Perspective

Effect of adjuvant chemotherapy with fluorouracil plus folinic acid or gemcitabine *vs.* observation on survival in patients with resected periampullary adenocarcinoma

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The authors are to be congratulated on the successful design and completion of this study, which addresses an infrequently examined question in a relatively rare disease complex. Seeking to discover whether adjuvant chemotherapy contributes to survival following an R0 or R1 resection of periampullary adenocarcinoma, they randomized a total of 434 patients to one of three arms. 145 patients were observed, 146 received adjuvant gemcitabine given in standard fashion 2 out of 3 weeks per month, and 143 received 5-FU/leucovorin as per the Mayo regimen, both for 6 months. In terms of anatomic classification, 297 cases were ampullary, 96 bile duct and 35 "other" in origin. Specifically addressing ampullary tumors, pathologic subclassification indicated that 80 tumors were intestinal subtype, 46 pancreaticobiliary subtype, and 9 mixed, but fully 162 were indeterminate.

While acknowledging that the use of adjuvant chemotherapy, as compared to observation only, was not statistically significant in the primary analysis, they have concluded that there is a statistically significant survival benefit when a multivariable analysis is performed. Further, they infer that the derived benefit of chemotherapy was independent of the regimen and finally suggest that the effects were modest at best.

In order to analyze these results and place them into context, it is important to recognize the complexity of the periampullary region where four disparate anatomical entities—duodenum, ampulla, bile ducts and pancreatic head—are in very close proximity. A malignancy originating in any one of these sites is often grossly indistinguishable from the others and a Whipple procedure is most often the surgery of choice regardless of anatomical origin or tissue type. As is common in many multi-center adjuvant trials following pancreaticoduodenectomy for pancreatic or peri-ampullary cancers, there is a presumption that the surgical techniques will be consistent and comparable for all patients. The data to support this presumption in the current series is scant or not provided. There appears to have been no standardization of protocols used for preoperative imaging studies and no central review of the radiographic staging prior to surgery. Thus, there is no way to know for sure if patients with borderline resectable tumors were identified and excluded. The fact that 20% of the entire surgical group had "extended or extended radical resections" and 16% had positive resection margins suggests that not all of these tumors were small, localized, and easily resectable cancers, and confounds the conclusions that can be drawn from a heterogeneous biologic group and one that likely has considerable anatomic and surgical variability.

This economy of surgical definition has been accompanied by a similar economy of pathologic description with a resultant uniformity to the selection of adjuvant therapy. The authors have made an attempt to tease out possible differences in outcome attributable to anatomic origin i.e. "ampullary" versus "bile duct" versus "other", but do not find statistical significance in their analysis. Unfortunately, there are many cases where anatomic origin and/or tissue subtype was unclear. As a result, this conclusion inherently risks missing critical differences in individual tumor subtype response and specific drug

efficacy. The end result is a study such as this—where data are incomplete, and where intrinsic differences are hinted at, and even considered, but then discarded as being statistically insignificant or unobtainable, owing to the large number of study subjects required. This then becomes an example of "lumping" rather than "splitting" and teaches us very little.

In many centers, as acknowledged by the authors, pathology reports are now routinely including immunohistochemical (IHC) staining in an attempt to better distinguish the different ampullary tumor types, and as a result may now have a descriptor which indicates either intestinal or pancreaticobiliary subtype. This is a step in the right direction, and may potentially inform the next generation of studies as to more specific treatment choices. A study from Oslo in 114 patients undergoing Whipple for periampullary carcinoma, confirms that pancreaticobiliary histologic subtype carries a poor prognosis relative to intestinal type and suggests that anatomical origin was not an independent prognostic factor given the association with tumor size and lymph node involvement (1). A second study of 118 similar patients in California reached an identical conclusion (2). Taking this a step further, a recent study of gene expression analysis in periampullary carcinomas identified the same 2 subgroups—biliary-like and intestinal-like with a poor and better prognosis respectively (3 years RFS of 31% *vs.* 75% P<0.05) (3). Unrelated factors such as perineural invasion, weight loss, pre-existing adenomas, and degree of blood loss during surgery could be additional stratifying variables in future study design (4). In the current study, patients with intestinal subtype had a median survival of 45.7 *vs.* 20.6 months for pancreaticobiliary subtype P=0.01.

