Role of radiotherapy, in particular intraluminal brachytherapy, in the treatment of proximal bile duct carcinoma

D. González González¹, D.J. Gouma², E.A.J. Rauws³, T.M. van Gulik², A. Bosma⁴ & C. Koedooder¹
Departments of ¹Radiation Oncology, ²Surgery, ³Gastroenterology, ⁴Pathology, University of Amsterdam, Academic Medical Centre, Amsterdam, the Netherlands.

Summary

Purpose: To perform an analysis of the results obtained with radiotherapy in patients with either resectable or unresectable cholangiocarcinoma of the proximal bile ducts. Emphasis will be paid to analyse the role of radiotherapy, particularly brachytherapy.

Patients and methods: Between 1985 and 1997, 109 patients received radiotherapy. In 71 patients (group I) tumor resection was combined with postoperative irradiation in 52 patients and pre- plus post-operative irradiation in 19 patients. Among this group, 41 patients had a boost of 10 Gy to the biliodigestive anastomosis using intraluminal brachytherapy. Median total dose was between 50–55 Gy. The other 38 patients (group II) had an unresectable tumor at laparotomy (16 patients) or were considered primary unresectable because locoregional tumor extension (22 patients). Brachytherapy boost through a nasobiliary approach was given to 19 patients (22-25 Gy). The median total dose varied between 60 to 68 Gy. Mean follow-up was 25 ± 23 months.

Results: In group I, the survival rates at 1, 3, and 5 year were 84%, 37%, and 24%, respectively. Median survival was 24 months. Sixteen patients did live longer than 4 years. Analysis of prognostic factors among resected patients showed the tumor differentiation grade, microscopically involved margins other than the upper (hepatic) and lower (choledocus) resection parameters analyzed, only the total dose had influence on margins, and elevated alkaline phosphatase as factors which significantly influence survival. From the different radiotherapy prognosis, patients receiving a total dose above 55 Gy had a shorter survival. It is important to note that patients receiving brachytherapy boost did not have a better survival than patients treated with external beam irradiation alone. Preoperative radiotherapy did not have impact on survival but recurrences in the surgical scars were not observed as compared to 15% recurrences if preoperative radiotherapy was not given. In group II the median survival was 10.4 months. Survival rates at 1 and 2 years were 43% and 10%, respectively. The only significant prognostic factor found was if unresectability was defined primarily or during laparotomy. As it was the case in group I, brachytherapy boost did not have influence on prognosis as compared to external beam irradiation alone. Observed late complications consisted of duodenal stenosis, upper digestive tract bleeding and cholangitis. Probably these complications were not only attributable to radiotherapy, as tumor relapse was also present in the majority of the cases.

Conclusions: The role of radiotherapy either as adjuvant or as primary treatment remains to be demonstrated in prospective randomized studies. From our results, it seems that high radiation doses could be dangerous and could detriment prognosis. Brachytherapy boost was not superior to treatment with external beam irradiation alone.

Key words: cholangiocarcinoma, intraluminal brachytherapy, radiotherapy, surgery

Introduction

Surgical resection continues to be the only treatment offering a chance of long-term survival to patients with cholangiocarcinoma of the hepatic hilus and common bile duct. After surgical tumor resection, 5-year survival rates in recently reported series vary between 20%-50% and median survival between 15-40 months [1-4]. The value of either neo-adjuvant or adjuvant treatment has never been studied in well-designed prospective randomized studies. Postoperative irradiation has been administered in several institutions on the basis of a low occurrence of microscopic free margins at the pathological analysis of the surgical specimen. However, in a recent report, the group of the Johns Hopkins Hospital concluded that postoperative radiotherapy did not add any benefit to surgery alone [5]. Unfortunately, at the moment of diagnosis only 20%-40% of patients are candidates for tumor resection and during surgery about 40% of the patients will have a resectable tumor [1; 6; 7]. In the non-resected group, either percutaneous or endoscopic drainage, surgical bypass or placing of a stent during surgery will be performed for treatment of obstructive jaundice and pruritus. The prognosis of this group of patients is very poor, median survival between 4-11 months [8-10]. Particularly intraluminal radiotherapy is gaining interest as palliative treatment of patients with unresectable tumors [11-14]. Our experience in the treatment of extrahepatic bile duct cancer has already been reported [15-18]. In the present paper the treatment results will be analyzed, particularly focussing on aspects dealing with either external beam irradiation or intraluminal brachytherapy. The literature on these topics will also be reviewed.

