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Multimodal treatment of an advanced intrahepatic cholangiocarcinoma and its recurrence – a case report

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ABSTRACT

Introduction: Intrahepatic cholangiocarcinoma (ICC) is rare and often diagnosed in an advanced stage. Neoadjuvant therapy is not established and data on its value are in palliative intention. In the case of a recurrence patients often are offered systemic chemotherapy as the only treatment option. We report on a patient with advanced intrahepatic cholangiocarcinoma who underwent multimodal treatment leading to a long-term survival.

Case report: A 61-year-old woman presented with an advanced intrahepatic cholangiocarcinoma of the right liver lobe without evidence of metastatic spread. She had already completed two cycles of chemotherapy of Cisplatin and Gemcitabine resulting in stable disease. An extended hemihepatectomy of the right lobe including segments I, IVa and partially IVb was performed. The TNM status (8th edition) was pT2b (3), pN0 (0/6), M0, V1, G2 and R0. Ten months later recurrence was diagnosed and treated with microwave ablation. Recurrence occurred again and the patient underwent repeated resection 22 months after primary resection. After detection of repeated recurrence once more, repeated resection was performed 46 months after initial resection. The patient is still alive and tumor-free 7 years after primary resection.

Conclusion: Multimodal treatment including preoperative chemotherapy, complete resection and repeated resection of recurrence as well as microwave ablation led to long-term survival in a case of advanced intrahepatic cholangiocarcinoma. Close follow-ups were crucial to offer the best treatment options.

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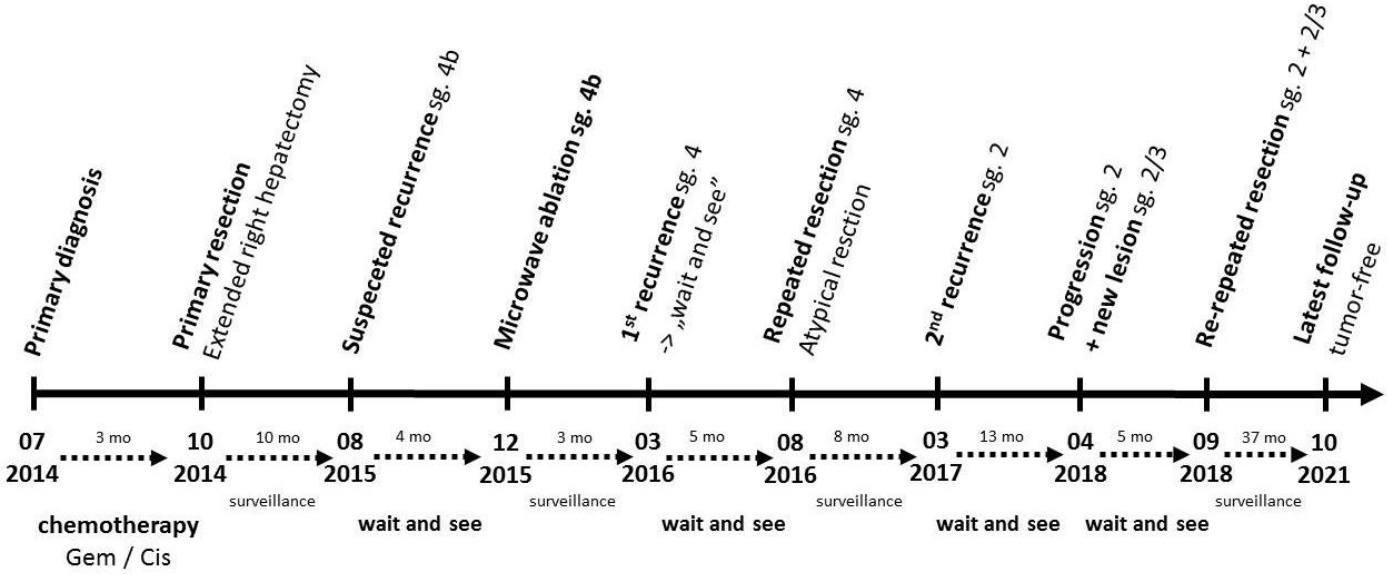
Introduction:

The intrahepatic cholangiocarcinoma [ICC] is a rare primary malignancy of the liver [1]. Because of the lack or late-onset of symptoms, it is often diagnosed in an advanced stage. This leads to a high number of negative laparotomies or initially palliative systemic chemotherapy [2]. Often extended resections are necessary for complete tumor removal in these patients [4].

