

## Over 6-year survival in locally advanced cholangiocarcinoma – a case report

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### Abstract

Cholangiocarcinoma is a malignancy of the biliary duct system that may originate in the liver and extrahepatic bile duct. Despite aggressive anticancer therapy and interventional supportive care, the overall survival is approximately 6 months, most patients not being eligible for curative resection.

Case description: A 64 year-old patient, diagnosed in 2008 with locally advanced bile duct neoplasm (T<sub>3</sub>N<sub>0</sub>M<sub>0</sub>), who underwent latero-lateral hepatoduodenal anastomosis and cholecystectomy in 2008, followed by neoadjuvant Gemcitabine chemotherapy and cephalic duodenopancreatectomy with tumor exeresis in 2009, uncompliant to follow-up, presents with abdominal meteorism, diffuse abdominal pain, inappetence, weight loss and increased fatigability. Initial ultrasonography showed a localized pancreatic tumor and liquid in the Douglas pouch, both confirmed by CT scan.

Discussion: The 6-year survival compared to the general mean survival rate of 17 months, depending on the type of the neoplasm, raises questions about the otherwise histopathology confirmed diagnosis of well differentiated cholangiocarcinoma. The present image documented pancreatic tumor makes the retrospective diagnosis assessment even more intricate. Slow-progressor outlier cases might represent new diagnostic entities, and their understanding can be instrumental in improving the therapeutic efficiency. Long time survival in such diagnostic entities is scarcely reported in literature.

**Keywords:** *Cholangiocarcinoma, survival rate, pancreatic tumor*

### Introduction

Cholangiocarcinomas (CCAs) are biliary tract malignancies with dismal prognosis [1]. CCA is classified as intrahepatic, perihilar or extrahepatic; the subtypes differ in their clinical presentation, biologic behaviour and management. Throughout the last decades, the incidence of CCAs had notably increased probably due to the high occurrence of some risk factors [2]. Tyson et al established some risk factors for CCAs including parasitic

infections, primary sclerosing cholangitis, hepatolithiasis, biliary-duct cysts and toxins [3]. Other less-proven, possible risk factors include inflammatory bowel disease (IBD), hepatitis C virus infection, hepatitis B virus infection, liver cirrhosis, mellitus diabetes, obesity, alcohol abuse, smoking, and host genetic polymorphisms [3].

Risk factors associated with cholangiocarcinogenesis are summarized in Table 1.

Anderson and colleagues report that patients with cholangiocarcinoma often present at advanced stages, and even with aggressive therapy the cure rates are low. The overall majority of patients present with incurable disease, and the mean survival rate is less than 12 months after the diagnosis [4].

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**Table 1.** Risk factors of cholangiocarcinogenesis, after Ghouri et al [2]

Primary sclerosing cholangitis
Hepatolithiasis
Liver flukes – <i>Opisthorchis vierrini</i> and <i>Clonorchis sinensis</i>
Caroli's disease
Congenital hepatic fibrosis
Viral hepatitis B and C infection
Liver cirrhosis
Obesity and diabetes
Chemical compounds – dioxin, thorotrast
Choledocal cysts

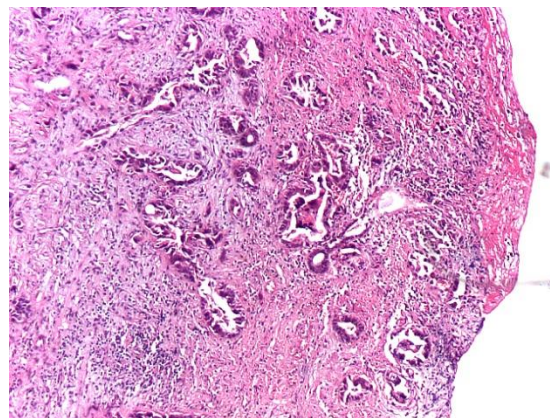
However, treatment alternatives have upgraded throughout the last two decades, combining neoadjuvant or adjuvant chemoradiation with surgical excision and/or radiotherapy [2]. This case may retrospectively rise questions regarding the precision of a diagnosis that otherwise is clearly defined by a positive histopathological result, in the everyday practice. Another interesting aspect of the case is the fact that it raises questions also about the subsequent management of the patient. This is a case in evolution – the patient is still treated. Facing the doubts about the precise cancer diagnosis makes the ulterior management even more intricate.