Patients and methods

Patients
Between 1985 and 1995, 109 patients received radiotherapy at the Radiation Oncology Department of the Academic Medical Centre in Amsterdam. All tumors were located in the hepatic ducts, confluence or common bile duct (CBD). Patients with tumors in the gallbladder and periampullary region were not included in the analysis. In 71 patients
(group I), tumor resection was combined with either postoperative irradiation (52 patients) or preoperative and postoperative irradiation (19 patients). Thirty-eight patients (group II) were unresectable during surgery or were considered to be unresectable during surgery or were considered to be unresectable due to the postoperative CT-scan in treatment position. Radiation fields, usually 3 or 4, were used encompassing a mean volume of 524 cm³ ± 250. Radiation was applied using 10 MV photons energy. CT-scan based computer planning dosimetry was performed in all patients excluding as much as possible high doses in the liver, small bowel and kidneys. It was not the intention to include in the irradiation fields all lymphatic chains in the vicinity of the hepatic hilus, head of the pancreas and small curvature of the stomach. The administered dose was 45 Gy ± 3 Gy in 41 patients who received additional brachytherapy. This dose was given in 3 fractions per day of 1.1 Gy, 4 hours interval between fractions, 5 days per week, 18 days overall time. The other 30 patients were exclusively treated with external beam radiation, mean dose 50 Gy ± 7 Gy given in 3 fractions per day of 1.67 Gy. No anticoagulation or heparin receptor block medication during radiotherapy and 6 months thereafter. Patients with confirmed diagnosis were treated with external beam radiation, mean dose 50 Gy ± 7 Gy given in 3 fractions per day of 1.1 Gy, 4 hours interval between fractions, 5 days per week, 18 days overall time. The other 30 patients were exclusively treated with external beam radiation, mean dose 50 Gy ± 7 Gy given in 3 fractions per day of 1.67 Gy. No anticoagulation or heparin receptor block medication during radiotherapy and 6 months thereafter. Patients who underwent tumor resection. Only variables which had p-values ± 0.10 in the univariate analysis were entered in the Cox regression analysis.

Results
The survival rates at 1, 3, and 5 year in the whole group of 109 patients were 75%, 33%, and 23%, respectively. Median survival was 21 months.

Group I (resection + radiotherapy)
The survival rates at 1, 3 and 5 year were 84%, 37% and 24%, respectively. Median survival was 24 months. Patients 50 year old or younger had a favorable prognosis as also it the case for well/moderate differentiated tumors. The survival rates at 1, 3 and 5 year were 75%, 33%, and 23%, respectively. Median survival was 21 months.

Group II (unresectable, radiotherapy + biliary drainage): Within group II, non-resected, 19 patients received brachytherapy boost. Under endoscopic control one or two nasobiliary probes were placed at the tumor site. In patients with tumor invading both hepatic ducts not always was possible to cross the stenotic ducts with the catheter so that a part of the tumor probably received a low boost dose. Simulator and planning procedures were similar as in group I. The mean dose at 1 cm from the sources was 21 Gy ± 6 at a mean dose rate of 73 cGy/hour.

Statistics
Univariate analysis of possible prognostic factors related to patient, tumor and treatment characteristics was performed using Kaplan-Meier survival curves and the log-rank significance test for comparison of survival between groups. Patients were censored, as they were alive without clinical evidence of disease at the moment of the analysis. All other patients were considered as events either they died from tumor progression or were alive with known progressive disease at the moment of the analysis. A forward stepwise Cox regression analysis was also performed in the group of 71 patients who underwent tumor resection. Only variables which had p-values ± 0.10 in the univariate analysis were entered in the Cox regression analysis.

Results
The survival rates at 1, 3, and 5 year in the whole group of 109 patients were 75%, 33%, and 23%, respectively. Median survival was 21 months.

Group I (resection + radiotherapy)
The survival rates at 1, 3 and 5 year were 84%, 37% and 24%, respectively. Median survival was 24 months. Patients 50 year old or younger had a favorable prognosis as also it the case for well/moderate differentiated tumors. The survival rates at 1, 3 and 5 year were 75%, 33%, and 23%, respectively. Median survival was 21 months.

