Trans-hepatic technique and intraluminal Pulsed Dose Rate (PDR-BT) brachytherapy in treatment of locally advanced bile duct and pancreas cancer

Janusz Skowronek MD, PhD, Ass. Prof. 1, Aleksander Sowier MD, PhD 2, Paweł Skrzywak MD, PhD 3

1 Brachytherapy Department, Greater Poland Cancer Centre, Poznań, Poland
2 NZOZ Olympus, Łódź, Poland
3 # Surgical Clinic, University of Medical Sciences, Poznań, Poland

Abstract

Purpose: To assess the feasibility of intraluminal palliative Pulsed Dose Rate (PDR-BT) brachytherapy in the treatment of locally advanced bile duct and pancreas cancer.

Material and methods: Forty-eight patients with advanced bile duct or pancreas cancer, disqualified from surgery or radical external beam radiation therapy (EBRT), were treated with trans-hepatic technique and intraluminal PDR-BT: 29 patients with bile duct cancer and 19 – pancreas cancer. Forty-four patients were treated exclusively with PDR-BT, 4 with PDR–BT and concomitant chemotherapy or surgery. Percutaneous trans-hepatic technique was used to implant the catheter into bile ducts. Most of patients (38/48, 79%) received 25 pulses of 0.8 Gy hourly with the total dose of 20 Gy. In 8 cases PDR was repeated after one week. Target volume encompassed tumor visualized at cholangiography with one or two cm margin measured proximally and distally. Dose was prescribed at 10-15 mm from the source axis.

Results: In all cases trans-hepatic technique allowed insertion of BT catheter into bile duct and safe application of PDR-BT. In 19 out of 29 (65.5%) of bile duct cancer cases and in 10 out of 19 (52.6%) of pancreas cancer patients clinical improvement (decrease of jaundice) was noted in first control after 4 weeks. Median overall survival time (OS) for bile duct cancer patients was 11.2 months and for pancreas cancer patients – 5.2 months.

Conclusions: 1. It has been established, that the use of PDR-BT was feasible and had a low early complication rate. A new percutaneous trans-hepatic technique allowed the treatment (insertion of catheter, PDR brachytherapy) to be performed in one day. 2. In most cases a satisfied palliative effect was achieved, however it was more apparent in bile duct cancer patients then in pancreas cancer patients.

Key words: bile duct cancer, pancreas cancer, PDR brachytherapy.

Purpose

Palliative treatment options for bile duct cancer or pancreas cancer remain limited due to large number of patients with advanced disease at the time of diagnosis. Furthermore, radical surgery is possible in less than 10-15% of cases [1-4]. Bile duct or pancreas cancers are very difficult to treat with external beam therapy alone due to the proximity of adjoining organs and high doses required to effectively irradiate these neoplasms [1, 5-8].

The majority of bile duct carcinomas involve hepatic duct bifurcation, common hepatic duct, cystic duct, and ampulla. Tumor can spread along sinusoids and neoplastic destruction of normal cholangioloes leads to retention of bile around the margin of the tumor. Tumor emboli in the portal and hepatic veins are common and vascular invasion can occur in up to 90% of cases. The tumor may also metastasize to lungs, peritoneum and intra-peritoneal organs. The majority of tumors are low grade cholangiocarcinomas. Patients are commonly presented with obstructive jaundice. The most important diagnostic procedure is cholangiography with the staging involving ultrasound and CT scans. The only curative treatment is radical surgical excision. However, due to the propensity of cholangiocarcinomas to invade the hepatic artery, portal vein and other vital structures this procedure is only possible in 10 to 15% of cases and is associated with an operative mortality of 5 to 10% [2, 9, 10]. Effective palliation is achieved by biliary decompression. This is applied either surgically by using bypass procedures such as hepaticoenterostomy or non-operatively by endoscopic or percutaneous insertion of biliary endoprosthesis [1, 11, 12].

Indications for brachytherapy include all malignant structures of the bile duct which can be cannulated. In palliative treatment of pancreas cancer, especially located in the head, in some locations, the same good palliative
result can be achieved. Combined treatment is possible in patients who are in reasonably good physical condition and reviewed in order to confirm that they are not suitable for resection. Combined treatment usually include brachytherapy (BT) and external beam radiation therapy (EBRT) [5, 13-18]. Although the results available in literature are to some extent contradictory with regards to possible use of intraluminal brachytherapy in a curative setting, some evidence indicates that intraluminal brachytherapy can add to the treatment of unresectable intrahepatic bile duct and pancreatic cancers if a proper subset of patients is identified and a rational and aggressive scheme of multimodality treatment is designed.