As technology advances, the emphasis in oncology is beginning to switch from IHC to molecular signatures of biologic behavior. In this regard, markers of poor prognosis in recent reports have included 17p LOH and MSI negativity (5), hepatocyte nuclear factor 4a (HNF4a) expression negativity (6), lack of promyelocytic gene expression (7), and COX-2 overexpression (8). Human equilibrative nucleoside transporter 1 (hENT1) expression may correlate with histologic subtype and treatment response to gemcitabine (9). Future stratification is likely to rely more heavily on this type of approach as opposed to the sometime subjective, and not always successful, IHC.

The statistical analyses conducted and reported by the authors are clear and of a high standard. However, we identified a couple of areas for discussion. Firstly, as pertains to the design of the trial, it appears that no interim analysis was planned. Classical group sequential methods could have been considered (10). An interesting exercise would be to apply a group sequential approach based on observed trial data, and examine if the trial would have been terminated earlier had the method been implemented. This exercise could shed light on future study designs. Secondly, the key statistical analysis in this study is on the "treatment effect", examining the survival benefits between the three treatment groups. As the authors suggest, there are no significant differences in the survival among the three groups. A P-value of 0.03 comparing the gemcitabine group *vs.* the observation group is suggested. However, with multiple comparison adjustment, the P-value should not be deemed statistically significant. Subsequently, an additional test is performed to compare the hazard ratio between the observation group and the combined chemotherapy groups, and a P-value of 0.03 is obtained. However, the authors did not provide a sound justification for combining the two chemotherapy groups, and the action is perhaps questionable given that the two chemo groups compared differently with the observation group. Regarding disease-free survival, no mention is made of how patients were followed, and the intervals for postoperative imaging to detect recurrent disease were not specified. Lack of a standardized postoperative imaging protocol limits any conclusions about the efficacy, or lack thereof, for these treatments in terms of local disease control.

Finally, the selection of chemotherapy used in the randomization is debatable. Given the results of RTOG 97-04, which compared gemcitabine to 5-FU/leucovorin pre-and post 5-FU/RT in pancreatic cancer, most oncologists would consider 5-FU/leucovorin as given via the Mayo regimen to be inferior to gemcitabine for this group and certainly more toxic. The median survival and 3-year overall survival for patients treated with gemcitabine-based chemoradiotherapy compared with 5-FU-based chemoradiotherapy was 20.6 *vs.* 16.9 months and 32% *vs.* 21%, respectively (11). As more patients are likely to have had either pancreatic or the pancreaticobiliary subtypes of disease, as opposed to the intestinal variety, it would make sense that gemcitabine would be more successful than 5-FU/leucovorin across the board and this is certainly hinted at in the results. This could definitely be a source of prejudice in determining outcomes. Further, in 2012 it is unlikely that either gemcitabine or the Mayo regimen, as opposed to a more intensive and otherwise successful regimen such as FOLFOX or XELOX, would be selected as adjuvant therapy for those patients with an intestinal

subtype of tumor.

In conclusion, while this is an interesting and diligently conducted study, the limitations discussed means that it adds only modestly to the current debate on the optimal approach to adjuvant therapy in periampullary cancer. For the present, given the continued lack of data, it might reasonably be inferred that gemcitabine-based therapy for pancreaticobiliary subtypes, and 5-FU-based therapy for intestinal subtypes is an acceptable, if not yet satisfactory, choice for those deemed at high risk of recurrence. The addition of radiation therapy to the treatment protocol is even more contentious, with most European groups believing that this adds nothing based on studies such as that of the EORTC (12) and ESPAC-1 (13). In the USA, however, radiation is often incorporated into the plan based on a retrospective review from the Mayo Clinic, specifically in ampullary cancer, which was positive in those with lymph nodal involvement (14) and on the results of RTOG 9704 (1). Future studies will need to be much more definitive in the definition and selection of appropriate subgroups for the exploration of disease specific therapy, and molecular markers of prognosis and response should be actively sought and incorporated. Empiric therapy in the setting of incomplete histologic and molecular analysis is no longer acceptable in contemporary study design.

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