Group II (unresectable, radiotherapy + biliary drainage): Within group II, non-resected, 19 patients received brachytherapy boost. Under endoscopic control one or two nasobiliary probes were placed at the tumor site. In patients with tumor invading both hepatic ducts not always was possible to cross the stenotic ducts with the catheter so that a part of the tumor probably received a low boost dose. Simulator and planning procedures were similar as in group I. The mean dose at 1 cm from the sources was 21 Gy ± 6 at a mean dose rate of 73 cGy/hour.

Statistics
Univariate analysis of possible prognostic factors related to patient, tumor and treatment characteristics was performed using Kaplan-Meier survival curves and the log-rank significance test for comparison of survival between groups. Patients were censored, as they were alive without clinical evidence of disease at the moment of the analysis. All other patients were considered as events either they died from tumor progression or were alive with known progressive disease at the moment of the analysis. A forward stepwise Cox regression analysis was also performed in the group of 71 patients who underwent tumor resection. Only variables which had p-values ± 0.10 in the univariate analysis were entered in the Cox regression analysis.

Results
The survival rates at 1, 3, and 5 year in the whole group of 109 patients were 75%, 33%, and 23%, respectively. Median survival was 21 months.
sources (≤ 4 cm versus >4 cm) did not affect the survival. The groups were, however, too small to draw definitive conclusions.

**Group II (unresectable, radiotherapy + biliary drainage)**

The median disease free survival of 38 non-resected patients was 10.5 months. Survival rates at 1 and 2 years were 43% and 10%, respectively (Fig. 1). It is noteworthy that patients with an unresectable tumor at laparotomy had a significant better prognosis that patient with a tumor considered primary unresectable. Probably related to this fact is that patients treated with preoperative radiotherapy also had a 17/01/99 favourable prognosis. The group of patients receiving brachytherapy as a part of the radiation treatment showed a trend (p=0.06) to live shorter than patients treated exclusively with external beam irradiation. In groups I and II, a total of 60 patients received brachytherapy. Median survival of these patients was 16 months as compared to 22 months in the 49 patients without brachytherapy, but this survival difference was not significant (p=0.29). Among the 60 patients receiving brachytherapy, dose rate at 1 cm (>65cGy/hour versus > 65 cGy/hour), and length of the sources (≤ 4 cm versus >4 cm) did not have any significant influence on prognosis.

**Cox Regression Analysis**

A Cox regression forward stepwise analysis was done in the group of patients undergoing tumor resection. Age (≤ 50 versus > 50 year old), dissection margins (negative versus positive), type of surgery (resection alone versus resection plus liver lobectomy), differentiation grade (good/moderate versus poorly differentiated), alkaline phosphatase pre-radiotherapy value (≤ 120 versus > 120 mmol/l), and total radiation dose (≤ 55 Gy versus >55 Gy), were entered in the analysis as categorical covariates. Only the pre-radiotherapy alkaline phosphatase value (p=0.02) and the differentiation grade (p=0.03) remained as independent variables.

**Complications**

In the entire group of 109 patients, acute complications attributable to the external beam irradiation were nausea and vomiting, requiring medication in 16% of the patients. Median weight before radiation was 63 kg ± 26 and the nadir weight during radiotherapy was 62 kg ± 29. No haematological complications were observed. In group I, planned irradiation was completed in all but 3 patients who stopped treatment because leakage of the temporary jejunostomy. In general, the jejunostomy was experienced by the majority of the patients as a considerable burden requiring a surgical intervention for closing. This procedure was abandoned in 1992 and at this time also brachytherapy was not further administered to surgically resected patients. Sixteen patients in group II had episodes of cholangitis, frequently transient, were observed in 21 out of 71 (30%) patients. In non-resected patients, obstructive syndrome is the overwhelming problem. In 29 out of 38 patients (76%), replacement of the endoprostheses was required to solve this problem.