**Aim**

The purpose of this study was to assess the feasibility of intraluminal palliative PDR brachytherapy (PDR-BT) and trans-hepatic technique of catheter insertion in the treatment of locally advanced bile duct and pancreas cancer. We decided to irradiate this patients due to clinical presence of the tumor and due to increased risk of jaundice. In several cases after consultation with radiologists we decided to use the same technique for pancreas cancer due to close presence of the tumor infiltrating part of bile duct tree. We choose PDR-BT instead of HDR-BT (High-Dose-Rate) because of short (one day) treatment time which was well accepted by patients and also, because of growing interest of using PDR-BT in treatment of different cancers. In view of a short time of observation and a small group of patients we present preliminary results.

**Material and methods**

**Patients – bile duct cancer**

Twenty-nine patients with advanced bile duct cancer were treated using PDR-BT between May 2002 and December 2007 in Greater Poland Cancer Centre. In all cases trans-hepatic technique was used. There were 15 women and 14 men, median age of 61 years, ranged from 40 to 81. Eleven patients underwent surgical procedures (prior cholecystectomy) or prosthesis implantation (12 patients) before being referred for brachytherapy. All patients referred for brachytherapy were regarded as no further operable by surgeons. The entire group of patients indicated jaundice symptoms, 21 suffered from pain in the upper abdomen, 9 from anorexia and nausea and 23 patients experienced rapid weight loss (up to 15 kg in 2-3 months). Histological confirmation of adenocarcinoma was obtained in 11 cases: in 8 cases adenocarcinoma, in 1 – cholangiocarcinoma, and in 2 – carcinoma solidum adenogenes were diagnosed. In 15 cases histological diagnosis was obtained – cellulae carcinomatosae. The diagnosis of cancer was established by radiographic, endoscopic, and other clinical evidence. Most of tumors were located in gall-bladder and extrahepatic bile duct – 14/29 (48.3%). Summarized clinical data are presented in Table 1.

**Pancreas cancer patients**

Nineteen patients with advanced pancreas cancer were treated using PDR-BT at the same time. In all cases trans-hepatic technique was used. There were 13 women and 6 men, median age of 62.7 years, ranged from 40 to 84. Eight patients underwent surgical procedures and 3 were treated after recurrence prior earlier surgical treatment. All patients referred for brachytherapy were regarded as no further operable by surgeons. The entire group of patients indicated jaundice symptoms, and suffered from pain in the upper abdomen, 16 patients experienced rapid weight loss (up to 10-15 kg in 2-3 months) and 9 cases of anorexia.

**Table 1.** Bile ducts cancer patients – clinical data

| Clinical data (29 patients) | Number, rate |
|----------------------------|--------------|
| **Age**                    |              |
| Median                    | 61           |
| Range                     | 40-81        |
| **Gender**                |              |
| Male                      | 14 (48.3%)   |
| Female                    | 15 (51.7%)   |
| **Tumor site**            |              |
| Klatskin tumor            | 8            |
| Perihilar and CHD         | 3            |
| Extrahepatic bile duct    | 8            |
| Gall-bladder and extrahepatic bile duct | 6 |
| Papilla Vateri            | 3            |
| Diffuse*                  | 1            |
| **Pathologic type**       |              |
| Adenocarcinoma            | 11           |
| Cholangiocarcinoma        | 1            |
| Carcinoma solidum adenogenes | 2            |
| Cell carcinoma            | 15           |
| **Treatment**             |              |
| Primary tumor – radical treatment | 4 |
| Primary tumor – palliative treatment | 21 |
| Recurrent tumor after surgery | 4 |
| **PDR description (pulse of 0.8 Gy)** |        |
| 1 x 20 Gy                 | 22           |
| 2 x 20 Gy                 | 5            |
| 1 x 25 Gy                 | 1            |
| Interrupted treatment     | 1            |
| (worsening of patients condition) | |
| **Interval**              |              |
| 60 minutes                | 14           |
| 55 minutes                | 12           |
| 50 minutes                | 3            |
| **Reference point**       |              |
| 1.5 cm                    | 6            |
| 1.0 cm                    | 23           |
| **LC after 4 weeks**      |              |
| CR                        | 3            |
| PR                        | 16           |
| NR                        | 6            |
| Progression               | 3            |
| Lack of observation       | 1            |

CHD – common hepatic duct, CBD – common bile duct

*included patients with > 2 sites of extrahepatic biliary ducts

LC – local control, CR – complete remission, PR – partial remission, NR – no remission

Janusz Skowronek, Aleksander Sowier, Paweł Skrzywanek

Journal of Contemporary Brachytherapy (2009/volume 1/number 2)
and nausea were noted. Histological confirmation of adenocarcinoma was obtained in 6 cases, in 13 cases histological diagnosis – cellulae carcinomatoseae was acquired. The diagnosis of cancer was established by radiographic, endoscopic, or other clinical confirmation. Most of tumors were located in head of pancreas, in 5 cases metastases to the liver and pulmonary area were noted. Summarized clinical data are presented in Table 2.