So far, neoadjuvant chemotherapy is not a standard procedure in the case of ICC but recent data show that neoadjuvant chemotherapy, most frequently a combination of Gemcitabine and Cisplatin, can downstage the locally advanced tumor and negative resection margins rates are raised [3].

Data on adjuvant chemotherapy are scarce as well and prospective studies with a high number of patients are lacking. In case of tumor recurrences, guidelines are inconclusive or often do not mention the therapy at all. Most often palliative systemic chemotherapy is applied but potentially curative alternatives like repeat resection or ablation are mentioned increasingly over the last two decades [9, 11, 13].

We report on a case of a patient who underwent multimodal treatment for advanced intrahepatic cholangiocarcinoma leading to long-term survival.



Case report:

A 61-year-old woman presented at our center with an advanced ICC of the right liver lobe extending to the liver segments 1 and 4a [**Figure 1**] initially diagnosed in July 2014. At the time of presentation, she had already completed two cycles of chemotherapy of Cisplatin and Gemcitabine. We conducted new imaging showing a stable disease and segments 2 and 3 appeared free of tumor. A volumetric calculation of segments 2 and 3 revealed a sufficient volume of the future liver remnant of 460ml at a weight of 67kg.

In October 2014, we performed a right trisectionectomy with lymphadenectomy, a reconstruction of the left hepatic vein as well as an atypical resection in liver segment 3 [**Figure 2**]. She developed a slight disturbance of liver synthesis resulting in edemas, but after reconstitution, we were able to discharge her on the 19th postoperative day. The final histology showed a bifocal growing moderately differentiated cholangiocarcinoma with two nodules and a diameter of the largest of 8.5 cm. The TNM status [8th edition] was pT2, pN0 [0/6], M0, L0, V1, Pn0, G2, R0. The additional immunohistochemical workup revealed a strong cytoplasmatic expression of Cytokeratin 7 with weak coexpression of CK8. CA19-9 was only positive focally. CK20, CDX2, TTF-1 and Hepar1.

Overall, morphology and immunohistochemistry were consistent with an intrahepatic cholangiocarcinoma of the small duct type.

Follow-up was carried on every three months with ultrasound and computed tomography [CT]. In August 2015 an arterially hyperintense lesion was detected [**Figure 3**]. The following control in December 2015 showed the lesion to be constant in size. After a detailed discussion of the findings the patient went for a microwave ablation [**Figure 4**].

