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**Neoadjuvant therapy in the treatment of hilar cholangiocarcinoma: Review of the literature**

Frosio F *et al.* RCT before resection/transplantation for hilar CCA

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**Abstract**

Cholangiocarcinoma (CCA) is a malignant tumor of the biliary system and includes, according to the anatomical classification, intra hepatic CCA (iCCA), hilar CCA (hCCA) and distal CCA (dCCA). Hilar CCA is the most challenging type in terms of diagnosis, treatment and prognosis. Surgery is the only treatment possibly providing long-term survival, but only few patients are considered resectable at the time of diagnosis. In fact, tumor’s extension to segmentary or subsegmentary biliary ducts, along with large lymph node involvement or intrahepatic metastases, precludes the surgical approach. To achieve R0 margins is mandatory for the disease-free survival and overall survival. In case of unresectable locally advanced hCCA, radiochemotherapy (RCT) as neoadjuvant treatment demonstrated to be a therapeutic option before either hepatic resection or liver transplantation. Before liver surgery, RCT is believed to enhance the R0 margins rate. For patients meeting the Mayo Clinic criteria, RCT prior to orthotopic liver transplant (OLT) has proved to produce acceptable 5-years survivals. In this review, we analyze the current role of neoadjuvant RCT before resection as well as before OLT.

**Key words:** Hilar cholangiocarcinoma; Klatskin tumor; Neoadjuvant treatement; Radiotherapy; Chemotherapy; Hepatic resection; Liver transplantation

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**Core tip:** Surgery is the only potentially curative treatment for hilar cholangiorcinoma; however, most of the patients are considered not resectable because of the local extent. Neoadjuvant radiochemotherapy is supposed to increase R0 margins rate, or even to allow radical resection for locally advanced tumors, but few studies are available. Moreover, for patients with early stage tumors meeting the Mayo Clinic criteria, neoadjuvant therapy before liver transplantation has produced very good survivals, gaining worldwide acceptance. This is the first review to consider the role of neoadjuvant treatment for hilar cholangiocarcinoma, before resection as well as before liver transplantation.

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**INTRODUCTION**

Cholangiocarcinoma (CCA) is a malignant tumor of the liver arising from the cholangiocytes of the bile ducts and it represents the second most common primary hepatic malignancy behind the hepatocellular carcinoma[1]. The cholangiocytes have different features in relation to their location in the biliary tree and this heterogeneity reflects the existence of different histological types of CCA[2], such as mucine producing, hepatocytic differentiated, etc. Established risk factors for CCA are primary sclerosing cholangitis (PSC), hepatobiliary parasites (*Opisthorchis viverrini* and *Clonorchis sinensis,* in Southest Asia especially), hepatolithiasis, Caroli’s disease and type I and IV choledocal cysts; more recently, cirrhosis has emerged as an independent risk factor too[3]; on the other hand, hepatitis B and C virus, diabetes mellitus and obesity are possible risk factors to be confirmed. Nevertheless, in most patients with CCA, no risk factor is identifiable. The current anatomical classification includes intra hepatic CCA (iCCA), hilar CCA (hCCA) and distal CCA (dCCA)[4]. hCCA notably refers to tumors located between the secondary branches of the right and left hepatic ducts and the common hepatic duct at the level of cystic duct origin[5]. The prognosis of CCA is quite miserable and surgery is the only potentially curative treatment.