**Method of treatment**

Brachytherapy treatment started at the day of insertion of intraductal catheter. In order to compare current status with earlier X-ray photos, cholangiography procedure was performed. Treatment planning was based on radiography with the applicator placement and cholangiogram showing malignant stenosis (Figs. 1 and 2). Cases with pretreatment stents insertion are presented in Figs. 3 and 4. An X-ray unit, the IBU (Integrated Brachytherapy Unit) was used for treatment planning. Target Volume included cholangiography tumor visualization with 1 or 2 cm margin taken proximally and distally. Dose was prescribed at 10 or 15 mm

**Table 2. Pancreas cancer patients – clinical data**

| Clinical data (19 patients) | Number, rate |
|-----------------------------|--------------|
| **Age**                     |              |
| Median                      | 62.7         |
| Range                       | 40-84        |
| **Gender**                  |              |
| Male                        | 6 (31.6%)    |
| Female                      | 13 (68.4%)   |
| **Tumor site**              |              |
| Head                        | 9            |
| Head and corpus             | 5            |
| Head and dissemination ad liver | 4       |
| Head and dissemination ad lungs | 1     |
| **Pathologic type**         |              |
| Adenocarcinoma              | 6            |
| Cell carcinoma              | 13           |
| **Previous treatment**      |              |
| Lack of                     | 8            |
| Stent                       | 2            |
| Stent and cholecystectomy   | 1            |
| Anastomosis                 | 4            |
| Cholecystectomy and chemotherapy | 1    |
| Recurrent tumor after surgery | 3    |
| **Treatment**               |              |
| Primary tumor – palliative treatment | 12       |
| Recurrent tumor after surgery | 3    |
| Palliative treatment and chemotherapy | 2 |
| Palliative treatment and anastomosis | 2 |
| **PDR characteristic** (pulse of 0.8 Gy) | |
| 1 x 20 Gy                   | 16           |
| 2 x 20 Gy                   | 3            |
| **Interval**                |              |
| 60 minutes                  | 10           |
| 55 minutes                  | 8            |
| 50 minutes                  | 1            |
| **LC after 4 weeks**        |              |
| PR                          | 10           |
| NR                          | 6            |
| Progression                 | 3            |

*LC – local control, PR – partial remission, NR – no remission*
from the source axis. The length of the reference isodose encompassed the Planning Target Length as closely as possible. PLATO brachytherapy planning system was used. For PDR brachytherapy microselectron PDR (Nucletron®) unit was applied with radioactive 192Ir (Iridium) source and 10 Ci (Curie) nominal activity. French 5 intraluminal catheter were attached to a remote afterloading machine providing PDR-BT pulses.

Forty-four patients were treated exclusively with PDR-BT, 4 with PDR-BT and concomitant chemotherapy or surgery (palliative). PDR-BT was the method of choice because of relative good performance status of all patients and reduction of overall treatment time [19]. Most of patients (38/48, 79%) received 25 pulses of 0.8 Gy hourly and the total dose of 20 Gy. In 8 cases PDR was repeated with 1 week interval because of rapid regression of jaundice and satisfied relief of pain.

**Trans-hepatic technique**

Nowadays, two techniques are commonly used in brachytherapy treatment of advanced bile duct carcinoma: trans-duodenal endoscopic technique and trans-hepatic procedure. Percutaneous trans-hepatic technique allows the passage of a catheter through the structure. A transhepatic cholangiogram is initially performed under fluoroscopic control; patients after a surgical procedure, the cholangiogram can be performed through the T-tube. After identification of obstruction site, a flexible catheter is inserted into the biliary tree to evaluate appropriate depth, under fluoroscopic control. To avoid the catheter changing the procedure, 10 French catheter was used, which could also be applied as a conduit to place brachytherapy catheter, therefore facilitating the procedure for medical team and a patient. A dual-lumen catheter or two separate catheters can be inserted in another technique, one for lodging the radioactive sources and the other for bile drainage. However, extra care must be taken to maintain biliary drainage. Otherwise, the patient will develop pain and fever as a result of obstructive cholangiolitis. The catheter is sutured into the skin.

**Results**

All patients had an unfavorable prognosis. In all 48 cases trans-hepatic technique allowed the correct insertion of BT catheter and save use of PDR-BT. Complications connected with technique were not observed. In all cases trans-hepatic technique permitted insertion of BT catheter into bile duct and safe application of PDR-BT. In 19 out of 29 (65.5%) of bile duct cancer cases and in 10 out of 19 (52.6%) of pancreas cancer cases, clinical improvement (decrease of jaundice) was noted in first control after 4 weeks. Median overall survival time (OS) for bile ducts cancer patients was 11.2 months and for pancreas cancer patients – 5.2 months. In 12 cases lack of remission was reported, in 6 cases – worsening of condition. In one case treatment was interrupted due to rapid deterioration of performance status. Decline in performance status was observed during brachytherapy in one patient with liver metastasis, which was not the reason for finishing the treatment, and in another case, after 4 weeks a massive progression to the liver was noted. Longest survival time carried out 60 months (bile duct...
cancer patient) and 11 months in case of pancreas cancer. 7 patients with bile duct cancer survive longer than 12 months. Due to small amount of patients in this pilot study, these results do not reach the level of significance.