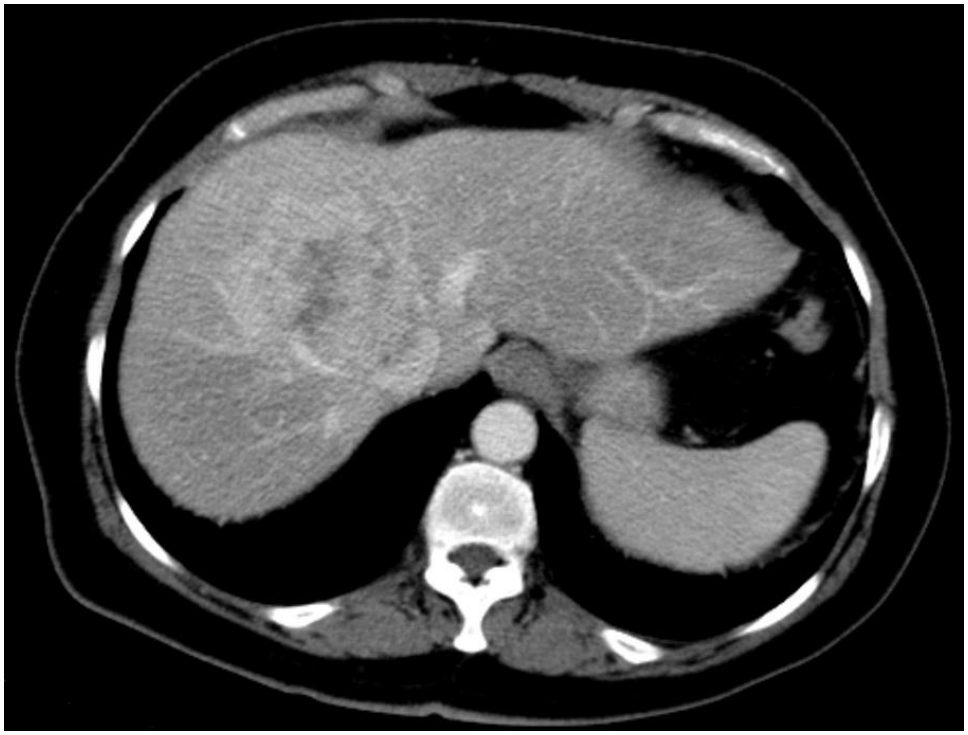


Figure 1: CT scan of the upper abdomen showing the intrahepatic cholangiocarcinoma with contact to the right and middle hepatic veins.

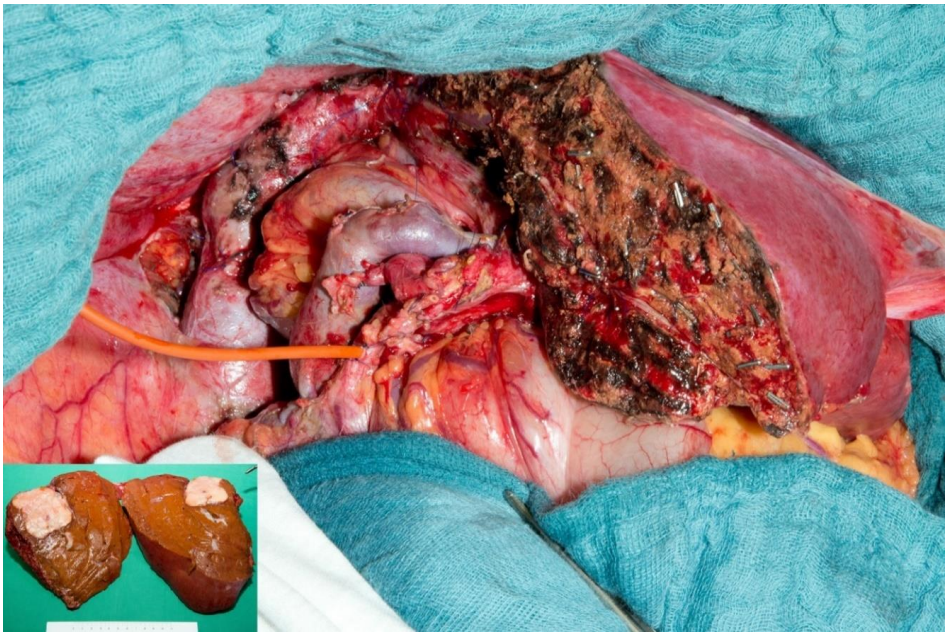


Figure 2: Intraoperative view after right trisectionectomy with the liver remnant [segments 2+3]. The left and main bile duct could be preserved and a T-drain was placed. In the lower left corner, the lamellated specimen showing the ICC.