In case of hCCA, which is the most common type[6], diagnosis and treatment are extremely challenging. First of all, most of the patients are not eligible for surgery, since one of the following conditions occurs: bilateral involvement of the second-order bile ducts, bilateral or contralateral vascular involvement, metastatic disease, underlying advanced hepatic disease and PSC[7]. An advanced preoperative work up is therefore needed: along with magnetic resonance cholangiography and computed tomography scan, the histologic mapping of the biliary tree obtained through the Spyglass cholangioscopy system appears crucial to establish the resectability and to plan the right operative strategy. Secondly, if feasible, surgery for hCCA consists of a major procedure, usually an extended lobar hepatic and bile duct resection, with regional lymphadenectomy and Roux-en-Y hepaticojejunostomy[8]; an accurate evaluation of the future liver remnant is always required, as preoperative portal vein embolization or staged hepatectomy as ALPPS are the available techniques to provide for its hypertrophy. Moreover, even when a R0 resection is accomplished, it can only produce 5-years survivals up to 40%[9], being the lymph nodes involvement a well-known negative prognostic factor[10]. For R1 resected patients, a marked decrease in disease free survival (DFS) and overall survival (OS) has been observed. Patients potentially at high risk of residual tumor (R1) after surgery are considered “borderline resectable”. For them, neoadjuvant radiochemotherapy (RCT) has been advocated as a possible treatment to allow R0 resections. In “unresectable” early stage hCCA patients, RCT has already been validated prior to Orthotopic Liver Transplant (OLT) as part of the Mayo Clinic protocol. The aim of the present paper is to review the history and the current role of neoadjuvant RCT in both settings, hepatic resection and OLT.

**RCT BEFORE HEPATIC RESECTION**

In literature, only few studies are available, all with a small number of patients included and a poor distinction between hCCA and dCCA; definition of “borderline resectable” and “unresectable” patients are often unclear as well.

In 1997 McMasters *et al*[11] published the results of a prospective study applying neoadjuvant RCT for extra hepatic CCA. Combined infusion of 5-FU (300 mg/m2 per day, from Monday to Friday) and external beam radiation (1.8 Gy per day, from Monday to Friday, to a total dose of 50.4 Gy or 45 Gy) were used. Nine patients, five with hCCA and four with dCCA, were included. Six of them had an unresectable disease, based on preoperative imaging or on surgical exploration performed in others hospitals. R0 resection was achieved in all the nine patients (100%), compared to 54% obtained in the group having received surgery alone. There were no major complications. Among the five patients with hCCA, two displayed a pathologic complete response, the others a partial one. The authors concluded that hCCA patients treated with neoadjuvant RCT obtained 100% of R0 resection (5/5) with a pathologic complete response in 40% (2/5). Despite the limited number and the questionable selection of the patients (both hCCA and dCCA, unresectable and resectable), this study demonstrated the achievement of R0 resection after neaodjuvant RCT for hCCA patients primarily not elegible for surgery.

In 2000, Gerhards *et al*[12] demonstrated that preoperative radiotherapy (RT) at the total dose of 10.5 Gy (three fractions of 3.5 Gy on three consecutive days the week before surgery) could decrease the risk of intra operative implantation metastases in patients with resectable hCCA who had undergone ERCP or PTC for biliary drainage; that risk had been previously assessed at 20% by the same group[13].

In a retrospective study, Nelson *et al*[14] considered a cohort of twelve patients out of forty-five with hCCA and dCCA, either “borderline resectable” or “unresectable”, who had received neoadjuvant RCT at different doses. R0 resection could finally be performed in 11/12 patients (91%); pathologic complete response was found in 3/12 (25%). A complication requiring surgery was developed by 2/12 patients (16%), without any difference in terms of morbidity if compared to the thirty-three patients who did not undergo neoadjuvant therapy. Definitely, the twelve patients with hCCA and dCCA showed a better trend in 5-years survival rate, 53% *vs* 23%, but not statistically significant. Also, this study is limited by small sample size, unclear choice of patients and different regimens of RCT.

More recently, a retrospective study about neoadjuvant RCT has been published by a South Korean group[15]. They focused on patients with locally advanced hCCA (Bismuth type III and IV, TNM stage III and IV). Twelve patients who had received various regimens of neoadjuvant RCT before surgery (neoadjuvant group) were compared to a control group of forty-five patients, homogeneous in terms of age, sex, stage of the disease and biological values, who had undergone surgery without RCT. The neoadjuvant group showed a higher rate of downstaging of the tumor after surgery [91.7% (11/12) *vs* 51.1% (23/45), *P* = 0.01] and a higher rate of R0 resections [83.3% (10/12) *vs* 64.4% (30/45), *P* = 0.32]. On other hand, recurrence rate [83.3% (10/12) *vs* 68.9% (31/45), *P* = 0.48], DFS (26.0 mo *vs* 15.1, *P* = 0.91) and OS (32.9 mo *vs* 27.1, *P* = 0.26) did not show any advantage for the neoadjuvant group.

