Ablative therapies of the biliary tree

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Abstract: Cholangiocarcinoma, a malignancy of the epithelial cells in the intrahepatic or extrahepatic biliary tree, is often diagnosed at later stages. Median survival duration ranges from 3 to 9 months with a less than ten percent 5-year survival rate. Thus, often treatment strategies are aimed more towards palliation instead of cure. With the majority of patients presenting with unresectable disease at the time of diagnosis, surgical intervention is not feasible, making less invasive endoscopic therapies more suitable. Initially, biliary stents were utilized for biliary decompression to mitigate cholestatic symptoms and prevent cholangitis; however, this strategy did not prove to provide significant survival benefit. Therefore, efforts to treat the tumor burden itself in addition to maintaining biliary patency became a focus of innovation and research in the endoscopic field. This study has led to the advent of therapies such as photodynamic therapy, radiofrequency ablation, and intraluminal brachytherapy. These options combined with biliary stenting have shown to not only offer the benefit of biliary decompression, but also to potentially improve stent patency and survival. Further, there is an anti-tumor effect of each of these modalities, portending an additional benefit in this subset of patients. Despite numerous retrospective and prospective studies assessing these ablative therapies, there is still a paucity of appropriately powered randomized controlled trials, and further research has yet to be done in the field. This review details the current literature entailing endobiliary ablative strategies.

Keywords: Photodynamic therapy; radiofrequency ablation; intraluminal brachytherapy; cholangiocarcinoma

Introduction

Ablative therapies of the biliary tree are typically utilized in the setting of malignant biliary obstruction, most commonly caused by cholangiocarcinoma (CCA) and pancreatic head cancer, but also by gallbladder cancer, ampullary cancer, malignant hilar lymphadenopathy, and hepatocellular carcinoma (1). Specifically, CCA, a malignancy of epithelial cells of the intrahepatic or extrahepatic biliary tree, presents as unresectable disease in 60–80% of patients at the time of diagnosis (2). In these patients, the 5-year survival is 5–10%, and the median survival duration ranged from 3 to 9 months (3). Thus in the majority of these cases, treatment is aimed at palliation as opposed to cure. Endoscopists play

a significant role in palliation of these patients by achieving and maintaining biliary patency via performance of endoscopic retrograde cholangiopancreatography (ERCP). The goals of biliary decompression are multiple including preservation of hepatic function, abatement of symptoms associated with cholestasis (i.e., pruritis, jaundice) and prevention of cholangitis. Biliary stent placement alone has not been associated with significantly improved survival (4,5). This has allowed for the emergence and study of endobiliary ablative technologies such as photodynamic therapy (PDT), radiofrequency ablation (RFA) and intraluminal brachytherapy (IB) as complementary treatment modalities to potentiate the goals of biliary

Table 1 Review of trials investigating effect of photodynamic therapy on survival outcomes in patients with unresectable CCA

Author	PDT + stent cohort size	Stent alone cohort size	Study design	Median survival outcomes (PDT + stent vs. stent alone)	P value
Ortner et al., 2003 (15)	20	19	RCT	493 vs. 98 days	<0.0001
Dumoulin et al., 2003 (17)	24	20	RS	9.9 vs. 5.6 months	0.05
Witzigmann et al., 2006 (18)	68	56	PS	12 vs. 6.4 months	<0.01
Kahaleh et al., 2008 (19)	19	29	PS	16.2 vs. 7.4 months	<0.004
Cheon et al., 2012 (21)	72	71	RS	9.8 vs. 7.3 months	0.029
Lee et al., 2012 (22)	18	15	RS	356 vs. 230 days	0.006
Leggett et al., 2012 (23)	170	157	MA (6 studies)	Weighted mean difference: 265 days	0.01
Moole et al., 2017 (24)	526	146	MA (10 studies)	413.04 vs. 183.41 days	0.0043

CCA, cholangiocarcinoma; PDT, photodynamic therapy; RCT, randomized controlled trial; RS, retrospective study; PS, prospective study; MA, meta-analysis.

decompression and provide additional benefits of longer stent patency and improved survival.