### Case presentation

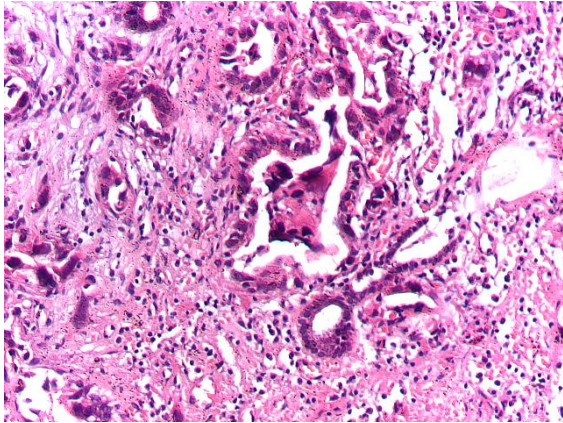
A 64 year-old female patient was admitted February 2015 in the Department of Gastroenterology and Hepatology of Iasi presenting abdominal bloating, diffuse abdominal pain, flatulence, loss of appetite, accelerated bowel transit, weight loss, increased fatigue and pale teguments. Physical examination showed a pale, dehydrated patient, with hypotrophic muscles. The abdomen was diffusely sensitive and distended, with no signs of acute peritonitis. An endoscopic diagnosis of chronic gastritis was established; she also has arterial hypertension since 2000, (now treated with Bisoprololum, Indapamine and Perindoprine arginine) and

bilateral hypoacusia. The patient was uncompliant to follow-up, being previously diagnosed with an extrahepatic bile duct neoplasm, T<sub>3</sub>N<sub>0</sub>M<sub>0</sub> (stage IVa). She underwent surgical latero-lateral hepatoduodenal anastomosis and cholecystectomy in August 2008. Afterwards, the patient received neoadjuvant chemotherapy in 6 cures with Gemcitabine and cephalo-duodeno-pancreatectomy with tumor exeresis in April 2009.

The retroactive tissue sample evaluation from the tumor exeresis revealed chronic cholecystitis with parietal fibrosis and isolated lymphoid infiltration in chorion (Figure 1) and a well differentiated adenocarcinoma, ulcerated and infiltrative with parietal invasion nearby parietal glands (Figure 2).



**Fig. 1.** Histological finding of tumor exeresis showing a well differentiated adenocarcinoma, ulcerated and infiltrative (HE, x40);



**Fig. 2.** Histological finding of tumor exeresis - well differentiated adenocarcinoma, ulcerated and infiltrative (HE, x100);

The significant pathological results of the blood tests include increased levels of glucose (125 mg/dl) and glutamic oxalacetic transaminase (AST 61 UI/L) and decreased levels of urea (15 mg/dl) and iron deficiency (30 ug/dl). The carcinoembronar CA19-9 tumor marker is two-folds increased – 73.9 U/ml. The blood tests also revealed thrombocytopenia (142,000/mm<sup>3</sup>), anemia (Hb=9.7 g/dl), erythropenia (3.25 million), and increased levels of glycolytic hemoglobin (13.3%). The urinary sediment showed pyuria (52 WBC/mm<sup>3</sup>) and a large amount of bacterial flora (19259.4 CFU/mL).