Discussion

The vast majority of bile duct and pancreas tumors are diagnosed late with upper abdominal discomfort, general malaise, fever, anorexia and jaundice. Bile duct tumors are much less common than hepatocellular carcinoma and the etiology is unknown. Prognosis is poor and related to the extent of spread within the liver and regional lymph nodes and to the site of tumor [1]. Most of bile duct and pancreas cancers patients are treated palliatively.

The role of radiotherapy in this disease has been the subject of a long debate. Since the majority of patients die from uncontrolled locoregional disease, postoperative adjuvant radiotherapy has been used at several centers [4, 5, 20-21]. Until the mid 70ies, cholangiocarcinoma was considered to be radio-resistant. There were several reasons for this. Firstly, cholangiocarcinomas were considered intrinsically radio-resistant. Secondly, the technical problem of delivering radical radiation without damaging the intestine or liver was quite alarming. Before the introduction of radiological techniques for decompression of the obstructed biliary tract, most of patients were in such poor general condition that the treatment was not attempted. However, during the second half of the 70s, a few published reports indicated that radiotherapy could provide useful palliation and possibly improve survival for patients with cholangiocarcinoma. Several reports indicated that radiotherapy could provide useful palliation [14, 21]. In some cases external beam radiotherapy (EBRT) was thought to contribute to prolongation of survival [16, 23, 24]. Kopelson et al. reported that obstructive jaundice was relieved in 7 out of 8 patients treated for extrahepatic bile duct cancer with EBRT [22]. Hanna and Rider retrospectively reviewed 17 patients treated at the Princess Margaret Hospital in Toronto [20]. Fourteen patients who received radiotherapy had a mean survival of 12.3 months compared with 1.1 months of no radiotherapy group. In 1980, intraluminal brachytherapy for cholangiocarcinoma was introduced and induced considerable enthusiasm. Since most cholangiocarcinomas remain localized until a relatively late stage in their natural history, the ability to provide a high radiation dose to the tumor without endanger adjacent radiosensitive structures was attractive. The ease of placing the radioactive source via transhepatic catheters was a further spur to develop the technique. The increasing use of percutaneous transhepatic catheters by interventional radiologists provided indications for applying brachytherapy treatment. 192Ir wire can be inserted through these catheters. Such treatment was also applied by insertion of 192Ir wire through endoscope and placing a nasobiliary catheter [26]. Several centers have reported their results of intraluminal brachytherapy alone or in combination with EBRT [5, 11, 13, 17, 20-29]. It was difficult to separate the effect of biliary decompression on survival from that type of radiotherapy. The median survival for this procedure is 10 to 12 months and approximately 15% of patients survive for the next 2 years or more. Late effects of treatment are often difficult to distinguished due to recurrence or blockage of the biliary drain. Blockage of the stent or biliary drain is fairly common and the stent may need to be replaced every 3 to 4 months. Others have reported improvements in survival using this technique.

In 1984 a protocol for treating advanced cholangiocarcinoma using both EBRT and BT was introduced at the Hammersmith Hospital [30]. An accelerated split course of EBRT was used. This allowed the reduction of overall treatment time (4 compared with 5 weeks for conventional fractionation) without concomitant decrease in total radiation dose. Reduction of overall treatment time reduce the opportunity for tumor cell repopulation during treatment and, therefore, it increase the probability of tumor control for a given dose. The fraction size used in the accelerated EBRT reported regimen was either 2.25 Gy (pre 1989) or 2.75 Gy. The latter was less well tolerated with smaller amount of patients completing the prescribed course of treatment. Large fraction sizes were associated with late radiation morbidity. Montemaggi et al. [18] evaluated intraluminal brachytherapy in patients with extrahaepatic bile duct or pancreatic cancers. Thirty-one patients with unresectable extrahaepatic bile duct (n = 18) or pancreatic (n = 13) cancer received BT exclusively or as part of a definitive treatment regimen. ILBT was performed with transhepatic percutaneous drainage in 4 patients and with endoscopic retrograde cholangiopancreatography in 27 cases. Fourteen patients with no metastases, in Eastern Cooperative Oncology Group performance score with ≤ 2, and good hematologic parameters received combined modality treatment: 30 Gy BT and 45 Gy external-beam radiation therapy with continuous infusion of fluorouracil. Seventeen patients underwent 50 Gy ILBT alone for palliation. Jaundice was palliated in all 29 patients; pain in 11 out of 13 patients. The survival rate in patients with extrahaepatic bile duct cancer was 62% (5 out of 8) at second year of combined modality treatment. No patient with pancreatic cancer lived for longer than 2 years. It was concluded that BT is an effective palliative treatment of unresectable extrahaepatic bile duct and pancreatic cancers. Results suggest possible “healing” character in specific clinical settings when properly integrated with other treatments.