**Discussion**

The results obtained in our study correspond quite well with other reported series, which have included patients with similar characteristics [14, 20, 36]. In a study by Kamada et al. [20] including 145 patients, median survival times of respectively, 21.5 months and 12.4 months were achieved in resected and unresectable patients receiving postoperative irradiation and radiation alone. Veeze-Kuipers et al. [14] reported a median survival of 15 months when postoperative irradiation was given to patients with R1 resections and 8 months if tumors were unresectable and treated with external plus intraluminal radiotherapy. Several authors agree that particularly in microscopic irradical resections, R1, postoperative radiotherapy improves long-term survival [21-23]. Cameron et al. [1] noted that radiotherapy extends survival in patients undergoing a palliative stenting but not in those undergoing resection. Pitt et al. [5], from the same institution, recently reported a similar survival in comparable patients treated with or without radiotherapy, but this study was non-randomised. Patients receiving brachytherapy in the series by Kamada et al. [20] showed significantly better survival than patients treated with external beam radiation alone. This was not the case in our experience. Other factors
such as type of surgery, age, sex, primary tumor location and lymph node involvement had no effect on survival. Klemmener et al. [4], in a series including 151 patients treated with surgery alone, identified tumor size, lymph node status, residual tumor (R0, R1, R2) and differentiation grade as factors with prognostic impact, in the univariate analysis. In the multivariate analysis, only lymph node status and residual tumor remained independent prognostic indicators. All our patients but two had R1 resections so that it is not possible to include this factor in the analysis. In our series, lymph node status had no effect on survival but the differentiation grading was one independent prognostic indicator in the multivariate analysis. Elevated alkaline phosphatase levels could reflect an irreversible hepatic damage or a suboptimal drainage, circumstances which may influence the long-term survival. In reported series where postoperative irradiation was given, the target volume is not always described. For external beam radiotherapy the target volume included the known tumor and/or the site with a high risk of relapse [20], the biliodigestive anastomosis [12], or the porta hepatis, common bile duct and regional lymph nodes (hepatoduodenal ligament and upper pancreaticoduodenal nodes) [14]. Our radiation portals only included the site of the anastomosis with a margin of 1.5-2 cm in all directions. We would advise to use limited fields in order to avoid toxicity. If brachytherapy is to be used as a boost, the sources are placed at the hepaticojejunostomy using the technique of percutaneous transhepatic cholangiography with drainage (PTCD) [24]. Our technique by creating a temporary jejunostomy was technically difficult to perform, the localization of the anastomosis was sometimes not possible and further frequent leakage problems were a burden for the patients. For these reasons and also because no survival improvement was observed in the patients treated with brachytherapy, actually we treat the patients with external radiotherapy alone. The administered radiation doses vary in the reported series and also depend on the use or not of brachytherapy. In general, a total dose of about 55 Gy is advised, 40 Gy - 45 Gy external beam and 10 Gy on the use or not of brachytherapy. In general, a total dose of 55 Gy is advised, 40 Gy - 45 Gy external beam and 10 Gy - 45 Gy high dose rate intraluminal brachytherapy specified at 1 cm from the sources [1; 5; 12; 14; 22]. In the adjuvant setting, we agree not to give total doses higher than 55 Gy. Our results showed that doses above this level could negatively influence survival. Because during the first year following resection implantation metastases in the surgical scars were observed in 15% [8/52] of patients [25], we decided in 1990 to administer a short course of preoperative irradiation, 3 times 3.5 Gy in 3 consecutive days, aiming at an impairment in the viability of tumor cells which are spilled during surgery. Since the introduction of this policy no recurrences in the surgical scar have been observed. Kamada et al. [20] reported on 9 patients treated with preoperative brachytherapy at doses between 40-90 Gy (specified at 0,5 cm from the sources) and they conclude that brachytherapy preoperatively was probably counterproductive, causing serious biliary bleeding. No other experiences with preoperative radiotherapy have been reported. Duodenal bleeding, duodenal obstruction and stenosis of the biliodigestive anastomosis causing disturbances in the biliary drainage are the more frequent complications following resection with or without radiotherapy. The rate of late complications, 9% duodenal obstruction, 8% upper digestive tract bleeding and 30% episodes of cholangitis correspond with other reported series [5; 12; 14; 22]. The possible contribution of radiotherapy to the origin of these complications cannot be established. Pitt et al. [5] found no differences in duodenal obstruction, small intestine problems, liver toxicity and occurrence of liver abscesses between radiated and non-radiated patients.