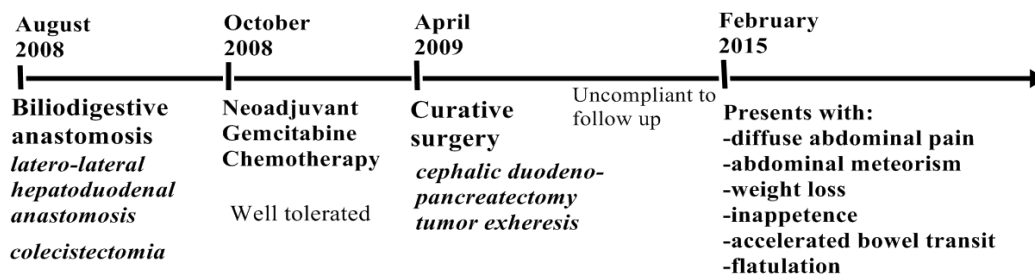
The imaging studies were revealing: ultrasonography showed liquid in the Douglas pouch, a diffusely hyper-reflective liver and a cephalic hyperechoic pancreatic nodule (Ø=33.6 mm); computed tomography confirmed the ultrasonographic findings: a native inhomogeneous pancreatic tumor 40/35/35 mm

(A-P, T, CC) that invades the common hepatic artery, the superior mesenteric artery and the left renal vein was observed. Two liver masses were also detected in the VI<sup>th</sup> and VIII<sup>th</sup> segment – inhomogeneous and hypodense 11/9.5/10 mm (A-P/T/CC) - remarked as possible liver metastasis despite atypical imaging features. The pancreas appears atrophic, with an irregularly dilated Wirsung canal. Eso-gastro-duodenal endoscopy showed biliary reflux, moderate mucosal congestion diagnosed as chronic gastritis.

There is a broad spectrum of differential diagnosis in patients presenting with diffuse abdominal pain, accelerated bowel transit, increased fatigability, weight loss, all of these symptoms, although not specific, should raise suspicion of a pancreatic or hepatobiliary neoplasm [4].

In this case, the tumor may have been confused with the vaterian ampulloma, but there was a normal endoscopic aspect of the papilla. The hypothesis of liver cancer is infirmed by the normal imagistics and histology, the possible absence of etiology and the normal α-fetoprotein levels.

The histopathological exam proves that there are no benign pancreatic nodules or benign biliary strictures (postoperative), all these being regarded as other possible differential diagnoses. Possible differential diagnoses include cephalo-pancreatic carcinoma, duodenal carcinoma, Mirizzi's syndrome and primary sclerosing cholangitis [4]. The patient outcome from August 2008 to February 2015 is presented in Figure 3.



**Fig. 3.** Patient outcome until date of admittance

To improve the life quality and to precisely assess the cancerous disease, we imagined a protocol that must be verified throughout the following sessions. The protocol is summarized in Figure 4. As the patient is currently under further treatment and evaluation, it is rather unlikely for us to present and predict a possible outcome for the case. Nevertheless, at the moment, exploratory laparoscopy and

histopathological reexamination are in our opinion mandatory.

Therapy alternatives depending on the local and anatomical findings would be either adjuvant chemotherapy or chemotherapy combined with exeresis of recidivated tumor. At this moment, radiation and/or molecular therapies are not standards of care for this type of tumors in our hospital unit.

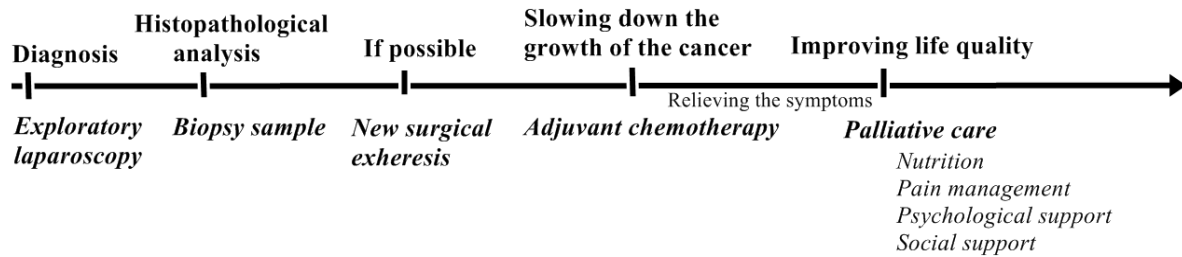


Fig. 4. Future management protocol and follow-up

**Discussion**

The 6-year survival compared to the general mean survival raises questions about the diagnosis and treatment protocol. Anderson et al state that most of the patients with incurable disease die within 6 months and 1 year following diagnosis, depending on the type of the neoplasm [4].