Karani et al. treated 30 patients with hilar cholangiocarcinoma by BT alone. Mean survival was 16.8 months and this was compared favorably with a mean survival of 8.5 months for patients treated with palliative surgery or stenting only at the same institution [31].

Fields et al. [5] found that eight patients receiving BT in addition to EBRT had a median survival of 15 months compared to 7 months with those receiving EBRT only. Seven patients were treated at Stanford University Medical Center using a combination of EBRT (50.0 Gy) and BT (31.0 Gy to 60.0 Gy) [15]. The mean survival was 15.4 months. Fritz et al. [14] reported treatment of 30 patients with extrahaepatic bile duct cancers using EBRT (30.0 to 45.0 Gy) and BT (20.0 to 45.0 Gy). The median survival was 10 months. Mahe et al. [27] treated 51 patients; 25 received...
EBRT, 8 – BT, and 17 – combined EBRT with BT. Median survival for the whole group was 12 months. Radiotherapy was associated with significant prolongation of survival in patients undergoing palliative stenting; actuarial 1-year survival of those receiving radiotherapy was 38% compared to 9% of patients with no radiotherapy applied. In none of these series patients were randomized in order to receive radiotherapy or not, since the real efficacy of treatment was difficult to estimate. Shim et al. [32] treated 31 patients with inoperable carcinoma of the extrahepatic bile ducts with a combination of EBRT and BT. Although locoregional recurrence was the most common pattern of failure in both groups, no statistically significant difference was found in the recurrence rates between those who receive and did not receive BT (53% for Group 1 vs. 36% for Group 2; p > 0.05).

However, a prolongation of the median time to tumor recurrence was observed in Group 2 (5 months for Group 1 vs. 9 months for Group 2; p = 0.06). With a median follow-up of 12 months, the overall actuarial 2-year survival rate for Group 2 patients was significantly better than that for Group 1 patients (0% for Group 1 vs. 21% for Group 2; p = 0.015). Schleicher et al. [33] treated 30 patients for extrahepatic proximal bile duct cancer with schedule consisted of EBRT (median dose 30 Gy) and a HDR-BT boost (median dose 40 Gy) delivered in four or five fractions. Fifteen patients in the brachytherapy and nine patients in the non-brachytherapy group received additional low-dose chemotherapy with 5-fluorouracil. The brachytherapy boost dose improved the effect of EBRT by increasing survival from a median of 3.9 months in the non-brachytherapy group to 9.1 months in the brachytherapy group. The effect was obvious in patients receiving brachytherapy dose above 30 Gy, and in those without jaundice at the beginning of radiotherapy (p < 0.05). Takamura et al. [34] treated 93 patients with non-resectable extrahepatic bile duct carcinoma with definitive radiotherapy. The dose of external beam radiotherapy was 50 Gy in 25 fractions. Low-dose-rate of 192Ir was delivered at a dose of 27-50 Gy (mean 39.2). An expandable metallic endoprosthesis was used to establish an internal bile passage. The median survival was 12 months, with a 1, 3, and 5-year actuarial survival rate of 50%, 10%, and 4%, respectively. Tumor length, hepatic invasion, and distant metastasis significantly affected the survival. Summarized data from published literature are presented in Table 3.

Gastrointestinal bleeding is a complication reported by other authors. Johnson et al. [15] found that 11 patients treated for a variety of malignant causes of biliary obstruction by EBRT and BT with three of them developed upper gastrointestinal bleeding from enteritis or frank duodenal ulceration at 4 weeks, 4 months and 7.5 months. The risk of gastrointestinal bleeding may be dose-dependent. Fritz et al. [14] reported the frequency of radiogenic ulcers in 25% of patients receiving BT doses of 37.5 to 40.0 Gy and in 7.6% in those receiving 20.0 Gy. Buskirk et al. [3] found that 4 out of 20 patients receiving radiotherapy for either gall bladder cancer or cholangiocarcinoma developed gastrointestinal bleeding. Three had received doses greater than 55.0 Gy to stomach or duodenum. Intestinal obstruction following radiotherapy for cholangiocarcinoma has also been reported [38].

These studies were neither randomized nor controlled, therefore it was not possible to make a definitive statement about the efficacy of this technique. The contribution of BT to survival in cholangiocarcinoma is still uncertain. A randomized controlled trial would require large numbers of patients in order to demonstrate a subtle effect.

However, it could be difficult to accumulate a sufficient number of cases since cholangiocarcinoma is rare and many patients are treated surgically or are considered unsuitable for radiotherapy for a variety of reasons. Even those patients who are submitted to radiotherapy are the heterogeneous group, having received a variety of different treatments before attendance at oncology clinic. One potential benefit of BT is that it may prevent encroachment of tumor into the stent and the necessity for frequent stent replacements. However, stent occlusion itself has become less of a problem since the introduction of self-expanding metal stents [12].

