Pancreatic cancer: are more chemotherapy and surgery needed?

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Most patients diagnosed with pancreatic cancer die from the disease. Although mortality from the most common cancers has declined in the past few decades, the mortality for patients with pancreatic cancer has remained high. On the basis of rising incidence, demographic data, and survival projections, pancreatic cancer is predicted to become the second most deadly cancer in the near future.[1]

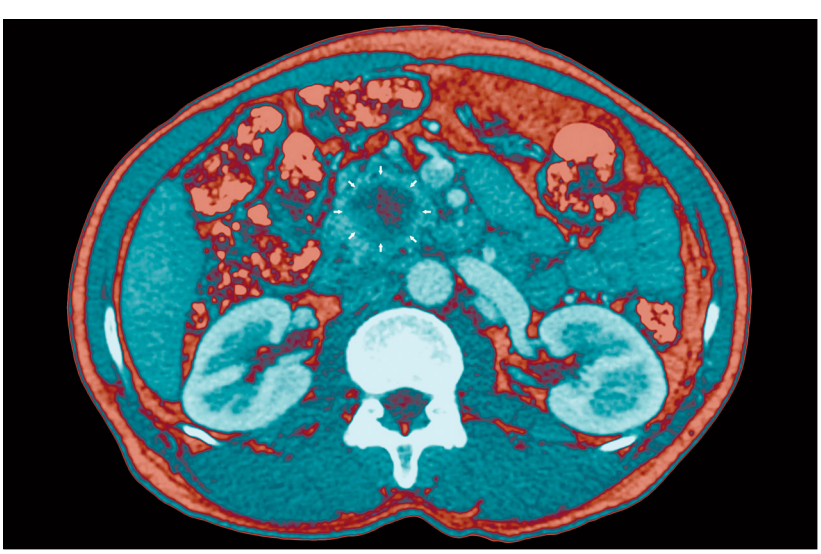
Pancreatic cancer is curable only in a small minority of patients with localised and resectable tumours, which accounts for only 5–10% of the cases, and only 10–20% of patients survive more than 5 years after surgery. With such bleak figures, every attempt made to improve the survival rates of patients with pancreatic cancer should be welcomed. This is the aim of the ESPAC-4 trial published in *The Lancet*.[2]

John Neoptolemos and colleagues report the first results of the ESPAC-4 trial for the pancreatic cancer cohort.[2] This was a multicentre, open-label, randomised trial of gemcitabine alone or in combination with capecitabine in the adjuvant setting for completely resected (R0 or R1) ductal pancreatic adenocarcinoma. The data show a significant improvement of median overall survival with an absolute increase of 2·5 months for the experimental chemotherapy combination group (28·0 months compared with 25·5 months in the standard gemcitabine group; hazard ratio [HR] for overall survival 0·82 [95% CI 0·68–0·98], p=0·032). The 5-year survival rates show an absolute improvement of 12·5%, with 28·8% of patients alive in the combination group versus 16·3% in the gemcitabine group. The toxicities of the combination group were as expected and more pronounced but easily manageable with no detrimental effect on quality of life. The authors conclude that the combination of gemcitabine and capecitabine is now the treatment of choice in the adjuvant setting following resection for pancreatic ductal adenocarcinoma.

These results open the field to several questions. Can an increase in chemotherapy cure more patients in a cancer considered for more than 60 years to be chemoresistant? Do the figures from the ESPAC-4 trial at 5 years really represent patients cured of pancreatic cancer? How can we now improve the survival of patients with pancreatic cancer further? Do we need to give patients more surgery or more chemotherapy?

First, the paradigm of pancreatic cancer as a chemoresistant tumour has been largely undermined in the past 5 years.[3] In the metastatic setting, oncologists can now choose between diverse monotherapy or a combination of gemcitabine, fluorouracil, nab-paclitaxel, oxaliplatin, irinotecan, and liposomal irinotecan. This means there are more chemotherapy drugs available for pancreatic cancer than for colon cancer.

A meta-analysis of adjuvant trials in pancreatic cancer published 10 years ago showed that adjuvant chemotherapy gave patients only an extra 3 months of median survival time, without offering a cure.[4] So does the addition of capecitabine to gemcitabine in the adjuvant setting of pancreatic cancer really translate into more patients being cured? In the ESPAC-4 trial, the 5-year relapse-free survival figures were 11·9% (95% CI 7·8–16·9) in the gemcitabine group and 18·6% (13·8–24·0) in the combination group, giving an absolute difference of 6·9%, but these were only estimates. The authors also state from the raw data that at the time of analysis, tumour recurrence was observed in 243 (66·4%) patients in the gemcitabine group and 236 (64·8%) in the combination group. Additionally, 43 (11·7%) patients in the gemcitabine group and 35 (9·6%) patients in the combination group died without recurrence. Therefore, the number of patients alive without disease at the end of the analysis was 80 (21·8%) patients in the gemcitabine group



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and 93 (25·5%) patients in the combination group; an absolute improvement and likely cure rate of 3·7%. This means that roughly we need to treat 25 patients with the combination of gemcitabine and capecitabine to save one more life. Of course, this further adds to the other gains achieved with the previous ESPAC trials as discussed by the authors. As for cure, more follow-up is needed to ascertain that this is the case and not only prolongation of survival. No patient has yet crossed the 5-year survival boundary, with a median follow-up in the current analysis of 43·2 months, ranging from 39·7 to 45·5. A more recent Bayesian network meta-analysis showed that adjuvant fluorouracil or gemcitabine reduced mortality after surgery by about a third, supporting the idea of likely cure in the present trial.[5]

So, even if modest, these figures are encouraging in a disease with such high mortality and clearly establishes the combination of gemcitabine and capecitabine as a new standard of care in the adjuvant setting of pancreatic ductal adenocarcinoma.

How can we further improve these results in the future? There is clearly a need for some kind of biomarker that could guide the choice of treatment or even surgery. The results of several other large adjuvant trials with new drugs or a combination of drugs are also eagerly awaited and it is likely that more chemotherapy will translate into more patients being cured. But again, this will be only for a small subset of patients with pancreatic cancer who received surgery.

More surgery is therefore clearly needed if we want to cure more patients, but more surgery means the possibility to offer surgery earlier in the disease evolution, and as a consequence more often. An earlier diagnosis would allow surgery to be offered earlier, for example, by the appropriate screening of individuals with higher risk for pancreatic cancer,[6] or for borderline resectable or unresectable patients, by the use of new neoadjuvant therapeutic approaches.[7] Surgical technique itself is well defined, with clear anatomic landmarks, and standardised techniques, including portal vein resection when necessary. Another positive aspect is the enhanced recovery pathway such as ERAS (Enhanced Recovery After Surgery) that significantly decreases postoperative complications.[8] This is of importance as fit patients after surgery are more likely to tolerate 6 months of adjuvant chemotherapy without interruption.

We clearly need to provide more surgery for patients especially those with R0 resections since this is the population benefiting most from postoperative chemotherapy in ESPAC-4 with a median survival of 27·9 months (95% CI 23·8–34·6) in the gemcitabine group, reaching 39·5 months (32·0–58·0) in the combination group versus 23·0 months (21·6–26·2) in the gemcitabine group and 23·7 months (20·7–27·1) in the combination group in R1 patients.

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