The prognosis of patients with unresectable tumors differs according to the approach used for the biliary drainage. Median survival is 2-7 months after percutaneous transhepatic endoprosthesis, 9-14 months after palliative biliary enteric bypass and 8-14 months following operative transtumoral stenting (see for a review reference [2]). In Table 1 a summary of results obtained in non-resected patients treated with biliary drainage plus intraluminal brachytherapy, either or not combined with external beam irradiation is presented. The differences in median survival between series are probably the result of patient selection as well as how the biliary drainage was achieved. The median survival of 17 months obtained in one of the first reported series [13] using a relatively low dose of intraluminal brachytherapy alone has not been emulated in more recent series. In general, it seems that if the biliary drainage is restored following a surgical procedure median survival is

<table>
<thead>
<tr>
<th>Author</th>
<th>No.</th>
<th>EBR (Gy)</th>
<th>ILR(Gy)</th>
<th>Median surv.</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lee et al.1997</td>
<td>15</td>
<td>45</td>
<td>28 (0.5 cm)</td>
<td>8.0 months</td>
<td>PTC</td>
</tr>
<tr>
<td>Ede et al.1989</td>
<td>14</td>
<td>45</td>
<td>60 (0.5 cm)</td>
<td>10.5 months</td>
<td>ERCP</td>
</tr>
<tr>
<td>v.d. Hul et al.1994</td>
<td>16</td>
<td>40</td>
<td>25 (1.0 cm)</td>
<td>13.8 months</td>
<td>Stenting</td>
</tr>
<tr>
<td>v.d. Hul et al.1994</td>
<td>5</td>
<td>40</td>
<td>25 (1.0 cm)</td>
<td>9.9 months</td>
<td>Biliary-enteric</td>
</tr>
<tr>
<td>Buskirk et al.1992</td>
<td>34</td>
<td>45</td>
<td>20 (0.5/1 cm)</td>
<td>12.0 months</td>
<td>Also IORT,sections</td>
</tr>
<tr>
<td>Bowling et al.1996</td>
<td>28</td>
<td>30</td>
<td>60 (0.5 cm)</td>
<td>10.0 months</td>
<td>ERCP; 3 Gy fract.</td>
</tr>
<tr>
<td>Kuvshinoff et al.1995</td>
<td>12</td>
<td>50</td>
<td>20 (1.0 cm)</td>
<td>9.0 months</td>
<td>Stenting</td>
</tr>
<tr>
<td>Karani et al.1985</td>
<td>30</td>
<td>45</td>
<td>45 (0.5 cm)</td>
<td>16.8 months</td>
<td>T-tube/U-tube;mean</td>
</tr>
<tr>
<td>Cameron et al.1990</td>
<td>25</td>
<td>50</td>
<td>20 (?)</td>
<td>&lt;12.0 months</td>
<td>Transhepatic stenting.</td>
</tr>
<tr>
<td>Pitt et al.1995</td>
<td>9</td>
<td>46</td>
<td>13 (?)</td>
<td>8.0 months</td>
<td>Transhepatic stenting</td>
</tr>
<tr>
<td>Veeze-Kuyipers et al.1990</td>
<td>31</td>
<td>40</td>
<td>15 (1.0 cm)</td>
<td>8.0 months</td>
<td>PTC</td>
</tr>
<tr>
<td>Kamada et al.1996</td>
<td>54</td>
<td>50</td>
<td>25 (0.5 cm)</td>
<td>12.4 months</td>
<td>PTC</td>
</tr>
<tr>
<td>Kamada et al.1996</td>
<td>23</td>
<td>50</td>
<td>–</td>
<td>4.3 months</td>
<td>Palliative</td>
</tr>
<tr>
<td>Schoenhaller et al.1994</td>
<td>39</td>
<td>46</td>
<td>–</td>
<td>9.0 months</td>
<td>Debukling</td>
</tr>
<tr>
<td>Fritz et al.1994</td>
<td>21</td>
<td>40</td>
<td>20 (1.0 cm)*</td>
<td>8.0 months</td>
<td>PTC/ERCP</td>
</tr>
<tr>
<td>Present series</td>
<td>38</td>
<td>40</td>
<td>25 (1.0 cm)</td>
<td>10.5 months</td>
<td>ERCP</td>
</tr>
</tbody>
</table>