Endoscopic retrograde cholangiopancreatography-guided

Photodynamic therapy

PDT is an ablative technology that utilizes an intravenous photosensitizing agent, to provoke biliary neoplastic cells that then become vulnerable to light-induced photoactivation and subsequent apoptosis. Porfimer sodium is the most commonly used agent in the United States. Though it has not yet been approved for CCA, it is still covered by most insurers for compassionate use (6,7). Other photosensitizing agents not available in the U.S. include meta-tetrahydroxyphenyl chlorine, hematoporphyrin derivatives (Photogem, Photoscan-3), and meso-tetrahydroxyphenylchlorin (8).

After porfimer sodium is intravenously administered, the substance is nonspecifically absorbed by cells of numerous tissues, but it is highly concentrated in malignant biliary epithelium due to its strong predilection for these cells. At 48 to 72 hours, the patient undergoes ERCP with cholangiogram, during which a diode laser fiber with a cylindrical diffuser at the distal-most end is positioned in the biliary tree across the target lesion or stricture. Once in the proper position, the laser fiber is illuminated to a specific

wavelength (generally 630 nm) for 750 seconds, which triggers a photoperoxidation reaction and generation of oxygen free radicals (9,10). This leads to membrane fluidity loss, DNA damage, DNA repair inhibition, mitochondrial activity destruction, and lysosomal and nuclear damage, all of which ultimately produce tissue necrosis and apoptosis. Additionally, PDT also activates inflammatory cascades and anti-angiogenic pathways that also assist in local tumor control (11-13). An additional benefit of PDT is that the light waves are capable of refracting through the bile, reaching proximal portions of the biliary tree that are beyond the reach of the fiber itself (11). Stent placement is subsequently performed as the inflammation and edema from PDT's destruction of tumor cells potentially causes biliary obstruction and cholangitis (8).

Preliminary descriptions of PDT were case reports and anecdotally since 1991 (14). A landmark trial studying PDT in 39 patients with unresectable CCA was performed in 2003. Patients were randomized to either receive PDT 48 hours prior to ERCP with stenting (n=20) or stenting alone (n=19). The patients who underwent unilateral or bilateral PDT with stenting had significantly longer median survival (493 vs. 98 days, P<0.0001), increased biliary drainage, and a significantly better life quality compared to those who were treated only by stent placement (15). Subsequent studies have showed improvement in overall survival in patients with unresectable CCA (16-22) (*Table 1*).

Since then, a meta-analysis assessed PDT in 170 patients with CCA over 6 studies. PDT plus stenting was associated with a significantly longer survival (265 days; 95% CI: 154–376 days, P=0.01), augmented performance status as per their Karnofsky scores (weighted mean difference 7.74; 95% CI: 3.73–11.76; P=0.01), and a similar pooled event rate specifically with regards to biliary sepsis (23). A more recent meta-analysis found significant improvement in survival in patients with CCA who underwent PDT plus stenting (n=526; 413.04 days; 95% CI: 349.54–476.54) versus those who received stenting alone (n=146; 183.41 days; 95% CI: 136.81–230.02). The generalizability of the study was hindered by its heterogeneity with percutaneous and endoscopic administration of PDT and both percutaneously or endoscopically placed biliary stents in the included studies (24). One randomized trial found worse survival outcomes in the PDT group compared to group treated with only a stent (median 6.2 *vs.* 9.8 months; HR 1.56, 95% CI: 1.00 to 2.43, P=0.048). Progression free survival was also worse in the PDT group (median 3.4 *vs.* 4.3 months; HR 1.43, 95% CI: 0.93 to 2.18, P=0.10). Interpretation of this study, however, was limited by the difference of chemotherapy regimens in the two groups (25).