Complex anatomical areas are characterized by multiple origin tumors, all of which with the same histological patten: adenocarcinomas – ampulloma, cholangiocarcinoma, gallbladder cancer and pancreatic or rarely duodenal cancer. Because of the invasive character, the tumor origin could have been missed. For any of those tumors, the mean survival rate is poor. Highly particular for the case is on the other hand the absence of lymphatics invasion both at the moment of diagnosis and presentation.

Surgical treatment is the only one offering the possibility of a curative therapy. Unfortunately, few patients qualify for surgical intervention [2]. The main treatment target should be full excision with R<sub>0</sub> resection (negative surgical margins). A prospective study proves that the 5-year survival rate post-surgical treatment of extrahepatic

cholangiocarcinoma is 10.8% [5]. Ghouri et al established that extrahepatic CCA is best healed surgically, the Whipple-resection usually being executed, as in the presented case. Systemic chemotherapy is elected in the treatment of advanced CCA [2]. Rizvi and colleagues consider that the combination of Gemcitabine and Cisplatin is the preferred regimen in this case because Cisplatin gives a survival advantage without an increase in toxicity, compared to Gemcitabine alone [1].

Radiotherapy cannot cure the cancer but may help to shrink it or slow it down – it can palliate symptoms and may contribute to increase the survival rate. Ionizing radiation acts by the formation of free radicals that cause damage to DNA resulting in double-stranded DNA breaks [6]. The patient did not undergo radiotherapy, but the R<sub>0</sub> surgical resection and the 6 cures of Gemcitabine chemotherapy were considered enough to slow down the cancer.

Another interesting aspect of the case is the increased level of glucose. The patient does not suffer from diabetes, but it is known that high levels of glucose promotes tumor invasion [8]. Also, secondary diabetes accompanies in many cases malignant tumors of the pancreas. Giovannucci et al agreed that diabetes may influence the neoplastic process

by several mechanisms, including hyperglycemia, or chronic inflammation. Most cancer cells express insulin and IGF-1 receptors, the insulin receptor being able of rousing cancer cell proliferation and metastasis. The level of glucose is high in cancer cells and free of insulin binding to its receptor; the effects of the insulin receptor activation on cancer cells may stimulate cell mitogenesis and survival, proliferation, protection from apoptotic stimuli, invasion and metastasis [7].

Not least, from an ethical point of view, as the patient did not realize the amplitude and prognosis of her disease she might have taken such a survival as a normal thing. This may explain also the lack of adherence to follow-up. All these are remarkable proofs of deficient professional communication. In other cases, such deficiencies may generate serious consequences regarding professional legal liability of the medical team. Luckily, in the case, all of these aspects were ignored by the patient.

## Conclusions

First, the case presents concerns about communication deficiencies between the attending physician and the patient. Errors in

communication may lead to poor adherence and deficient follow-up. Even a better than expected evolution may raise legal consequences, and medical liability in case of bad consequences in the doctor-patient relationship. Whereas in most cases, such patients would have cheerfully received medical information about such a good survival rate, there could also be patients considering themselves entitled to ask for explanation about the precision of the first diagnosis.

Secondary, massive tumor penetration and regional spreading with possible massive desmoplastic resections of locally advanced adenocarcinomas may alter normal local anatomic structure distribution and therefore may generate errors in precise definition of primary tumor site. Oncology team assessment and diagnosis is mandatory in such circumstances.

Finally, the important oncologic conclusion of the case is once again stressing possible increased incidence of slow-progression cancers. These cases might represent new diagnostic entities, and their understanding can be instrumental in improving the therapeutic efficiency. Otherwise, in the current practice, long time survival in such diagnostic entities is scarcely reported in literature

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