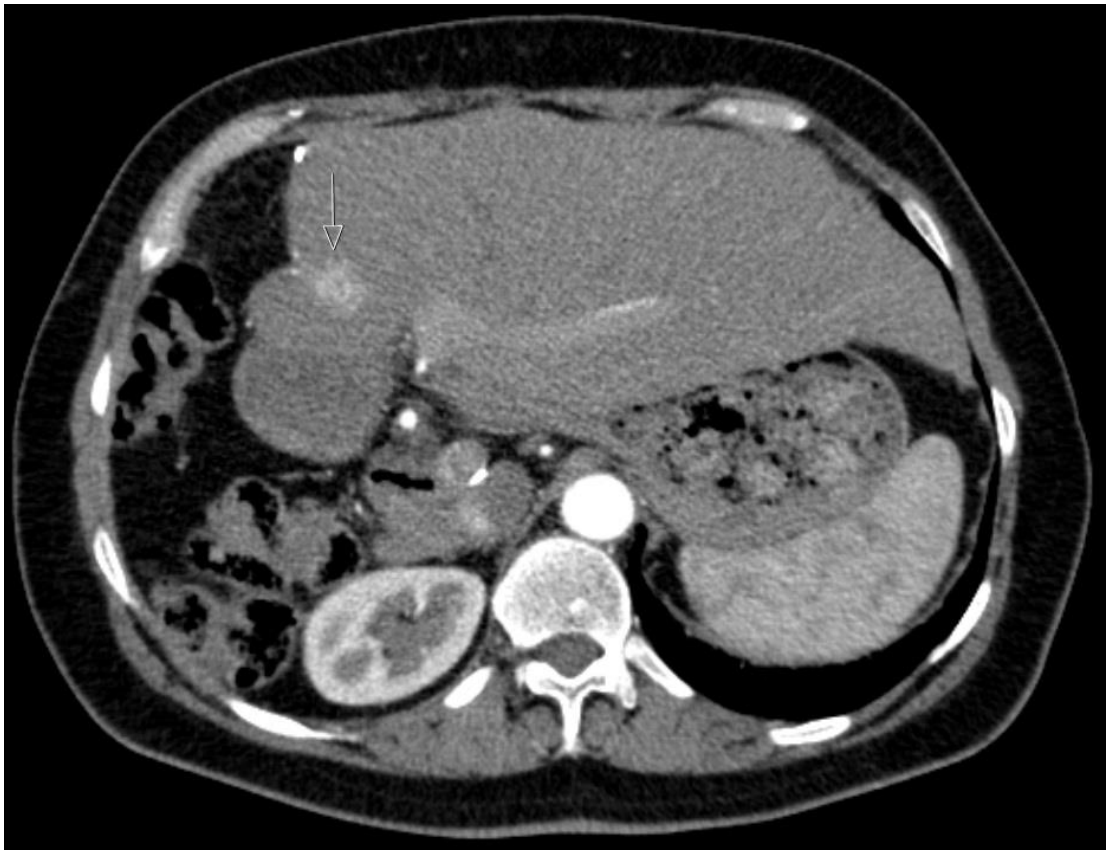


Figure 3: CT scan as part of follow-up showing a lesion [arrow] with arterial uptake of contrast agent highly suspect for recurrence of ICC.

