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Gastrointestinal Cancers: Timing Is Everything

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In this edition of Oncology Scan, we have some transitions to announce. First, Stanley Liauw will be rotating off the editorial board. Dr Liauw has been an Associate Editor since 2013, during which time he has been an integral member of the editorial team, providing thoughtful reviews and carefully rendered, well-balanced decisions. We thank him for his service these past 4 years. Additionally, I will be stepping down as Senior Editor of the gastrointestinal section, and we are very pleased to announce that Salma Jabbour will assume the role as the new Senior Editor.

Dr Jabbour has served as an Associate Editor for nearly 2 years, and I have also very much appreciated her hard work and dedication in ensuring high-quality, timely, and thoroughly considered reviews and decisions. I am confident she will be successful in her new role as she takes over a group of outstanding Associate Editors. It has been a pleasure working with them, with Dr Anthony Zeitman, and the entire staff of the *International Journal of Radiation Oncology, Biology, Physics* (the Red Journal) to continually improve the journal's quality through original research publications, special edition articles, these Oncology Scans, and newer article formats to engage the radiation oncology community. I would like to thank Anthony for this rewarding opportunity to be involved with the Red Journal and for his support, along with the rest of the Red Journal staff and editorial board.

We have selected 6 important articles for this edition of the Oncology Scan. The first is the recently published ESPAC-4 trial, showing that the combination of gemcitabine with capecitabine has improved survival compared with gemcitabine alone as adjuvant therapy for resected pancreatic cancer (1). Although the trial does not directly address a management decision in radiation oncology, the results are important nonetheless in moving the needle forward toward improving survival and systemic control, hopefully paving the way for an increased role for radiation therapy to meaningfully improve survival through better local-regional control. The next study is a secondary analysis of the landmark ACT II trial for anal cancer, looking at optimal timing of clinical assessment (2). The results should give clinicians guidance on when to assess for treatment response and when diagnostic and therapeutic interventions should and should not be considered. In keeping with the theme of timing, the next 2 articles are important prospective trials for rectal cancer. The Stockholm III trial, which previously reported interim toxicity results (3), was recently published showing outcome data (4). This trial tested short-course radiation therapy with 4 to 8 weeks' delay before surgery compared with the traditional short course and surgery 1 week later and long-course radiation, showing no difference in local-regional control or survival with delay after short-course radiation. The second article reports results of the GRECCAR-6 trial, which examined 7 versus 11 weeks' delay after chemoradiation and surgery for rectal cancer (5). These data help shed further light on the issue of optimal timing of pathologic response assessment, which is relevant to consider given the increasing interest in alternative treatment approaches including local excision and nonoperative management (NOM) for rectal cancer. Finally, the last 2 articles, which come from the same author group, use the National Cancer Database (NCDB) to describe the use of NOM in the United States and its associated outcomes (6, 7). We believe these articles are important for readers to be aware of because the authors use these data to caution against the use of NOM, though for reasons discussed below, these conclusions may be called into question.

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Neoptolemos et al. Comparison of adjuvant gemcitabine and capecitabine with gemcitabine monotherapy in patients with resected pancreatic cancer (ESPAC-4): A multicentre, open-label, randomised, phase 3 trial. *Lancet* 2017. (1)

Summary: In this randomized trial, 730 patients with an R0 or R1 resection for pancreatic cancer were randomized to adjuvant gemcitabine chemotherapy (1000 mg/m^2, weeks 1-3) for 6 monthly cycles, alone or in combination with capecitabine (1660 mg/m^2, days 1-21) for 6 monthly cycles. The primary endpoint was overall survival (OS). Patients were drawn from 92 hospitals across the United Kingdom, France, Germany, and Sweden.

With a median follow-up of 43.2 months, the trial showed improved OS ($P = .032$) with gemcitabine and capecitabine compared with gemcitabine alone (Table 1).

