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High-dose rate intraluminal brachytherapy: An effective palliation for cholangiocarcinoma causing bile duct obstruction

Nhu-Tram A. Nguyen[a,*], Emilia Timotin[a], Robert Hunter[b], Ranjan K. Sur[a]

[a] Division of Radiation Oncology, McMaster University-Juravinski Cancer Centre, 699 Concession Street, Hamilton, ON, L8V 5C2, Canada
[b] Department of Physics, McMaster University, 699 Concession Street, Hamilton, ON, L8V 5C2, Canada

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1. Introduction

Cholangiocarcinoma is a rare cancer, affecting 0.9% of individuals [1]. It is associated with a poor prognosis, with a 5-year survival of approximately 17%, according to the Surveillance, Epidemiology and End Results database [1]. Although radical resection represents the only curative treatment, 80–90% of patients are not surgical candidates, due to unresectable or metastatic disease or due to their poor condition [2–5]. Most of these patients will eventually experience biliary obstruction during the course of their disease and as a result, disabling jaundice, intense pruritus, loss of appetite and weight, acholic stools, painful hepatomegaly, change in bowel habits, nausea, vomiting, coagulopathies and even cholangitis and sepsis [4]. Restoration of bile flow is thus required to prevent complications and because most patients ultimately die of liver dysfunction due to tumour obstruction of biliary drainage [6].

Multiple palliative treatment options are available, such as endoscopic retrograde biliary drainage through sphincterotomy and/or stent placement [7], percutaneous anterograde drainage [8], external beam radiation [9,10], intraluminal brachytherapy (ILBT) [4], palliative chemotherapy [11], surgery [12], photodynamic therapy (PDT) [13] or a combination of these modalities. Each method has its advantages and drawbacks. Endoscopic biliary drainage through sphincterotomy and stent placement is usually performed as primary intervention in the US and in Europe [14]. The stents inserted may be either made of uncovered metal or plastic [15]. However, these are associated with a significant incidence of infection, stent migration and most importantly, re-occlusion from tumour ingrowth [7,16]. When the stent fails, percutaneous drainage may be inserted instead. However, in these circumstances, further re-intervention is again often required because of catheter occlusion following tumour ingrowth or overgrowth or infection [16]. Because of the low incidence of this cancer, there is limited evidence as to the effectiveness of intraluminal brachytherapy (ILBT) in a palliative setting.

At our institution, we offer to patients who are not surgical candidates a course of palliative high-dose rate intraluminal brachytherapy (ILBT) with the goal of maintaining bile flow for a durable period of time, either as a first-line palliative therapy or after they have failed other treatments, such as endoscopic drainage. In this prospective case series we present our experience over the last 10 years in treating these patients. To our knowledge, this is one of the largest series describing the use of ILBT for unresectable cholangiocarcinomas.

2. Methods and materials

Our local Integrated Research Ethics Board reviewed and approved this restrospective case series.

2.1. Data collection

We identified from our database 28 consecutive patients treated with ILBT in 2005–2014.

* Corresponding author.
E-mail address: nhu.t.a.nguyen@gmail.com (N.-T.A. Nguyen).

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Patients were included if they were 18 years or older with had biopsy proven cholangiocarcinoma or with clinical presentation highly suspicious for cholangiocarcinoma if histological diagnosis was not obtainable and if they were deemed unsuitable for radical treatments (non-operable or had unresectable tumour).

Patients were excluded if they did not have follow-up or if they received ILBT peri-operatively.

Patients' demographic data, Zubrod performance status [17], symptoms, tumour data (histology, location and size of tumour, stage based on the 7th AJCC staging manual [18]), treatment-related descriptions and outcomes were recorded. Levels of bilirubin pre- and post-IBT, frequency of percutaneous drain changes and peri-ILBT complications were also recorded. The age-adjusted Charlson Comorbidity Index (CCI) [19] was calculated using comorbidities retrieved as part of the chart review.

2.2. Endpoints evaluation

The primary endpoints were rates of 30- and 60-day biliary drain patency and bilirubin responses.

Secondary endpoints included overall survival (OS) and rates of biliary drain changes. Peri-ILBT complications were also evaluated and were defined as adverse events occurring within 30 days post-ILBT. The dates and causes of death were retrieved from the charts and correlated with the Cancer Care Ontario database.

2.3. Follow-up

At follow-up, history, physical, blood work and radiological examinations (such as ultrasound or CT images) were performed, when indicated. Patients were seen during the course of ILBT to assess for toxicities and manage symptoms. Patients had a follow-up at 4–6 weeks post-ILBT and were followed thereafter every three months and/or discharged from the clinic when too unwell to continue follow-up. Patients could also receive other palliative treatments, such as EBRT, chemotherapy or stenting during the time of follow up.