In 2018, a Japanese group[16] reported a retrospective study of 8 patients who received S-1 chemotherapy and 50 Gy RT as a neoadjuvant protocol for locally advanced hCCA. The authors defined as locally advanced a tumor for which a radical surgery was not technically feasible, not even by performing extreme surgery. In particular, three patients had broad extra-hepatic perineural invasion, three displayed broad bile duct infiltration, one had bilateral portal vein invasion and one bilateral hepatic artery involvement. Six of the eight patients (75%) succeeded in being reclassified as resectable after the neoadjuvant treatment and underwent left/right hemihepatectomy/trisegmentectomy with caudate lobectomy. Only one resection turned out to be R1. Three patients were relapse-free 104, 37 and 7 mo later, while three died from primary disease at 37, 31 and 17 mo from surgery.

A phase I trial named NACRAC[17], carried out by the Sendai team, established at 600 mg/m2 the recommended dose of gemcitabine (at day 1 and day 8, every three weeks) to associate at external beam radiation (1.8 Gy daily, total dose 45 Gy) for the neoadjuvant treatment of CCA. The phase II trial of the NACRAC study[18], aimed at evaluating the pathological curability after RCT as well as DFS and OS, is currently in progress. So far, twenty-five patients with advanced extrahepatic CCA have been enrolled and treated with neoadjuvant RCT. Three were not operated (for liver metastases, progression of the tumor, heart failure), two were not resected (both due to peritoneal carcinomatosis) and one patient was found to have a pancreatic cancer. Among the nineteen patients who were finally resected, seventeen (89.6%) got an R0 resection. Considering all the twenty-four patients recruited with CCA, R0 resection accounted for 70.8%. Since there were no deaths nor severe complications, up to now neoadjuvant RCT prior to surgery has proved to be safe and effective in enhancing free-margins resection for advanced hCCA and dCCA. At the end of the study (40 cases are necessary), once DFS and OS are known, proper indications for CCA will be defined.

Few cases of R0 resection after neoadjuvant chemotherapy (CT) alone for unresectable hCCA have been reported. Tada *et al*[19] achieved an R0 resection after an extended left hepatectomy with partial resection of the portal vein and regional node dissection in a patient with a Bismuth type III hCCA involving the portal bifurcation, treated by gemcitabine and S-1 combination chemotherapy in neoajduvant setting during four months. The 52-year-old patient was alive and disease-free at 29 mo from surgery. Sano *et al*[20] described another case report of unresectable hCCA, in which R0 resection required an arterial resection too, after neoadjuvant gemcitabine (two courses) at the high dose of 1000 mg/m2.

Photodynamic therapy (PDT) has been evaluated as a neoadjuvant treatment before surgery for advanced hCCA, by a German group[21]. Seven patients were included and managed to undergo an R0 resection; on the specimens, no viable tumor cells were found on the superficial layer of the bile duct into the depth of 4 mm. However, as the initial resectability was not assessed, there was no evidence of the role of PDT in getting negative margins. Thus, PDT is a low-risk procedure allowing destruction of the inner biliary epithelium, whose utility in neoadjuvant environs remains to be determined. (Table 1)

**RCT PRIOR TO LIVER TRANSPLANTIATION**

As previously mentioned, many hCCA patients are considered “unresectable” at diagnosis for a wide tumor extension at both hepatic lobes, for bilateral involvement of the segmental hepatic ducts or of the main vessels, for poor liver function in case of PSC or other liver chronic disease. In such a complex setting, RCT is considered as neoadjuvant treatment before OLT with the aim to downstage the tumor burden and to confine that within the organ to replace.