* 4 fractions of 5 Gy high dose rate
12-13 months [26; 27] in comparison to a median survival of 8-10 months when PTC or ERCP is performed [1; 12; 28-30]. However, this difference in survival could be caused by a better general condition and less tumor load in patients undergoing surgery. In our series patients found unresectable at laparotomy had a significant better median survival than patients primarily unresectable, 18 months versus 8 months, respectively. Administered radiation doses were very similar in the majority of the series. Median doses of external beam radiation were between 40 - 50 Gy and median doses of 20 - 25 Gy specified at 1 cm from the sources were given as a boost using intraluminal brachytherapy. Although limited by the small number of patients univariate analysis of prognostic factors disclosed the comparison between tumors primarily unresectable versus tumors unresectable at laparotomy as significant. Age, sex, tumor location and total dose did not influence the prognosis. Patients receiving preoperative irradiation have a tendency to have a longer median survival which probably correlated to unresectability during laparotomy. Surprisingly patients treated with brachytherapy had a shorter survival than patients treated with external beam irradiation alone (p=0.06). We could not find an explanation for this fact. When patients were stratified by the factor primary unresectability versus unresectability at laparotomy, a significant longer survival (p=0.02) was observed if brachytherapy was not given in the group "laparotomy" but not in the primary unresectable group. As it was the case for resected tumors, the reported series do not always provide information about the target included in the radiation fields. Our portals encompassed the tumor at the hilus or CBD with a margin without intending to treat all the regional lymph node areas. The last years 3-D planning dosimetry has been introduced using spiral CT-scan for tumor delineation and localization of the organs in the upper abdomen. It is not yet proved that radiotherapy and in particular the increasing use of brachytherapy, influence the natural course of the disease after reestablishment of the biliary drainage. Pitt et al. [5] prospectively stratified 19 patients treated palliatively by radiotherapy or no radiotherapy. They did not observe differences in survival. Bowling et al. [28] in an interesting paper retrospectively compared endoscopic stenting alone (28 patients) with stenting plus radiotherapy (28 patients) in non-resected patients. The patients in the group without radiotherapy were recommended to receive radiation but never pursued. The two groups were well matched for sex, age, and type of stricture. Median survival was not significantly different between the two groups but during the first 9 months there was a survival advantage in the radiotherapy group. This difference became significant (p=0.01) if only patients with stricture type II and type III were considered. However, since this improvement in survival was at the price of longer hospital stay and more stent changes per patient, the authors raise doubts over the routine use of radiotherapy in the management of non-resectable cholangiocarcinoma. Gastric and duodenal obstruction as well as duodenal ulceration and bleeding are the most frequently found complications following radiotherapy in non-resectable cholangiocarcinoma [12; 14; 31]. We did not observe these problems but frequent episodes of cholangitis were the dominant complications requiring stent changes. Whether radiotherapy did play a role in the occurrence of cholangitis is impossible to assert. Intraoperative radiotherapy seems to increase the survival of patients with unresectable tumors [32; 33], however this treatment modality is only available in few centres. Chemotherapy (see for review [34]) in various combinations achieves responses in about 30% of the patients and in a randomised trial beneficially influenced survival and quality of life. Results after combined chemotherapy and radiotherapy are encouraging, median survivals between 12-30 months have been reported [35, 37]. In conclusion, our results compare quite well with other published series. We could not demonstrate that patients receiving a boost dose using intraluminal brachytherapy had a better survival than patients treated with external beam irradiation alone. That was the case in both patient groups with resectable and unresectable tumors. Although no survival improvement was observed, low dose preoperative irradiation seems to diminish the recurrences in the surgical scars. Prospective randomised studies are still lacking but these are the only way to demonstrate the value of new treatment strategies. Quality of life and cost-benefit aspects should also be incorporated as an objective of these studies.

References


Correspondence to:
D.González Gonzalez, MD, PhD
Department of Radiation Oncology
Academic Medical Center,
University of Amsterdam
Meibergdreef 9
1105 AZ Amsterdam
the Netherlands
e-mail address: D.Gonzalez@amc.uva.nl