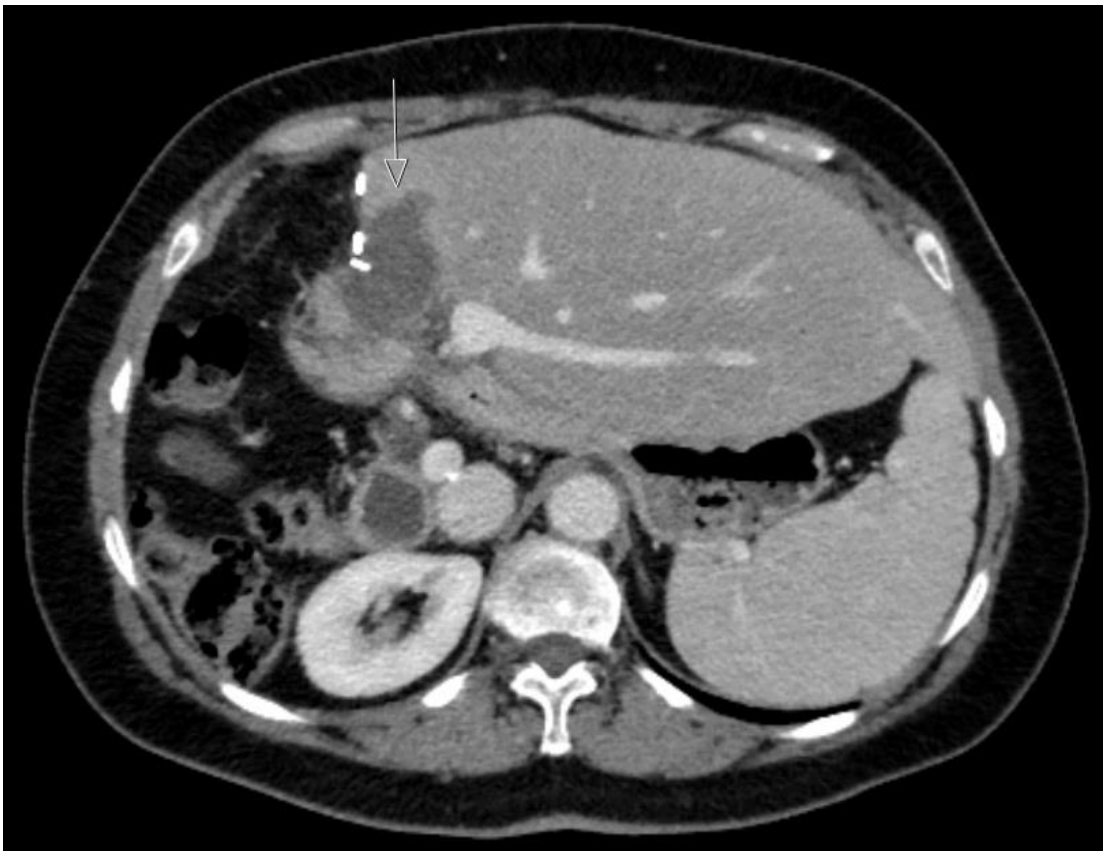


Figure 4: CT scan after microwave ablation showing the ablation zone necrosis [arrow].

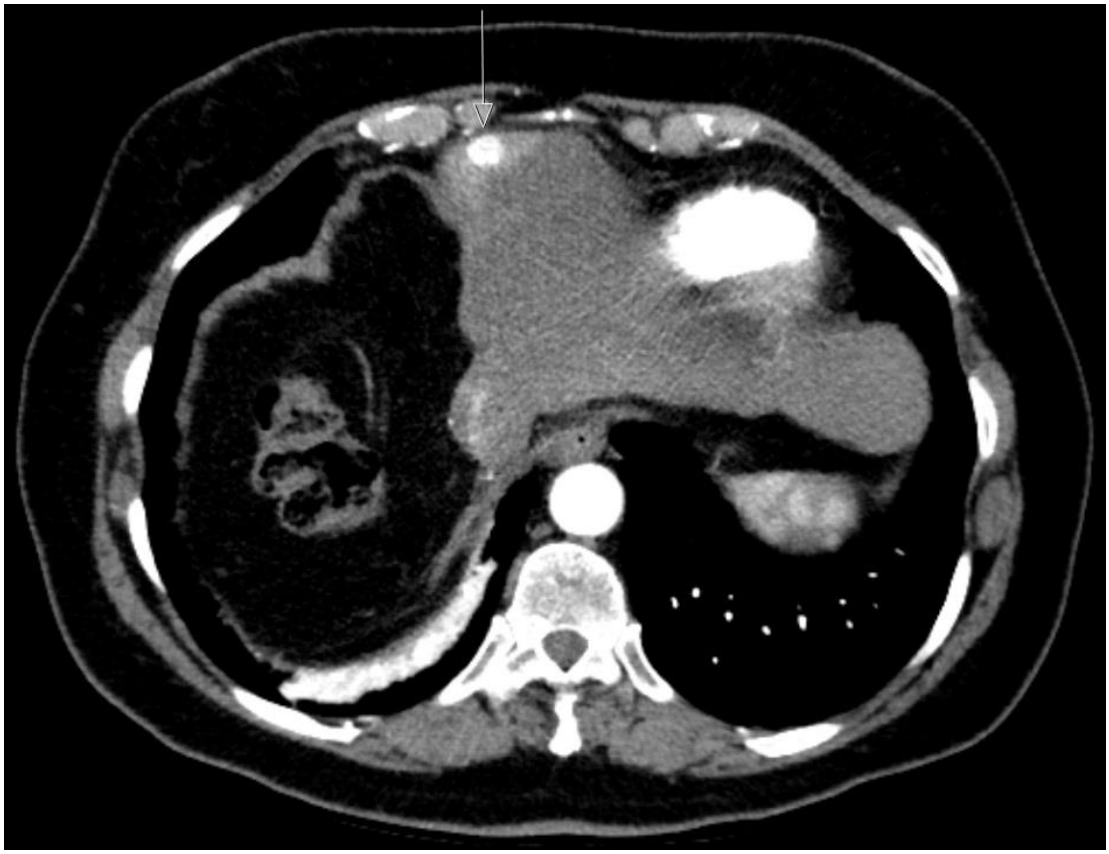


Figure 5: CT scan showing 2nd recurrence [lesion with arterial uptake of contrast agent, arrow] at the liver surface. Resection seemed feasible and was performed.