2.4. ILBT procedure

All patients had a percutaneous biliary drain inserted prior to the first fraction of ILBT, most commonly 9–12 French size catheter. Upon arrival into the brachytherapy suite, the areas around the percutaneous drains and the drains were adequately cleansed and prepped; the sutures securing the drains were cut out. Under fluoroscopic guidance, the drains were flushed with normal saline to verify their patency. This was followed by a cholangiogram, to identify the point of stricture within the biliary system. A single radiopaque 2 mm hollow Teflon catheter (Varian Medical Systems, Inc., Palo Alto, CA) was inserted into the drainage tube(s) under fluoroscopic vision and positioned into the common bile duct (CBD) and advanced across the tumour, to its distal extent, then going further up to the hepatic ducts. A single-line marker wire was thereafter inserted into the Teflon catheter and x-ray images were obtained to ensure adequate positioning into the biliary system (Fig. 1).

ILBT planning was done in real-time, using BrachyVision Treatment Planning Program (Varian Medical Systems Inc, Palo Alto, CA). The treatment volume encompassed the stricture site visualized during the cholangiogram with an additional 1 cm margin proximally and distally. The dose was prescribed at 0.5–1 cm from the centre of source axis. An example of an ILBT plan is illustrated in Fig. 2. The treatment was delivered with a VariSource HDR-^{192}Ir afterloader (Varian Medical Systems Inc, Palo Alto, CA). The ^{192}Ir sources measured 0.4 mm in radius and 5 mm in length. Most patients underwent two treatments during the same day, separated by a 6h-interval. They did not receive concurrent systemic treatments.

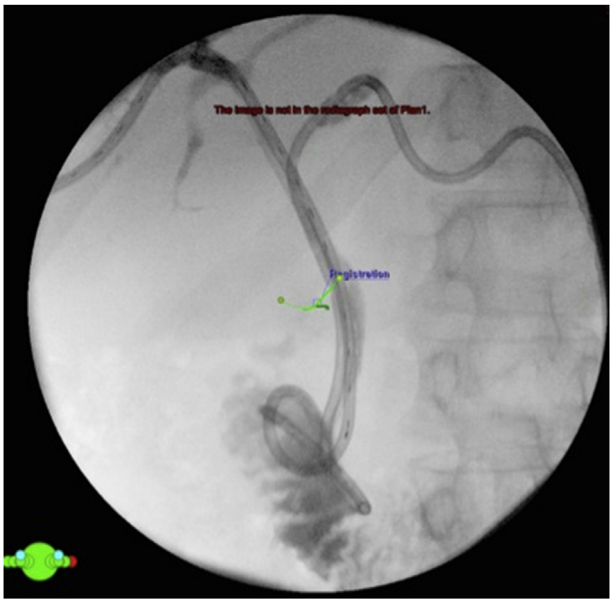

Fig. 1. X-ray images confirming the position of the marker-wire with a centimeter scale. The wire was inserted into the percutaneous biliary drains to aid in the marking the position of the tumour and length of the intraluminal brachytherapy radiation field.

2.5. Statistical analysis

Descriptive statistics were used to summarize the patients' characteristics and outcomes. Time to events was calculated using the date of the first brachytherapy treatment. Time to event outcomes, such as OS was estimated using Kaplan-Meier analyses. Bilirubin responses were evaluated using descriptive analyses. Rates of 30- and 60-day biliary drain patency, cholangitis and drain changes were analyzed using descriptive analyses. Peri-ILBT complications were defined as toxicities occurring within 30 days post-ILBT and were evaluated using descriptive analyses. All analyses were performed in SAS version 9.2 (SAS Institute, Cary, NC).

3. Results

3.1. Patients, tumours and treatments data

Between 2005 and 2014, 28 patients with cholangiocarcinoma underwent palliative ILBT treatments. A total of 24 patients were included in the final analysis; four patients were excluded as they were referred from an institution from a distant geographic location and could not continue their follow-up at our cancer centre.

At time of analysis, 21 patients (78%) had died, all from their cancer. The median follow-up was 9.5 months (range 0.9 month–6.6 years). The patients and tumours characteristics are shown in Table 1. The median age was 72 years (range: 46–89 years) and median Zubrod performance status was 2 (range: 0–3). Twenty-three patients (96%) have had other treatments prior to their ILBT, such as endoscopic stenting (n = 12), internal/external drains due to technical inability to stent endoscopically (n = 4), upfront internal-external drains (n = 13), chemotherapy (n = 1). Most patients (14/24) did not receive further treatments after ILBT due to poor performance status (n = 11) or personal preference (n = 3). Following ILBT, only 4/24 patients underwent CRT; five patients received palliative chemotherapy alone and one patient EBRT alone as they were not candidate for combined treatments. Patients did not receive concurrent chemotherapy with ILBT.

A median CBD length of 8.5 cm (6–14 cm) was treated to a most commonly to a dose of 10 Gy in 2 fractions, delivered within the same day, separated by a 6-hour interval (10–15 Gy/2–3 fr).