In addition to survival outcomes, studies have also examined the role of PDT in stent patency, predictors that could portend a better prognosis after PDT, and the impact of PDT prior to and after surgical resection. Specifically, one study looked at 33 unresectable CCA patients, 18 of whom had PDT and uncovered metal stents and 15 of whom were treated with uncovered metal stents alone. Those who received PDT had significantly longer stent patency (median 244 +/– 66 *vs.* 177 +/– 45 days; P=0.002) and survival (median 356 +/– 213 *vs.* 230 +/– 73 days; P=0.006) (22). With regards to predictive factors, Prasad *et al.* identified 25 patients with unresectable CCA that received PDT endoscopically and percutaneously as well as biliary stenting. Increased mortality was associated with a longer time before PDT administration (HR 1.13; 95% CI: 1.02–1.25; P=0.029), imaging with an appreciable mass (HR 3.55; 95% CI: 1.21–10.38; P=0.021), and lower albumin (HR 0.16; 95% CI: 0.04–0.59; P=0.005) (26). PDT prior to surgical resection was also studied in 7 patients in an attempt to downstage unresectable CCA.

There were no significant differences in overall survival between 7 patients with PDT followed by surgical resection in 30–72 days compared to 35 patients with surgical resection alone (27).

Several studies have looked at the effects of combination therapy with systemic chemotherapy and PDT. Most recently, a retrospective analysis from 2019 investigated the role of combination therapy in 96 patients with unresectable perihilar CCA and distal CCA. 34 patients underwent PDT (photoactive compounds porfimer, hematoporphyrin, and temoporfin), 26 patients underwent chemotherapy (mostly gemcitabine based), and 36 patients underwent PDT and chemotherapy. There was a trend towards increased median overall survival in patients who received PDT plus chemotherapy (20 months, 95% CI: 16.38–23.62) compared to the PDT group (15 months, 95% CI: 10.02–19.98) and the chemotherapy alone group (10 months, 95% CI: 8.45–11.55) (28). A previous retrospective analysis of patients with perihilar CCA after biliary stenting investigated PDT (n=35) versus PDT and chemotherapy (n=33). The mean overall survival in those who underwent PDT plus chemotherapy was significantly longer than the PDT group alone (520 *vs.* 374 days, respectively; P=0.021), with similar rates of cholangitis (29). A prospective, randomized, phase II trial explored the effects of oral fluoropyrimidine S-1 to PDT in unresectable CCA. Those receiving combination therapy had a longer overall median survival (17 *vs.* 8 months, P<0.005), and a longer median progression-free survival (10 *vs.* 2 months, P=0.009). With regards to feasibility, systemic chemotherapy and PDT is tolerable. A phase II trial of PDT and gemcitabine/capecitabine (GemCap) examined 20 patients with recurrent or metastatic bile tract cancers including CCA and gallbladder cancers. Ten patients received PDT, GemCap, and biliary stents while 10 patients received only GemCap and biliary stents. There were no significant differences in the quality of life as measured by the EORTC QLQ-C30 score (30). Again, these trials are limited by their small sample sizes, and interpreted with caution, but generally it seems that PDT may have an additive benefit to chemotherapy in terms of overall survival (*Table 1*).

Adverse events/limitations

The most common side effect of PDT is phototoxicity as the photosensitizer absorption is not restricted to malignant biliary epithelial cells. Other skin effects include erythema, pruritus, blistering, and diffuse pain. Patients are typically educated on avoiding direct sunlight for 4–6 weeks post PDT, which can severely minimize patients' life quality when the life expectancy is also truncated due to incurable malignancies that are prompting the PDT therapy in the first place (4,8). Biliary obstruction can theoretically occur from localized tissue edema, however, studies have shown

that PDT might not necessarily increase the risk of biliary sepsis. Nonetheless, endoscopic biliary stenting after PDT is recommended (8,23). From a practical standpoint, the fiber optic laser diffuser is expensive, with the specific Optiguide DCYL700 fiber optic model priced at $850 U.S. dollars. Furthermore, the average-wholesale cost of one 75-mg vial of porfimer sodium was $24,512, which is half the total amount an average 75 kilogram patient would require. Another practical hindrance is the three-day gap required after administration of the photosensitizer before treatment with PDT can be accomplished (31). Other logistical challenges of the procedure include procurement of the laser tower itself and time commitments of the procedure especially if multiple applications are planned in a single setting.