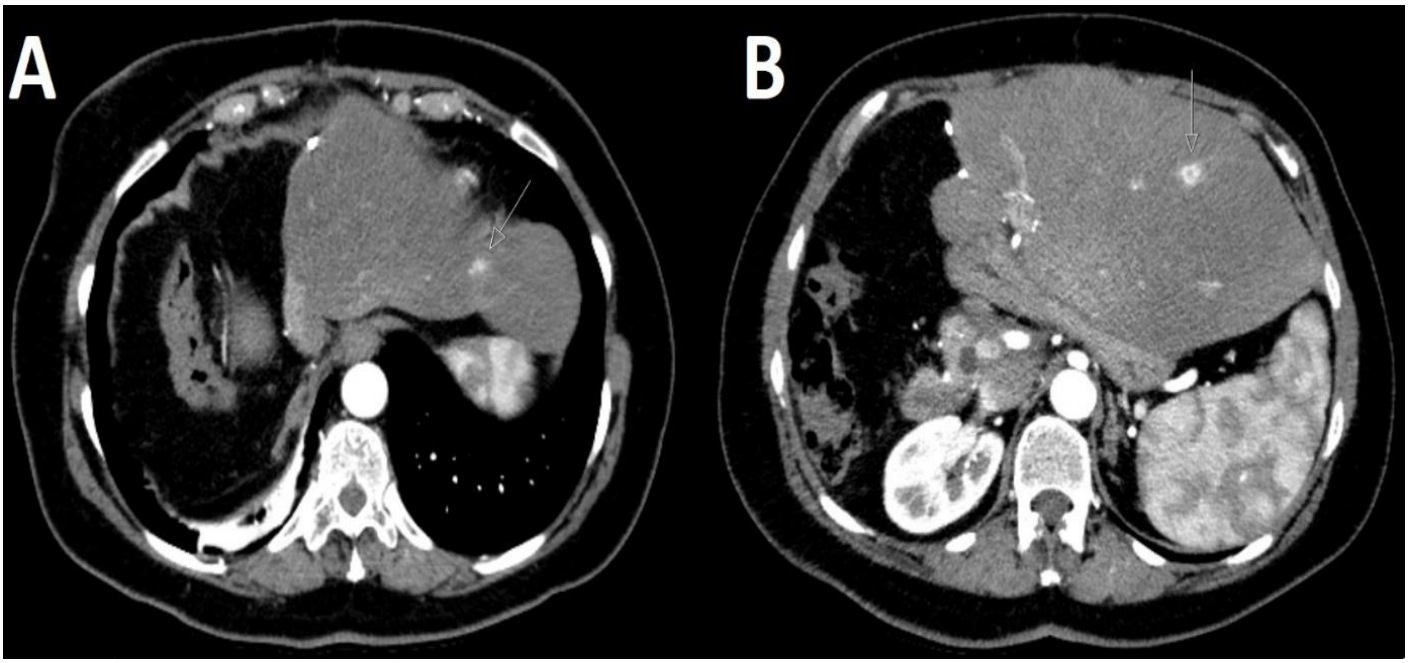


Figure 6: CT scan showing the 3rd recurrence with two lesions [A and B] with arterial uptake of contrast agent in the liver remnant. Both lesions were resected as well.

