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EDITORIAL – HEPATOBILIARY TUMORS

Comparing Apples to Oranges: Commentary on a Secondary Analysis of SWOG 0809

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We read with interest the post hoc secondary analysis of long-term outcomes from SWOG 0809[1] by Gholami et al.[2] The original SWOG 0809 was a nonrandomized controlled phase II trial of adjuvant capecitabine and gemcitabine followed by radiotherapy and concurrent capecitabine for extrahepatic cholangiocarcinoma and gallbladder carcinoma. With primary outcomes of 2-year overall survival as a function of R0 versus R1 resections, and examination of patterns of relapse and toxicity, SWOG 0809 included 13 patients with distal cholangiocarcinoma, 38 with hilar cholangiocarcinoma, and 25 with gallbladder cancer treated between 2008 and 2012. A total of 25 patients (36%) were enrolled after radical resection for stages pT2–4, or node-positive disease, or positive margin resections. In 2014, the trial reported similar overall survival (median 35 months) between R0 and R1 patients.[1] Considering the question of radiation, it is important to note that 14 (18%) patients experienced local recurrence at median follow-up of 25 months; of those, 9 had concurrent distant recurrence. A total of 10 patients received no radiotherapy (XRT), and of those, 3 developed local recurrence. Among the 69 patients who received radiation, local recurrence was significantly higher in patients who deviated from the prescribed radiation treatment protocol (42% vs 11%, $p = 0.02$), though reasons for this deviation that might elucidate selection bias were not provided. In this new secondary analysis, Gholami et al. report survival as a function of heretofore unreported nodal status of the 69 patients completing XRT. The stated aim is to benchmark survival for node-positive patients and inform future investigations. Gholami and colleagues conclude that 2-year survival was higher for N0 patients (62.5% vs 49.8%), and that N0 patients also enjoyed lower rates of distant recurrence (25% vs 42.2%).

Acknowledging that clinical trials in this space are understandably notoriously difficult to both accrue and analyze, we commend the trial collaborative and Gholami and colleagues for their efforts. This said, it is important to highlight what we can and cannot discern from both reports, given we are essentially comparing apples to oranges. First, it is challenging to draw meaningful conclusions about individual disease processes when they are grouped with maladies of widely disparate biology that require equally disparate considerations for resection. The nuanced differences of resectability definitions between gallbladder cancer (GBCA), hilar cholangiocarcinoma (hCCA), and distal cholangiocarcinoma (dCCA) are enough to make tumor boards and case conferences quite lively. Even if we make the argument that tumorigenesis of extrahepatic cholangiocarcinoma is similar and thus warrants grouping, we must consider GBCA as its own entity warranting standalone trials. The authors allude to this and demonstrate some major differences between GBCA and extrahepatic cholangiocarcinomas (eCCA), including the significantly higher nodal involvement of patients with eCCA (75.6%) versus GBCA (24.4%). They also note that distant recurrence rates differed more significantly by disease type, with 39% of patients with GBCA and 35% of patients with dCCA suffering distant recurrence, versus only 8% with hCCA.

Building on this, a few additional technical points of the work by Gholami et al. are worth discussion. Intriguingly, most node-negative patients were female, but most patients with GBCA were also female, and GBCA was less likely to

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be N1. Thus, we wonder if the conclusions made about nodal status are more a commentary on GBCA versus eCCA. Additionally, adequate nodal staging depends upon number of lymph nodes excised. Yet, number of nodes examined per patient is not listed in this new analysis focused on nodal positivity or in the original 0809 results that were published.[3] Even if we acquiesce to the summation of these disparate diseases as a viable whole worthy of analysis, inadequate lymphadenectomy may also contribute to insignificant signal of N1 disease effects on overall survival. Lastly, the authors conclude that node-positive patients had higher disease-free survival rates compared with historical controls. These controls are not referenced, and it seems that they are likely generated from equally heterogenous data borne of an historical era. Thus, one must be careful when suggesting that this particular adjuvant regimen confers a survival advantage.

As we consider the adjuvant regimen proposed, we must dive further into the details. In the original trial, of the 79 analyzed patients, only 24% completed all prescribed adjuvant treatments without interruption. Reported treatment disruptions are noted as either dose reductions or omissions of either gemcitabine or capecitabine. In this newly analyzed 69-patient cohort who completed XRT, the authors report that 21 (30%) patients experienced some form of treatment interruption, with 7 patients having interrupted XRT and 13 chemotherapy disruption. How many node-positive patients experienced treatment disruption is not noted in either analysis. In the original trial, neither R0 nor R1 patients differed in their disease-free survival. By noting that local-only recurrence is a relatively rare event (two patients with distal cholangiocarcinoma and one patient with hilar), Gholami et al. highlight the inevitable question: absent the potential for abscopal effects, what are we gaining with postoperative locoregional therapy?

While trials in this space are laudable in their efforts to clarify the role of adjuvant treatment in these patients with dismal prognoses, we find it difficult to use as benchmarks 69 heterogeneous patients with widely disparate disease subtypes and treatment courses; especially when only 24% of patients completed the prescribed regimen. Furthermore, given the exploratory nature of this analysis, the conclusion that adjuvant treatment "is associated with favorable outcome" regardless of nodal status "and may impact local control" in node-positive patients reaches a bit past what these hard-fought data can tell us. Thus, while we congratulate the study team and their post hoc analyzers for attempting to make sense of these aggressive and rare diseases and their management, we would love to see future studies more vigorously stratifying disease types so that we are indeed comparing apples to apples. In this context we want to particularly emphasize the relevance of molecular profiling of these cancers and the importance of integration of these aspects in future clinical trials.[4] By incorporating these endpoints in the future, we might not only better understand and stratify these biologically unique cancers, but also personalize treatment options for individual patients.

As a community, those who surgically treat biliary malignancies desperately await effective adjuvant treatment options to improve prognosis of our patients after resection of these rare tumor types. By incorporating more specific molecular and pathological stratification into our future trial designs, we can more rapidly use targeted therapies to improve the outcome of our patients.

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