Endoscopic retrograde cholangiopancreatography-guided

Radiofrequency ablation (RFA)

The utilization of electric currents to generate heat has been employed in medicine since the early 1900s. Specifically, RFA applies an alternating current that creates electromagnetic wave frequencies ranging from 10^4 to 3×10^{12} Hz (32). This subsequently heats tissue, causes protein coagulation, and destructs tissue (33). It has been purported that RFA might induce indirect anti-tumor effects including T-lymphocyte activation and localized inflammatory response stimulation, both of which are recognized after RFA treatment of other malignancies (34-38). From a technical standpoint, the success of RFA can be limited by substances that conduct current poorly such as charred tissue, vapor and gas, and by blood flow in the target tissues which serve as heat sinks (39). Nonetheless, RFA has become a viable option in the evolving management of perihilar and extrahepatic CCA, benign biliary strictures, and ampullary neoplasms. Currently the only approved biliary RFA catheter in the United States the Habib catheter (Boston Scientific, Natick, MA). This is an 8 French catheter with two 8 millimeter (mm) ringed electrodes at the distal end of the catheter providing a 2.5 centimeter (cm) elliptical range of ablation using a 7–10 watt application for 60–120 seconds. Other ablation catheters are available internationally including the ELRA system (STARmed, Goyang, Korea) which comes in various sizes and has a unique built in temperature monitoring system.

Malignant biliary obstruction

Steele *et al.* first reported in 2011 RFA as a therapeutic option for biliary decompression in unresectable malignant biliary obstruction. This open-label pilot study investigated 22 patients with pancreatic cancer (PC, n=16) and CCA (n=6). Out of the 21 patients who received RFA with subsequent metal stent placement, 20 patients and 16 patients maintained biliary patency at 30 and 90 days, respectively (40). A retrospective study of 66 patients with biliary obstruction (CCA in 37 patients, PC in 27 patients) compared RFA and self-expanding metal stents (SEMS) with SEMS alone. The cohorts were controlled for age and diagnosis. There were no significant differences in bile duct diameter, survival, or adverse effects (41). These same authors went on to investigate RFA followed by stent placement and compared to data from the Surveillance, Epidemiology, and End Results database registry. There was improved survival in the RFA cohort (42). Kallis *et al.* compared 23 PC patients who received RFA and SEMS to 46 patients who underwent SEMS placement alone. The RFA cohort had a significantly higher survival of 226 *vs.* 123.5 days (P=0.01) (43).

Zheng *et al.* conducted a meta-analysis that included nine studies with 263 patients who had malignant biliary obstruction secondary to CCA (65.8%), PC (29.3%), other cancer types (4.9%), or metastatic cancer (1.5%). RFA significantly improved stricture diameter by 3.446 mm (95% CI: 3.356–3.536 mm). There was a 17% (95% CI: 10–25%) pooled rate of adverse events, with most complications being mild and managed conservatively, though two deaths from hemobilia and one case of partial liver infarction also occurred (44).

A randomized controlled trial published in 2018 describing 65 patients with types I and II Klatskin tumors (n=19) and distal CCA (n=46) that were randomized to RFA and plastic stent (n=32) and plastic stent (n=33). Stent patency and overall survival time were significantly longer in the RFA plus stent cohort, 6.8 *vs.* 3.4 months, P=0.02 and 13.2 +/− 0.6 *vs.* 8.3 +/− 0.5 months, P<0.001, respectively. Multivariable Cox regression analysis showed that RFA was the main protective factor in patients' survival (P<0.001). The incidence of adverse events was similar in each group (45). Similarly, a recent systematic review of nine studies investigated the outcomes of endoscopically or percutaneously administered RFA with stent placement compared to stent placement alone in 505 patients with

malignant biliary strictures. Patients who received RFA had longer stent patency of 50.6 days (95% CI: 32.83–68.48) and improved survival (hazard ratio, 1.395; 95% CI: 1.145–1.7; P<0.001). There were no significant differences in post-procedural adverse events including cholangitis, acute cholecystitis, pancreatitis, and hemobilia, though patients who received RFA had a significantly higher risk of post-procedural abdominal pain (31% *vs.* 20%, P=0.003) (46).

While RFA is an FDA-approved technology, the generalizability of these studies is limited by the small number of patients, the observational designs of the majority of the studies, the heterogeneity in the study population (i.e., inclusion of PC and CCA induced biliary strictures), and route of RFA administration (i.e., percutaneously and endoscopically). Nonetheless, it has thus far shown to be an effective modality for improving stent patency and survival and merits further study.