The efficacy of BT is still uncertain and controlled, prospective studies are required to address this aspect of radio-therapeutic management of cholangiocarcinoma. In order to examine whether the results of radiotherapy for cholangiocarcinoma can be improved by the use of synchronous chemotherapy, our current protocol consists of combined chemotherapy (5-fluorouracil) and EBRT. This is a strategy that has recently been reported as being well tolerated in a Phase I Eastern Cooperative Oncology Group Trial [39].

In our opinion indications for brachytherapy should include all malignant structures of bile duct which can be cannulated. Patients should be fit enough for the procedure and reviewed to confirm that they are not suitable for resection or sole radical external beam radiation therapy. In patients who are in reasonably good physical condition, the usual procedure is to combine bile duct brachytherapy with external beam radiation. 30 to 40 Gy are delivered to a volume which encompasses the porta hepatitis, the common bile duct and regional nodes. Careful and individual evaluation of this therapy is needed. HDR brachytherapy permits irradiation on out-patient basis what makes the treatment more accessible. In turn of relatively good prognosis PDR (LDR) brachytherapy should be taken into consideration. For LDR or PDR irradiation, the dose of 15 to 20 Gy can be given at 1 cm distance from the centre of the source axis at a dose rate of 0.6 to 0.8 Gy/hr. This is combined with the prior external beam radiation. For HDR brachytherapy, 5 Gy per fraction is prescribed at 1 cm distance from the centre of the catheter and can be applied once or twice daily with a minimum of 6 hours interval between treatments. A total dose of 20 Gy in 4 fractions over 2 or 4 days can be applied if combined with external beam radiation. If the patient is being treated by brachytherapy alone, 30 Gy in 6 fractions over 3 or 6 days may be given [1].

No information about using trans-hepatic PDR-BT in treatment of advanced bile duct or pancreas cancer were found. Our decision to use this technique was based on earlier results of LDR brachytherapy.
PDR brachytherapy in treatment of bile duct and pancreas cancer

Table 3. Results of palliative EBRT and BT – literature review. Regarding the outcome with different treatment schedules, the very inhomogeneous patient groups should be taken into account

| Author              | Number of patients | EBRT, dose (Gy) | BT, number of fractions fraction dose, method | Results of treatment | Statistical analysis |
|---------------------|--------------------|----------------|---------------------------------------------|----------------------|----------------------|
| Shin et al. [32]    | 27                 | 36-55 (median 50.4) | 1. No 2. 3 x 5 Gy HDR                       | 1. RR – 53% 2. RR – 36% 1. MDC – 5 months 2. MDC – 9 months 1. OS (2 y) – 0% 2. OS (2 y) – 21% | RR – p > 0.05 MDC – p = 0.06 OS – p = 0.015 |
| Schleicher et al. [33] | 30               | median 30        | 1. No 2. median 40 Gy, 4-5 fractions HDR    | 1. OS – 3.9 months 2. OS – 9.1 months | OS – p < 0.05 |
| Eschelmann et al. [35] | 11                | 25-56           | 15-31 Gy HDR                                | MS – 22.6 months     | n.d.                 |
| Kamada et al. [36]  | 145               | 1.40-50 2.40-50 | 1. No 2. 25 Gy LDR                         | 1. MS – 4.3 months 2. MS – 9.3 months | n.d.                 |
| Gonzalez et al. [37] | 38                | 1.44-68 2.33-47 | 1. No 2. 22-25 Gy LDR                      | 1. MS – 10.5 months 2. MS – 10.5 months | n.s.                |
| Takamura et al. [34] | 93                | 50             | 27-50 Gy (median 39.2) HDR                  | MS – 12 months       | n.d.                 |

Note: in papers of Shin [32], Schleicher [33], Kamada [36] and Gonzalez Gonzalez [37] two different groups are compared

EBRT – external beam radiotherapy, BT – brachytherapy, HDR – high dose rate brachytherapy, LDR – low dose rate brachytherapy, RR – recurrence rate, MDC – median time to tumor recurrence, OS – overall survival, MS – median survival

n.d. – no data, n.s. – no significant

(PDR-BT) treatment is a new brachytherapy modality that combines physical advantages of high-dose-rate (HDR) technology (isodose optimization, planning flexibility, radiation safety) with radiobiological advantages of low-dose-rate (LDR) brachytherapy (repair advantages) [6]. PDR-BT uses a single stepping source of 15-37 GBq (0.5-1Ci) of 192Iridium. This produces treatment dose rates of up to 3 Gy per hour which can be utilized (pulsed) each hour, 24 pulses per day. PDR – BT consists of using stronger radiation source than for LDR brachytherapy and is applied in a series of short exposures of 10 to 30 minutes in every hour to approximately the same total dose in the same overall as with the LDR. Although low-dose-rate BT (LDR) and high-dose-rate BT (HDR) has been applied successfully for a long time in the treatment of bile duct cancer, recent interest in PDR brachytherapy has gradually expanded its application to the management of breast and head and neck cancer, as well as bile duct cancer. From a therapeutic point of view, it seems that PDR-BT is a safe modality for treatment of bile duct cancer. Although this study has an inherent flaw because of retrospective analysis and insufficient amount of patients, our observations suggest that an approach of using PDR-BT has a good outcome in case of non-operable carcinoma of the extrahepatic bile ducts or non-operable advanced pancreas cancer.