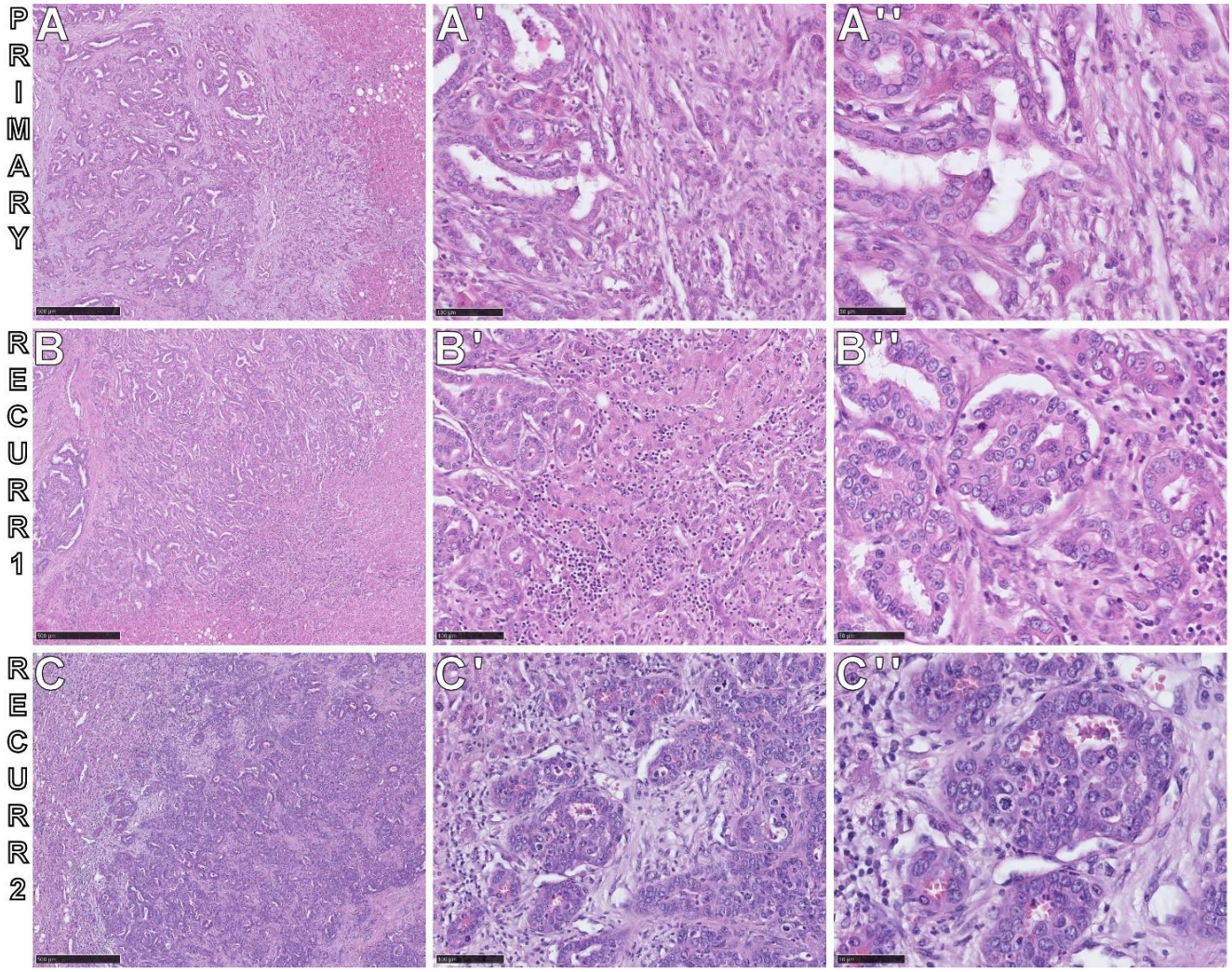


Figure 7: Histopathology of the intrahepatic Cholangiocarcinoma of the small duct type. The primary tumor [A], as well as the first [B] and second [C] recurrences, are depicted. Morphology shows a moderately pleomorphic, proliferative tubular and cribriform growing adenocarcinoma with eosinophilic cytoplasm, hyperchromatic nuclei and prominent nucleoli. No evidence of tumor grade progression between primary and recurrent tumors was found. Minimal resection margin distance was 0.2 mm [primary tumor], 11mm [first recurrence], and 3 mm [second recurrence]. H&E staining. [A-C] Overview. [A'-C' and A''-C''] Intermediate and high magnifications.

In the next follow-up in March 2016 another arterially hyperintense lesion was detected [**Figure 5**].

After 6 months of watchful waiting, no other lesions appeared. Concluding a stable disease, we decided to perform a repeated resection [atypical resection] in August 2016. The postoperative course was uneventful. The histological result showed a complete resected recurrence of the known ICC [TNM status [8th edition] rpT1, rpNx, L0, V0, G2, R0].