On multivariate analysis, treatment arm, resection margin, postoperative CA 19-9, tumor grade, lymph node positivity, and maximum tumor size were significantly correlated with OS. Median dose intensity was 93% in the gemcitabine-alone arm and 83% in the gemcitabine and capecitabine arm, and 65% of gemcitabine patients received all 6 cycles, compared with 54% of gemcitabine and capecitabine patients. The distant relapse rate was similar between the gemcitabine-alone (66%) and the gemcitabine and capecitabine arms (65%). The overall local relapse rate was 50%, higher in the gemcitabine alone arm (53%) than in the gemcitabine and capecitabine (46%). Grade 3 to 4 adverse events were significantly worse for gemcitabine and capecitabine with respect to diarrhea (5% vs 2%), neutropenia (38% vs 24%), and hand-foot syndrome (7% vs 0%). No difference in quality of life was noted between the 2 arms.

Comments: For resected pancreatic cancer, the ESPAC-4 study establishes that gemcitabine combined with capecitabine is a new standard of care in adjuvant chemotherapy regimen. This combination provides a median survival benefit of 2.5 months over gemcitabine alone. This trial also demonstrates outstanding collaboration among the European community, having accrued 732 patients, but it is not entirely uniform in the patient characteristics and styles of management. For example, the study design did not specifically dictate the method of follow-up, and options for follow-up could include hematology, clinical chemistry, and use of a tumor marker. Additionally, there did not seem to be a clear plan at which time points to monitor patients or to routinely image patients as part of their surveillance. Likewise, it is unclear what methods were taken to classify patients into resectable versus borderline resectable status preoperatively, if at all.

Table 1 Survival outcomes for each arm of ESPAC-4

Outcome	Gemcitabine	Gemcitabine + capecitabine
Median OS (mo)	25.5	28
2 year OS (%)	52.1	53.8
5-year OS (%)	16.3	28.8
Median OS (R0 resection) (mo)	27.9	39.5
Median OS (R1 resection) (mo)	23	23.7

Although patients underwent up-front surgery, 60% of patients in this study had R1 resections, which are known to portend a worse survival rate than R0 status (8). It is known that the prognosis of pancreatic cancer resection may be improved with higher-volume pancreatic cancer hospitals (9). In addition, in the United States the paradigm has generally shifted to favor preoperative therapy if the pancreatic cancer is deemed "borderline resectable," because this term implies that up-front surgery would result in R1 resections, owing to vasculature abutment. For patents with borderline resectable pancreatic cancer, preoperative therapy should be considered (10, 11). In a prospective study consisting of induction FOLFIRINOX and 50.4 Gy of chemoradiation, 68% of patients underwent surgery and 93% had negative margins. Median OS was 21.7 months (12).

In the ESPAC-4 study, subjects with R1 status experienced median survival rates of 23 and 23.7 months, compared with patients with R0 resections who experienced a median survival of 27.9 and 39.5 months for gemcitabine alone and gemcitabine plus capecitabine, respectively. These data suggest that intensifying chemotherapy is not beneficial in the setting of positive margins. It is possible that the high rate of R1 resections resulted in higher local recurrence rates, and in total, 50% of patients had local recurrence at a site of relapse. However, the article does not correlate pattern of relapse to margin status, and local recurrence may have been alone or with synchronous systemic relapse (liver 41%, other intra-abdominal 23%, lung 11%, bone 3%). These high rates of local recurrence beg the question of whether postoperative radiation therapy has a role.

An enduring question in pancreatic cancer management, both in the resectable and borderline settings, is whether radiation therapy is of benefit. To date there seem to be no survival benefits from the incorporation of postoperative radiation therapy in addition to traditional chemotherapy in modern series (13). However, with incremental improvements in systemic therapy, the potential for local-regional control to meaningfully impact OS increases. Ongoing prospective studies such as Radiation Therapy Oncology Group protocol 0848 will elucidate the role of radiation therapy in the postoperative setting, and the Alliance trial A021501 will do so in the preoperative setting for borderline resectable pancreatic cancers.

Glynne-Jones et al. Best time to assess complete clinical response after chemoradiotherapy in squamous cell carcinoma of the anus (ACT II): A post-hoc analysis of randomised controlled phase 3 trial. *Lancet Oncol* 2017. (2)

Summary: The ACT II trial randomized 940 patients with squamous cell carcinoma of the anal canal (SCCA) in a