We found that PDR – BT for cholangiocarcinoma was feasible. A new percutaneous trans-hepatic technique allowed to perform whole treatment (insertion of catheter, planning, PDR brachytherapy) in one day. Until recently, however, no conclusive data were available regarding the optimal numbers and size of the fractionation and the total radiation dose in BT for malignant bile duct cancer. This is why we’ve decided to use similar doses like in LDR brachytherapy. Achieved palliative effect was satisfactory. We believe that in patients disqualified for radical treatment, one-day PDR-BT allows to achieve possible palliative effect which earlier was achieved pharmacologically only in some cases. We think that in a group of patients, especially with recurrence in stents, PDR-BT is a reasonable alternative. In most of cases, satisfied palliative effect was achieved, however more noticeable in bile duct cancer patients then in pancreas cancer patients. Although our technique provided encouraging results with minimal side effects, additional investigation is needed to determine the appropriate time-dose fractionation scheme through systematic clinical trials.

References
1. Gerbaulet A, Potter R, Mazeron J-J et al. (editors). The GEC ESTRO Handbook of Brachytherapy. ESTRO, Brussels 2002.
2. Baer HU, Stain SC, Dennison AR et al. Improvements in survival by aggressive resections of hilar cholangiocarcinoma. Ann Surg 1995; 221: 20-27.
3. Buskirk SJ, Gunderson LL, Adson MA et al. Analysis of failure following curative irradiation of gallbladder and extrhepatic bile duct carcinoma. Int J Radiat Oncol Biol Phys 1984; 10: 2033-2035.
4. Cameron JL, Pitt HA, Zinner MJ et al. Management of proximal cholangiocarcinomas by surgical resection and radiotherapy. Ann Surg 1990; 159: 91-97.
5. Fields JN, Emami B. Carcinoma of the extrahepatic biliary system – results of primary and adjuvant radiotherapy. Int J Radiat Oncol Biol Phys 1987; 13: 331-338.

6. Skowronek J, Sower A, Skrzypawiec P. Intraluminal Pulsed Dose Rate (PDR) brachytherapy and trans-hepatic technique in treatment of locally advanced bile duct cancer – preliminary assessment. Rep Pract Radiat Oncol 2007; 2: 125–133.

7. Montemaggi P, Costamagna G, Dobellower RR et al. Intraluminal brachytherapy (ILBT) in the treatment of pancreas and bile duct carcinoma. Int J Radiat Oncol Biol Phys 1995; 32: 437-443.

8. Veeze-Kuijpers B, Meerwaltd JH, Lameris JS et al. The role of radiotherapy in the treatment of bile duct carcinoma. Int J Radiat Oncol Biol Phys 1990; 18: 63-67.

9. Hadjis NS, Blenkharn JI, Alexander N et al. Outcome of radical surgery in hilar cholangiocarcinoma. Surgery 1990; 107: 597-604.

10. Nagorney DM, Donohue JH, Farrell MB et al. Outcomes after curative resections of cholangiocarcinoma. Arch Surg 1993; 128: 871-879.

11. Adam A, Chetty N, Roddie M et al. Self-expandable stainless steel endoprosthesis for treatment of malignant bile duct obstruction. Am J Radiol 1991; 156: 321-325.

12. Davidis HRE, Groen AK, Rausw EAJ et al. Randomized trial of self-expanding metal stents versus polyethylene stents for distal malignant biliary obstruction. Lancet 1992; 340: 1488-1492.

13. Foo ML, Gunderson LL, Bender CE et al. External Radiation Therapy And Transcatheter Iridium In The Treatment Of Extrahepatic Bile Duct Carcinoma. Int J Radiat Oncol Biol Phys 1997; 39: 929-933.

14. Fritz E, Brambs H-J, Schraube E et al. Combined external beam radiotherapy and intraluminal high dose rate brachytherapy on bile duct carcinomas. Int J Radiat Oncol Biol Phys 1994; 29: 855-861.

15. Johnson DW, Safai C, Goffinet DR. Malignant obstructive jaundice: treatment with external-beam and intracavitary radiotherapy. Int J Radiat Oncol Biol Phys 1985; 11: 411-416.

16. Fogel TD, Weissberg JB. The role of radiation therapy in carcinoma of the extrahepatic bile ducts. Int J Radiat Oncol Biol Phys 1984; 10: 2251-2258.

17. Gonzalez DG, Gerard JR, Maners AW et al. Results of radiation therapy in carcinoma of the proximal bile duct (Klatskin tumor.). Sere Liver Dis 1990; 10: 131-141.