Further follow-up was carried out and in March 2017 recurrence was detected [**Figure 6A**]. Together with the patient we agreed on watchful waiting with regular follow-ups every three months via CT scans. In April 2018 another lesion appeared [**Figure 6B**]. After another period of watchful waiting and monitoring the known lesions in September 2018, a re-repeated resection was performed without any complications. The histological results of the two atypical resections confirmed the tumor recurrence of the known primary ICC in both cases. The TNM-status [8th edition] was rpT2, rpNx, L0, V0, G2, R0. Histological grade was

comparable between primary tumors and first and second recurrences **[Figure 7]**.

Since then, the follow-ups have not shown any signs of recurrence including the current CT scan in October 2021. Overall survival from the day of first diagnosis is more than 87 months to date and the patient is alive and tumor-free at the moment.

Discussion:

We report on a patient with an advanced ICC who received a multimodal treatment with a result of being alive and tumor-free more than 7 years after diagnosis. Multimodal treatment with neoadjuvant chemotherapy, resection, microwave ablation of the first recurrence, and repeated resections of second and third recurrence is uncommon.

So far multicenter studies with higher sample sizes have to follow on neoadjuvant therapy options for ICC. The present findings strongly suggest a neoadjuvant therapy for locally advanced tumors [6]. Buettner and colleagues showed in an international multicenter study as well as Le Roy and colleagues in a unicenter study, that preoperative/neoadjuvant chemotherapy may lead to secondary resectability and equivalent overall and disease-free survival compared to primary resectable patients [7, 8]. Akateh and colleagues advocate that besides neoadjuvant chemotherapy TACE and hepatic artery infusion have shown good results in downsizing and achieving secondary resectability in advanced ICC [3].

In our case, the preoperative chemotherapy did not lead to a downsizing effect, but the stable disease could be shown and resection seemed feasible. Extended resections for ICC are often necessary to gain complete resection [4, 5] and even in patients with visceral or vascular infiltration, resection offers the chance of long-term survival [10, 14]. In our case, the left hepatic vein needed to be reconstructed due to suspected infiltration, which had not been proven in final histology.

Recurrence is common in ICC with rates of up to 60-70% [11, 15]. The patterns differ between isolated intrahepatic [about 40%], isolated extrahepatic [about 30%], and intra- and extrahepatic [about 30%] recurrence [16]. In the case of recurrence, the commonly offered treatment is a systemic chemotherapy with Gemcitabine and Cisplatin, but different alternatives exist and are offered increasingly. Besides hepatic artery infusion as artery-based chemotherapy also transcatheter arterial chemoembolization [TACE] and selective internal radiotherapy [SIRT] are utilized for unresectable [17] or recurrent ICC mostly as palliative intended therapy. Furthermore, potential curative possibilities are repeated resection or ablation of isolated intra- or extrahepatic recurrence [6, 17, 18, 19, 20].

Repeated resection or ablation are both feasible in selected patients. Tumor biology plays an important role in selection on this behalf. After detection of recurrence, we pursued a watch-and-wait strategy twice. We aimed to exclude other lesions which might have been too small to be recognized through imaging at that time. ICC often shows aggressive biologic behaviour in general and regarding recurrence [21]. Therefore, sometimes patients undergo surgery or ablation with early recurrence and distinct tumor spread leading to a palliative situation. In our case, tumor biology was favorable. Despite local recurrence twice, extrahepatic recurrence did not occur and the intrahepatic recurrence was locally limited. So, through ablation once and two repeated resections a long-time tumor-free status was achieved.

Conclusion:

Multimodal treatment of advanced ICC may lead to long-term survival in selected patients. Patients who undergo supposed palliative treatment should be monitored through regular imaging and be discussed in an interdisciplinary tumor conference with an experienced liver surgeon and interventional radiologist to find an adequate and individualized treatment. In some cases, a chance of secondary resectability is

possible. Moreover, even in the case of recurrence of ICC different treatment modalities exist which can help to achieve a good long-term outcome like in our presented case. After surgery regular follow-ups should be carried on to detect recurrence early and offer the affected patient individualized treatment options.

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