Benign biliary strictures

These strictures can arise from a wide array of causes including, but not limited to, hypoperfusion during liver transplantation, post-operative bile duct injury, chronic bile duct inflammation or chronic pancreatitis (47). Pathogenesis of benign biliary strictures (BBS) is related to fibrous tissue hyperplasia causing narrowing of the duct lumen (48). Stents, both plastic and SEMS, are comparable in terms of clinical success (49), but consequent stricturing is a significant problem (50). It has been postulated that the thermal effect of RFA can alter the fibrous scar tissue, improving the efficacy of subsequent endoscopic therapy more efficacious in the future. A prospective study conducted in 2014 explored the role of RFA in 9 patients with refractory BBS due to post-operative complications (n=4), post-anastomotic after liver transplantation (n=3), chronic inflammatory strictures (n=1), and obstructive tissue hyperplasia inside a previously placed SEMS for chronic pancreatitis (n=1). About 80% of patients already failed previous endoscopic or percutaneous interventions. RFA was performed with balloon dilation post-ablation. Plastic or SEMS were placed if there was no stricture resolution post treatment. Five patients had stricture resolution, and 4 patients had stricture improvement after RFA application. Further stenting was not requisite in 3 cases. The patient with tissue hyperplasia inside a previously placed SEMS

required surgery for stent retrieval, but did have good biliary drainage post-ablation. Adverse events included, mild post-procedural pain (n=2), mild post-procedural acute pancreatitis (n=1), and transient leukocytosis (n=2). More studies, certainly of larger sizes, would be helpful in making further conclusions about the safety and efficacy of RFA application in BBS (51).

Ampullary neoplasm

Despite advances in the endoscopic therapies of ampullary adenomas, the management of intraductal extension has remained challenging. Traditionally, involvement of the biliary or pancreatic ducts has been an indication for surgical management. However, ampullectomy and pancreaticoduodenectomy are associated with significant morbidity and mortality, making recent evolutions in minimally invasive options such as RFA attractive (52). Also, some patients with intraductal extension of ampullary neoplasms are not fit for surgery and may not have adequate therapeutic options.

A small case series reported that 3 of 4 patients had complete eradication of intraductal residue without any immediate adverse events in the immediate setting (53). A retrospective multicenter study evaluated the efficacy, feasibility, and safety of RFA for ampullary neoplasms with intraductal extension in 14 patients. These patients underwent a median of one RFA session (range 1–5 sessions), and at a median follow-up of 16 months, complete intraductal ablation was accomplished in 91.6% of patients. There was a 43% adverse event rate, which included ductal strictures and a retroduodenal abscess, both of which were successfully treated endoscopically (54).

A prospective open-label multicenter study examined twenty patients with endobiliary adenomas, of which fifteen were low grade dysplasia and five were high grade dysplasia. All patients underwent one successful RFA treatment and biliary stent placement with an uneventful recovery. The rates of residual neoplasia were 15% (3/20) and 30% (6/20) at 6 and 12 months, respectively. 40% (8/20) had at least one adverse during follow up, mild pancreatitis melena while on clopidogrel, cholangitis, and biliary strictures (55).

Though these studies are limited by their sample sizes, they document efficacy of RFA with a relatively minimal side effect profile, suggesting this could be a viable

alternative to surgery. Post-ablation pancreatitis is likely the most significant concern for performing RFA in this region and techniques to minimize this adverse event (i.e., prophylactic pancreas duct stenting, non-steroidal anti-inflammatory medications) will need to be optimized. Nonetheless, the limited study sizes and the scarce number of studies regarding this application make further investigation requisite.

Adverse effects

RFA has shown to have a relatively low incidence of significant adverse events, though more serious side effects have been reported. The main adverse events include abdominal pain, pancreatitis, cholangitis, cholecystitis, most of which were shown to be mild and managed conservatively (41,43,44,56). However, the two deaths from hemobilia, one case of partial liver infarction, and one hepatic artery pseudoaneurysm are major adverse events thought to be secondary to RFA use in intrahepatic biliary segments leading to vascular injuries of branches of the hepatic artery (44,57-59). Subsequently lower energy settings for intrahepatic use of RFA are recommended by experts.