18. Montemaggi P, Morganti AG, Dobelbower Jr RR et al. Role of Intraluminal Brachytherapy In Extrahepatic Bile Duct And Pancreatic Cancers: Is It Just for Palliation? Radiology 1996; 199: 861-866.

19. Skowronek J, Piotrowski T, Zwierzchowski G. PDR brachytherapy – describing of a method and a review of clinical applications. Rep Pract Radiat Radioth 2001; 4: 197-202.

20. Hanna SS, Rider WD. Carcinoma of the gallbladder or extrahepatic bile ducts: the role of radiotherapy. Can Med Assoc J 1978; 118: 59-61.

21. Hayes JK, Sapozink MD, Miller FJ. Definitive radiation therapy in bile duct carcinoma. Int J Radiat Oncol Biol Phys 1988; 15: 735-744.

22. Kopelson H, Harisadiis L, Trettet R et al. The role of radiation therapy in cancer of the extra-hepatic biliary system: an analysis of 13 patients and a review of the literature of the effectiveness of surgery, chemotherapy and radiotherapy. Int J Radiat Oncol Biol Phys 1977; 2: 883-894.

23. Minsky BD, Wesson MF, Armstrong JG et al. Combined modality therapy of extrahepatic biliary system cancer. Int J Radiat Oncol Biol Phys 1990; 18: 1157-1163.

24. Verbeek EC, Van Leeuwen DJ, Van Der Heyde MN et al. Does additive radiotherapy after hilar resection improve survival of cholangiocarcinoma? An analysis in sixty four patients. Ann Chirurgie 1991; 45: 350-354.

25. Pilepich MJ, Lambert RM. Radiotherapy of carcinomas of the extrahepatic biliary system. Radiology 1978; 127: 767-770.

26. Levitt MD, Laurence BH, Cameron F et al. Transpapillary iridium-192 wire in the treatment of malignant bile duct obstruction. Gut 1988; 29: 149-152.

27. Mahe M, Romestaing R, Talon B et al. Radiation therapy in extrahepatic bile duct carcinoma. Radiother Oncol 1991; 21: 121-127.

28. Molt R, Hopfian S, Watson RC et al. Intraluminal radiation therapy in the management of malignant biliary obstruction. Cancer 1986; 57: 536-544.

29. Mornex F, Ardiel J, Bret E et al. Radiotherapy of high bile duct carcinoma using transcatheter iridium 192 wire. Cancer 1984; 54: 2069-2073.

30. Peters LJ, Ang KK. Accelerated fractionation. In: Withers HR, Peters LJ (editors). Innovations in Radiation Oncology. Springer Verlag, Berlin: 231-238.

31. Karani J, Fletcher M, Brinkley D et al. Internal biliary drainage and local radiotherapy with iridium-192 wire in treatment of hilar cholangiocarcinoma. Clin Radiol 1985; 36: 603-606.

32. Shin HS, Seong J, Kim WC et al. Combination of external beam irradiation and high-dose-rate intraluminal brachytherapy for inoperable carcinoma of the extrahepatic bile ducts. Int J Radiat Oncol Biol Phys 2003; 57: 105-112.

33. Schleicher UM, Staatz G, Alzen G et al. Combined External Beam and Intraluminal Radiotherapy for Irresectable Klatskin Tumors. Strahlenther Onkol 2002; 178: 682-687.

34. Takamura A, Saio T, Kamada T et al. Intraluminal low-dose-rate 192Ir brachytherapy combined with external beam radiotherapy and biliary stenting for unresectable extrahepatic bile duct carcinoma. Int J Radiat Oncol Biol Phys 2003; 57: 1357-1365.

35. Eschelman DJ, Shapiro MJ, Bonn J et al. Malignant biliary duct obstruction: long-term experience with Gianturco stents and combined-modality radiation therapy. Radiology 1996; 200: 717-724.

36. Kamada T, Saio H, Takamura A et al. The role of radiotherapy in the management of extrahepatic bile duct cancer: an analysis of 145 consecutive patients treated with intraluminal and/or external beam radiotherapy. Int J Radiat Oncol Biol Phys 1996; 34: 767-774.

37. Gonzalez Gonzalez D, Gouma DJ, Rauws EAJ et al. Role of radiotherapy, in particular intraluminal brachytherapy, in the treatment of proximal bile duct carcinoma. Ann Oncol 1999; 10: 215-220.

38. Mogavero GT, Jones B, Cameron J et al. Gastric and duodenal obstruction in patients with cholangiocarcinoma in the porta hepatitis: increased prevalence after radiation therapy. Am J Gastroenterol 1992; 159: 1001-1003.

39. Whittington R, Neuberg D, Tester WJ et al. Protracted intravenous fluorouracil infusion with radiation therapy in the management of localized pancreaticobiliary carcinoma: a Phase I Eastern Cooperative Oncology Group Trial. J Clin Oncol 1995; 13: 227-232.