



## Emerging local ablative therapies for unresectable perihilar cholangiocarcinoma: Time for re-appraisal

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To the editor,

With great interest we have read the recent report by Schmidt et al., who analyzed the short-term effects and adverse events of endoscopically applied radiofrequency ablation (RFA) and photodynamic therapy (PDT) in perihilar cholangiocarcinoma (PHC) patients.<sup>1</sup> Local ablative therapies for PHC are gaining interest; however, evidence of survival benefit is lacking because of the absence of large randomized controlled trials. Considering the rarity of the disease and the large number of emerging new treatment modalities, a worldwide registration of outcomes might be essential to reliably study the outcomes of all these treatment strategies.

PHC is a rare tumor and the majority of patients have unresectable disease. In contrast to resected patients, in whom median overall survival (OS) is 40 months,<sup>2</sup> patients with unresectable disease have poor survival with median OS of 9 to 12 months after stenting. Given that 70–80% of patients have unresectable disease and that systemic chemotherapy prolongs life expectancy by only a median of three months, additional therapies are of major interest.<sup>3</sup> Considerable heterogeneity in survival time is observed among unresectable tumors, most likely due to differences in tumor genotype and phenotype. Patients with “favorable” tumor characteristics may live longer than predicted on the basis of survival curves, and could therefore benefit considerably from local treatments.<sup>4</sup>

PDT increases OS from 7 to 10 months<sup>5</sup> and, according to more recent reports, up to 15–21 months.<sup>6–8</sup> However, cutaneous phototoxicity due to photosensitizer accumulation in the skin is a major limitation that necessitates complete protection from sunlight for one week and protection of direct sunlight for at least one month.<sup>6</sup> It is undesirable to expose patients to this burden, as their quality of life is severely affected in the short time they have left. Nevertheless, PDT has been shown to increase stent patency in unresectable patients, thereby reducing biliary interventions and reducing complications.<sup>9</sup> Additionally, new third-

generation photosensitizers may further improve therapeutic efficacy and reduce skin phototoxicity.<sup>10</sup> As many patients ultimately die from undrainable, recurrent biliary obstruction, any treatment that can prolong stent patency can make a difference in palliative care.

Schmidt et al. demonstrated that intraluminal RFA is superior to PDT in terms of stent patency and decreases associated complications. Adverse events induced by the RFA treatment itself appear limited. However, a heat-based local ablative therapy applied in the liver hilum may be risky. Bile duct injury and major vessel thrombosis are potential major hazards (National Institute for Health and Care Excellence (NICE) interventional procedure guidance). Detailed complication registration and information on the employed biliary drainage strategies (plastic or metal stents, unilateral or bilateral drainage) prior to RFA would be of interest. For example, metal stents conduct heat differently than plastic stents, which is critical when applying RFA.<sup>11</sup>

Recently, a phase I/II trial using irreversible electroporation (IRE) was started for patients with unresectable PHC (Netherlands Trial Register number NTR5948). The mode of action of IRE is primarily based on current-induced permeabilization of the cell membrane in the tumor bulk. The electrical field disrupts intracellular homeostasis and leads to cell death in the IRE-subjected tissue. Theoretically, IRE may be safer compared to RFA because of the lesser thermal component and, in addition, the technique is less affected by the so-called heat/cold-sink effect in the

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presence of adjacent large vascular structures. Furthermore, IRE can also be performed during laparotomy when tumors are found unresectable, in contrast to retrograde intraluminal RFA, which is applied endoscopically.

Local ablative techniques and other alternative therapies are emerging for unresectable PHC. However, controlled high-quality evidence to guide the clinical management of unresectable PHCs is scarce. Since PHC is rare and its treatment complex, all efforts should be made to publish outcomes with the fullest possible extent of detail, including study setup, patient selection, adverse events, and survival data. An international, multi-center registry may be a good start to collect sufficient data of patients in order to assess the value of the available local therapies in a large cohort study.

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