Intraluminal brachytherapy

Intraluminal brachytherapy (IB) entails using iridium-192 (192Ir) or iodine-125 (125I) seeds contained in a ribbon or a wire that is advanced into the biliary lumen via a trans-hepatic approach and a trans-duodenal endoscopic technique. In the endoscopic technique, ERCP identifies the site of the tumor, the length of bile duct involved, and the extent of disease. A guide wire is advanced through the malignant stricture, after which the endoscope is removed and a naso-biliary tube is threaded over the guidewire into the biliary tree. An afterloading catheter that contains the radio-opaque marker wire is passed under fluoroscopy through the naso-biliary tube. The radio-opaque wire has markers at intervals to specify the position where the radioactive source should be placed. Radiographic confirmation is performed (60). The trans-hepatic approach is preferable and can provide internal drainage across the tumor as well as external drainage (61). IB causes directly destructs DNA, inhibits cellular replication, and induces apoptosis of tumor cells (60,62).

First reported in 1981 (63), multiple subsequent studies have attempted to validate the efficacy of this modality with regards to stent patency and overall survival in CCA. Their small sample sizes, heterogeneous prior treatment approaches, and different cancer types causing biliary obstruction make interpretation difficult (64). A meta-analysis of 12 studies in 2018 compared outcomes in those with malignant biliary obstruction who underwent IB and stenting (n=340 patients) versus stenting alone (n=301 patients). Patients with IB and stenting experienced less stent occlusion (odds ratio, 0.19; 95% CI: 0.13–0.28; P<0.00001) and prolonged mean survival (mean difference, 3.15 months; 95% CI: 2.64–3.66 months; P<0.0001) without significant differences in adverse events or changes in bilirubin levels (62). IB has also been studied in patients with unresectable CCA undergoing neoadjuvant chemotherapy as a bridge therapy to liver transplantation (65).

The usage of IB is hindered by practical inconveniences and adverse effects of the therapy. As the material is radioactive and has a short half-life, there are logistical challenges in handling, storing, and delivering the substances. Immediate adverse events include biliary obstruction, cholangitis, and hemobilia, whereas delayed complications include gastrointestinal bleeding, duodenal stenosis, and hemobilia, all of which are direct results of radiation (60). PDT and RFA have largely replaced IB at the endoscopic ablative technologies of choice in malignant obstruction.