The first experiences of OLT for CCA included both intra and extra hepatic CCA. The results were absolutely discouraging in terms of recurrence and survival and CCA was regarded as a contraindication to OLT. In particular, Meyer *et al*[22] reported the largest series, made up of 207 patients from the Cincinnati Transplant Tumor Registry (1968-1997): 5 years survival was 23%, 51% recurred - almost all within two years - and survival after recurrence was extremely poor. Robles *et al*[23] described similar findings on a Spanish cohort of 59 patients, of which 36 with hCCA and 23 with iCCA; 5 years survivals were respectively 30% and 42%, recurrence rate 53% and 35%. OLT with incidentally found CCA did not show better intermediate and long-term survivals, according to a Canadian study[24].

The benefit of high dose combined external beam radiation and brachitherapy for extra hepatic CCA was already known thanks to the works published by Alden *et al*[25] in 1994: 2 years survival was 48% for patients treated with 55 Gy or more, 0% without RT. Moreover, Foo *et al*[26] in 1997 had observed an improved survival with the concomitant use of 5-FU chemotherapy. Following these findings, the Nebraska University group[27] was the first to combine neoadjuvant RCT and OLT in a selected cohort of seventeen patients with hCCA (Bismuth types III and IV) < 2 cm and no intra or extra-hepatic metastases. Neoadjuvant protocol provided only intra biliary brachitherapy, delivered through percutaneous trans hepatic catheters to a total dose of 60 Gy, and intravenous infusion of 5-FU (300 mg/m2/d), given until the transplantation. An exploratory laparotomy was performed while on the waiting list, when a liver donor was available: an extended lymphadenectomy was carried out and in the presence of extrahepatic involvement OLT was precluded. This happened to four patients, while two died from disease progression before the staging surgery. Eleven patients finally underwent OLT, seven of which had PSC and ulcerative colitis. Recurrence was confirmed in two patients, 4 and 5 mo after the transplantation. Four other patients died from post-operative complications while five patients (45%) were definitely alive and tumor-free with a median follow up of 7.5 (2.8-14.5) years from OLT. Although the high rate of septic complications due to the brachiterapy, the Nebraska University’s work did manage to achieve long term survivals in selected patients with unresectable hCCA.

The Mayo Clinic group proposed his original neoadjuvant protocol in 1993, combining irradiation and CT. Patients with early stage hCCA either judged unresectable by an experienced hepatobiliary surgeon or developed in the context of PSC were considered. Criteria for anatomic unresectability were well defined: bilateral segmental ductal extension, encasement of the main trunk of the portal vein, unilateral ductal extension with controlateral vascular encasement, unilateral liver atrophy in the presence of controlateral segmental ductal or vascular involvement. The first inclusion criteria embraced maximum tumor size of 3 cm, no extension below the cystic duct for hCCA without PSC, absence of intra or extra-hepatic metastases (including hepatic hilar lymph nodes metastases). Uncontrolled infections, previous RT or CT treatments or any attempts of surgery or percutaneous procedures (due to the risk of peritoneal tumor seeding) motivated the exclusion. Neoadjuvant treatment involved firstly external beam radiation (1.5 Gy twice a day, five days a week over three weeks, to a total of 45 Gy) followed by intra biliary brachitherapy (20-30 Gy, through iridium wires placed endoscopically or percutaneously). Intravenous 5-FU was administered at the dose of 500 mg/m2/d for the first three days of RT; 225 mg/m2/d were given later, from the beginning of the brachitherapy to the transplantation, with one-month pause for the staging surgery: an exploratory laparotomy was performed two to six weeks after the brachytherapy; a celiac and peripancreatic lymphadenectomy extended to the hepatic artery and distal common bile duct was performed, avoiding hepatic hilum dissection. Patients with no evidence of peritoneal, hepatic or lymphatic metastases were listed for OLT. In the pilot study published in 2000[28] nineteen patients were enrolled for neoadjuvant RCT. Four patients experienced biliary complications, one of which died from uncontrolled sepsis. Of the eighteen patients who underwent the staging surgery, six had metastases (five lymphatic, one peritoneal) and one developed a malignant ascites. Eleven patients were finally transplanted (of which one underwent retransplantation for early arterial thrombosis). All patients were alive, three with a follow up < 12 mo, the remaining eight with a mean follow up of 44 mo. Only one patient recurred 40 mo after OLT.

