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**Pancreatic cancer and FOLFIRINOX: should we resect all responders?**

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The Heidelberg group has again taken another bold step in the fight against pancreatic cancer showing that 61% of initially non-resectable pancreatic cancers can be resected following neoadjuvant FOLFIRINOX therapy 1.

With 575 patients, this is by a substantial amount the largest ever single cohort series producing a resection rate that readily exceeds those previously reported in any single centre 2 as well as the 25.9% and 26.1% pooled resection rates reported respectively in two recent meta-analyses 3, 4. Criteria for non-resectability in 76.3% of 570 patients comprised arterial (211 patients), venous (61 patients) or combined vascular involvement (163 patients). The resectability criteria seem similar to those proposed by the ISGPS and NCCN5, 6. Interestingly there were also metastases in 23.7% (135) patients, significantly more in the FOLFIRONOX group (47.2%) compared to the remainder (16.9%).

Progress, which is so urgently needed for pancreatic cancer 7, is usually achieved with bold new ideas and approaches. The emboldened surgical approach, combined with FOLFIRINOX may account for some of the greater resectability rate seen in the FOLFIRINOX group. It is not clear however, whether all of the 575 patients were seen in Heidelberg from initial diagnosis with planned neoadjuvant treatment or whether for at least a significant proportion of these, this was undertaken by referring centres. If so, this would introduce an important level of bias.

The overall median time from diagnosis to resection was 5.1 months (6.5 months for FOLFIRINOX) and median overall survival was 15.3 months (16.0 months for FOLFIRINOX) after resection, resulting in an estimated median overall survival of 20.4 months after diagnosis (22.5 months for FOLFIRINOX).

A recent meta-analysis of 315 patients with locally advanced pancreatic cancer who were treated with FOLFIRINOX had a median survival of 24.2 months (95% confidence interval 21.7–26.8 months) but only a quarter had resectional surgery 3, suggesting that patients that respond to therapy might have a significant survival benefit even without surgery. Selection bias remains a confounding factor in all studies however, unless controlled by randomization. There were 51 patients in the Heidelberg series who had a resection with M1 disease comprising 29 (38.2%) in the FOLFIRINOX 11 (7.4%) in the gemcitabine based group and 11 (16.7%) in the others. This challenges the current notion to exclude all metastatic patients from neoadjuvant and resectional treatment.

FOLFIRINOX has the drawback of being quite toxic requiring normalisation of liver function and a performance status of zero for drug administration but there may be better options than gemcitabine alone in such cases. In the adjuvant ESPAC-4 trial, there was a remarkable almost doubling of the 5 year survival rate with the combination of gemcitabine and capecitabine (to 29%) compared with gemcitabine alone (16%) but with minimal toxicity 8. The recent findings of LAP07 should put to bed any argument in favour of routine radiation therapy in this setting 9, 10. Patients should be encouraged to participate in randomized controlled trials such as ESPAC-5F, which is comparing neoadjuvant FOLFIRINOX versus gemcitabine plus capecitabine versus chemoradiation compared to straight to surgery for borderline resectable disease, or the NEOPAN trial that compares FOLFIRINOX to gemcitabine for locally advanced cancers.

A key aspect of the Heidelberg experience was that adjuvant therapy, mainly gemcitabine based for a 6-months, was also given to 69.6% of all patients – this is despite the fact that that they had received a similar duration of neoadjuvant treatment and then major surgery. This combined modality approach probably likely accounts for the reported outcomes. This might not be precision medicine but it is combination chemotherapy with precision surgery and is hugely progressive.

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