lung shunt and gastrointestinal leakage can be evaluated by whole-body scintigraphy. Lung shunting of 20%, estimated lung dose > 30 Gy for single session and >50 Gy for multiple sessions and uncontrollable gastrointestinal leakage are contraindication for TARE, although most potential “off-target” gastrointestinal deposition is manageable via embolization of the culprit artery (gastroduodenal, right gastric, cystic artery, etc.) or positioning of the catheter beyond the origin of these arteries [4]. Very high activities of Tc-99m MAA could lead to overtreatment in certain areas, also endangering the surrounding normal liver parenchyma. To reduce the radioactivity dose to healthy liver, a partition method using lung, healthy liver, and the tumor as separate dosimetric compartments offers a more personalized dosimetry than an empiric method based only upon the percentage of tumor involvement [70].

2.4. Know Treatment-Related Potential Complications and Clinical Factors Affecting Treatment Efficacy

2.4.1. Ablation

Potential complications requiring medical management must be considered. They include mostly bleeding complications since, unlike surgeons, interventional radiologists usually do not have direct control of hemostasis. In recent consensus guidelines, despite its thermal coagulative properties, ablation is considered a procedure with a high risk of causing bleeding, and thus evaluation of prothrombin time (PT), International Normalised Ratio (INR), and platelet count before starting the procedure is routinely recommended. The thresholds for correction are: for INR, corrected if outside the range of 1.5–1.8; for platelet count, corrected if $<50 \times 10^9/L$ [71]. In patients with liver cirrhosis, abnormal screening coagulation test results do not correlate with bleeding risk because of

the physiology of rebalanced hemostasis, resulting in a decreased tendency to bleed than expected. In addition, splenomegaly also plays a central role in thrombocytopenia, and hyperfibrinolysis is emerging as a cause of bleeding. Therefore, transfusion strategies for the management of patients with chronic liver disease have been recently revised, though they are currently based on expert opinion rather than on formal empiric studies. The suggested laboratory thresholds for procedures with a high risk of bleeding in patients with chronic liver disease are: INR correction to <2.5 ; platelet transfusion if platelet count is $<30 \times 10^9/L$; fibrinogen > 100 mg/dL (with one dose of cryoprecipitate if <100 mg/dL) [71].

Another dreaded potential complication is infection. Ablation is classified as a “clean-contaminated” procedure, that is, a procedure performed without active inflammation that does not compromise sterility, with limited risks, mainly due to cutaneous bacteria [72]. In these low-risk patients, the large amount of necrotic material created during ablation poses a risk for bacterial seeding during percutaneous access, and the use of a single antibiotic agent targeted to the skin flora (i.e., cefazolin) is deemed most reasonable [71]. On the other hand, patients with a history of biliary colonization as a result of an incompetent sphincter of Oddi or biliary–enteric anastomosis undergoing liver tumor ablation are at substantially higher risk for the development of an abscess. In these patients, ablation should be considered a contaminated procedure, and specific prophylaxis is recommended (i.e., oral levofloxacin 500 mg/d and oral metronidazole 500 mg twice daily, beginning 2 days before and continuing for 14 days after ablation; bowel preparation with neomycin 1 g and erythromycin base 1 g orally t.i.d. on the day before ablation) [72].

2.4.2. Intra-Arterial Treatments

The potential adverse events after intra-arterial treatments are most often strictly related to liver function. Specifically, most guidelines use the Child–Pugh score of $>B7$ and bilirubin (BrB) values > 2 mg/dL as relative contraindications for chemo/radioembolization, with some arguing that BrB values between 2 and 3 mg/dL are safe for TACE if superselective tumor embolization is achievable [3,14]. Furthermore, TACE with degradable beads can be a solution for selected advanced clinical patients ineligible for standard TACE [30] due to a poor underlying liver function.

Like ablation, biliary abnormalities such as obstruction, biliary–enteric anastomosis, or indwelling biliary stents lead to a marked increase in the risk of biloma formation, abscess, and cholangitis after liver intra-arterial treatment, potentially leading to death. Thus, the real risk–benefit profile for intra-arterial treatment needs to be discussed, and potential complications reviewed when discussing for patients’ consent. If TACE is still considered the most reasonable option, in these situations, prophylactic coverage with antibiotics is mandatory over the week following treatment (using piperacilinetazobactam, 4 g/0.5 g, i.v. every 8 h or levofloxacin, 500 mg qd p.o. plus metronidazol 400 mg, b.i.d. p.o. for 5–7 days) [3].

By contrast, TARE has minimal or no embolic effect, as non-radioactive individual carrier microspheres prompt virtually no inflammatory reaction in the embolization zone [73]. Thus, though TARE has its own radiation-induced complications, PES is less of an issue than for TACE, which has an apparent embolic effect. The most feared TARE-related complications are radioembolization-induced liver disease (REILD) and pneumonitis, which are fortunately rare. Radiation cholecystitis, gastritis, duodenitis, and pancreatitis can also be seen and are related to offtarget radioembolization. Although REILD mostly occurs 4–8 weeks after radiation therapy, it can present as early as two weeks or as late as seven months. Its incidence ranges between 0 and 4%. Baseline abnormal hepatic function and activity applied to liver have an impact on the risk of developing REILD [74].

3. Conclusions

Interventional oncology is playing a pivotal emerging role in the management of primary and secondary hepatic tumors. Treatments need to be both effective and safe, with a mandatory aim to reduce the risk for complications. Factors that contribute to this aim include an adequate multidisciplinary approach, correct indication, accurate treatment planning, and comprehensive

knowledge of complications as well as of clinical factors affecting treatment efficacy. A thorough knowledge of indications, complications, imaging-guidance tools, and treatment modalities is needed, as well as of alternative approaches. Patients should be asked to take an active part in their care process, and their approval of an updated informed consent after discussion of the therapeutic plan is essential.

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