Since 1999, patients with tumor extension below the cystic duct were also included: in this case, a pancreatoduodenectomy had to be combined at OLT. In 2001, oral capecitabine (2000 mg/m2 per day, two out of every three weeks) was adopted as the maintenance chemotherapy from the brachitherapy to the OLT. Furthermore, since 2002, endoscopic US needle aspiration of the hepatic regional nodes before the beginning of the neoadjuvant treatment was added to the protocol: if positive, the patient was excluded and this did decrease the rate of positive staging laparotomy.

In 2006 Heimbach *et al*[29] updated the results of the Mayo Clinic (1993-2006): at that time, one hundred and six patients had begun the neoadjuvant treatment, ninety-four had undergone the staging operation, of which eighteen (19%) had shown contraindication for OLT; for the sixty-five patients finally transplanted, 1-year and 5-years survival were respectively 91% and 76% and 5-years DFS was 60%. Four patients (6%) died from complications of OLT and eleven (17%) recurred at the mean time of 29 mo after OLT. Recurrence was associated with older age, CA 19.9 > 100/mL before OLT, longer time on the waiting list; tumor grade, perineural invasion and residual tumor > 2 cm on the explanted liver were correlated as well.

An exception MELD score for patients having completed the neoadjuvant protocol had already been introduced by the United Network for Organ Sharing since 2002: from 2009 the score adopted was the same given for HCC, with additional points every three months on the list. A multicenter study[30] conducted on 12 American centers including 287 patients confirmed the excellent results already known. Considering all the patients who had started the neoadjuvant treatment (intention-to-treat), 5-years and 10-years OS were respectively 53% and 42%. With specific regards to the transplanted cohort of 214 patients, 5-years DFS was 65%, as in Heimbach’s previous report, and 10-years DFS 59%. Seventy-one patients dropped-out with a drop-out rate attested at 11.5% every three months, which confirmed the suitability of the additional MELD points introduced. Post-transplant recurrence was 20% (*n* = 43), post-transplant mortality 22% (*n* = 62). No significant difference in terms of survival was detected between patients with or without underlying PSC.

All these studies definitely confirmed that for patients with unresectable early stage hCCA meeting the Mayo Clinic criteria, neoadjuvant RCT followed by OLT can provide excellent long term DFS and OS. In terms of survival, the results are comparable to those achieved with OLT for chronic (hepatitis C) or malignant (hepatocarcinoma) disease and seem to exceed those accomplished with resection. That is the reason why RCT prior to OLT has been advocated as a choice even for resectable hCCA; actually, a French prospective randomized multicenter trial named TRANSPHIL[31] is currently in progress.

In the attempt to expand the strict Mayo Clinic criteria, the UCLA group has proposed a protocol[32] for locally advanced iCCA and hCCA in the absence of distant metastasis. They developed a prognostic risk score based on seven survival predictors, of which five were histological ones, to stratify patients in three different risk groups: low, intermediate and high risk. Tumor biopsy before the neoadjuvant treatment to assess the predictive variables and to determine the risk class was required. Low and intermediate patients underwent OLT after negative exploratory laparotomy. A second biopsy was necessary after the staging surgery only for high risk patients, in order to evaluated their response to the neoadjuvant treatment; in case of downstaging to intermediate or low risk class, OLT could be performed also for them. Adjuvant CT was eventually given based on the biological features of the pretreatment biopsy. For low risk group, a 5-years DFS at 78% was attested, while for intermediate 19%. Thus, this experience definitely showed that very good and acceptable 5-years DFS can be achieved respectively for low risk and for intermediate risk patients with locally advanced iCCA or hCCA, by expanding the Mayo Clinic criteria according to the UCLA stratification system.

RCT produces serious adverse-effects and technical issues. Before the transplant, hilar necrosis with intraductal debris can result in cholangitis, cholecystitis and hepatic abscesses, requiring hospitalization, antibiotics therapy and percutaneous procedures. Fibrosis makes isolation of the pedicle challenging during the transplant surgery. Above all, a high rate of post-transplant late vascular complications is due to the neoadjuvant regimen: considering the Mayo Clinic series up to 2006, Mantel *et al*[33] reported a 21% of arterial and a 22% of portal vein complications, as 40% of patients experienced a vascular impairment. In that series, the interposition of a donor iliac artery graft has reduced late complications only in deceased donor recipients as, on the other side, it is associated with more early technical problems in living donor recipients.