Summary

Malignant biliary obstruction very commonly becomes the responsibility of the advanced endoscopist to maintain patency for palliation given the low rate of curative resection of these lesions (66). While ERCP with serial stenting has long been the gold standard, ablative therapies including PDT, RFA, and IB have risen to prominence in this subset of patients because of the potential benefits of improved survival and stent patency in addition to the anti-tumor effects of each of the modalities (*Figure 1*). Though these options have emerged over the last two decades, better powered studies in more homogenously controlled cohorts are required to make more informed decisions about the application of these technologies (*Table 2*).
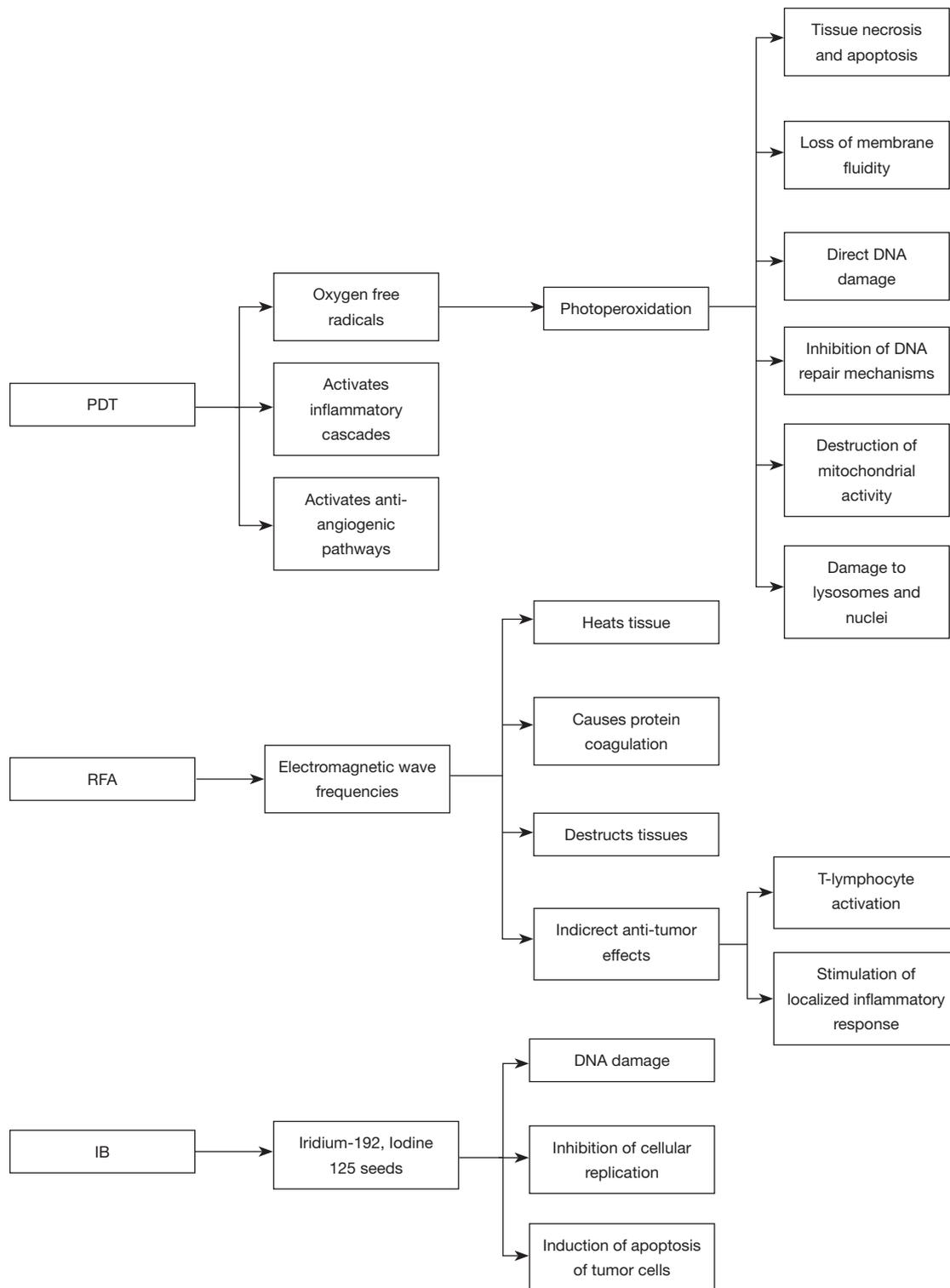
Figure 1 The pathophysiology of each ablative therapy. PDT, photodynamic therapy, RFA, radiofrequency ablation; IB, intraluminal brachytherapy.

Table 2 This table summarizes the outcomes compared to stents alone, adverse effects, and practical considerations to take into account prior to application

Therapy	PDT	RFA	IB
Outcomes compared to stent alone	Longer survival	Improved survival	Lower stent occlusion rate
	Improves biliary drainage	Improved stent patency	Prolonged mean survival
	Better quality of life	Improved stricture diameter	
	Improvement in performance status		
	Longer stent patency		
Adverse effects	Phototoxicity	Abdominal pain	Biliary obstruction
	Erythema	Cholangitis	Cholangitis
	Pruritus	Acute cholecystitis	Hemobilia
	Blistering	Pancreatitis	Gastrointestinal bleeding
	Pain	Liver infarction	Duodenal stenosis
	Biliary obstruction	Hepatic	
		Pseudoaneurysm Hemobilia	
Practical considerations	Expensive	May require more than 1 session	Radioactive material
	Three-day interval between photosensitizer administration and photoactivation	Low energy settings in intrahepatics	Short half life
	750 sec per application		Challenges in handling, storing, delivering substances

PDT, photodynamic therapy; RFA, radiofrequency ablation; IB, intraluminal brachytherapy.

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