**CONCLUSION**

Up to now, there is no general consensus regarding the effectiveness of RCT as a neoadjuvant treatement before liver resection. Anyway, considering all the limitations of the studies cited, neaodjuvant RCT for patients with locally advanced hCCA is feasible and seems to allow R0 resections for initially unresectable tumors. The definitive results of the phase II trial of the NACRAC study will eventually confirm that and they will suggest whether neoadjuvant RCT can affect survival or not. A prospective multicenter trial based on a well-shared definition of unresectability of hCCA is absolutely needed.

Combined RCT and OLT are nowadays the treatment of choice for patients with early stage hCCA either unresectable or on underlying PSC who match the strict Mayo Clinic criteria. For these patients such synergism appears to provide DFS and OS higher than resection for resectable tumors, so that RCT prior to OLT is being investigated also for the latter ones. Protocols assessing the effectiveness of the combination RCT - OLT even for selected patients with locally advance hCCA and iCCA are ongoing, too.

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**Table 1** **Papers about neoadjuvant therapy before resection considered in this review**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Author** | **Yr** | **Type of study** | **Patients treated with NA RCT** | **Resectability** | **Neoadjuvant regimen** | **% of R0 (R0/resected)** | **Results achieved** | **Conclusions** |
| McMasters *at al*[11] | 1997 | Non randomized, prospective | 5 hCCA and 4 dCCA | All unresectable | 5-FU at 300 mg/m2, EBRT to 50.4 or 45 Gy | 100% (9/9) | Recurrence for hCCA: 0% | NA RCT can safely allow R0 resection. |
| Nelson *et al*[14] | 2009 | Retrospective | 12 (hCCA and dCCA) | 10 unresectable | 5-FU, EBRT to 50.4 Gy (11/12) ± brachitherapy (5/12) | 91% (11/12) | Better trend in 5-yr survival rate for NA RCT group | NA RCT can safely allow R0 resection. |
| Jung *et al*[15] | 2015 | Retrospective | 12, all hCCA | All unresectable | 5-FU/Gemcitabine, EBRT to 50.4 or 45 Gy | 83,3% (10/12) | Better R0 rate for NA RCT group; no advantage in DFS and OS | NA RCT can safely allow R0 resection, without improving DFS and OS. |
| Sumiyoshi *et al*[16] | 2018 | Retrospective | 8 hCCA | All unresectable | S-1, EBRT to 50 Gy | 71,4% (5/7) | Better DFS and OS for patients who underwent surgery after downstaging with NA RCT | NA RCT can safely allow R0 resection, improved DFS and OS for patients operated. |
| Katayose *et al*[18] | 2015 | Non randomized, prospective | 24 (hCCA and dCCA) | All advanced, possibly resectable | Gemcitabine 600 mg/m2, EBRT to 45 Gy | 80,9 % (17/21) | R0 rate: 80.9% of patients operated, 70.8% of all patients enrolled | NA RCT followed by surgery effective and well tolerated, DFS and OS yet to determine. |
| Tada *et al*[19] | 2012 | Case report | 1 hCCA | Unresectable | Gemcitabine + S-1 | 1/1 | R0 resection with portal resection, no recurrence at 29 mo | NA CT can allow R0 resection. |
| Sano *et al*[20] | 2011 | Case report | 1 hCCA | Unresectable | Gemcitabine | 1/1 | R0 resection with portal and arterial resection, no recurrence at 18 mo | NA CT can allow R0 resection. |

NA RCT: Neoadjuvant radiochemotherapy; hCCA: Hilar cholangiocarcinoma; dCCA: Distal cholangiocarcinoma; EBRT: External beam radiation therapy; 5-FU: 5-Fluorouracil; DFS: Disease free survival; OS: Overall survival.