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PRESS REVIEW

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■ Hammel P, Huguet F, van Laethem JL, et al. Effect of chemoradiotherapy vs. chemotherapy on survival in patients with locally advanced pancreatic cancer controlled after 4 months of gemcitabine with or without erlotinib: the LAP07 Randomized Clinical Trial. JAMA 2016;315:1844—53. DOI: 10.1001/jama.2016.4324

IMPORTANCE: In locally advanced pancreatic cancer, the role of chemoradiotherapy is controversial and the efficacy of erlotinib is unknown.

OBJECTIVES: To assess whether chemoradiotherapy improves overall survival of patients with locally advanced pancreatic cancer controlled after 4 months of gemcitabine-based induction chemotherapy and to assess the effect of erlotinib on survival.

DESIGN, SETTING, AND PARTICIPANTS: In LAP07, an international, open-label, phase 3 randomized trial, 449 patients were enrolled between 2008 and 2011. Follow-up ended in February 2013.

INTERVENTIONS: In the first randomization, 223 patients received 1000 mg/m^2 weekly of gemcitabine alone and 219 patients received 1000 mg/m^2 of gemcitabine plus 100 mg/d of erlotinib. In the second randomization involving patients with progression-free disease after 4 months, 136 patients received 2 months of the same chemotherapy and 133 underwent chemoradiotherapy (54 Gy plus capecitabine).

MAIN OUTCOMES AND MEASURES: The primary outcome was overall survival from the date of the first randomization. Secondary outcomes were the effect of erlotinib and quality assurance of radiotherapy on overall survival, progression-free survival of gemcitabine-erlotinib and erlotinib maintenance with gemcitabine alone at the second randomization, and toxic effects.

RESULTS: A total of 442 of the 449 patients (232 men; median age, 63.3 years) enrolled underwent the first randomization. Of these, 269 underwent the second randomization. Interim analysis was performed when 221 patients died (109 in the chemoradiotherapy group and 112 in the chemotherapy group), reaching the early stopping boundaries for futility. With a median follow-up of 36.7 months, the median overall survival from the date of the first randomization was not significantly different between chemotherapy at 16.5 months (95% CI: 14.5—18.5 months) and chemoradiotherapy at 15.2 months (95% CI: 13.9—17.3 months; hazard ratio [HR]: 1.03; 95% CI: 0.79—1.34; $P = 0.83$). Median overall survival from the date of the first randomization for the 223 patients receiving gemcitabine was 13.6 months (95% CI: 12.3—15.3 months) and was 11.9 months (95% CI: 10.4—13.5 months) for the 219 patients receiving gemcitabine plus erlotinib (HR: 1.19; 95% CI: 0.97—1.45; $P = 0.09$; 188 deaths vs. 191 deaths). Chemoradiotherapy was associated with decreased local progression (32% vs. 46%, $P = 0.03$) and no increase in grade 3 to 4 toxicity, except for nausea.

CONCLUSIONS AND RELEVANCE: In this open-label, randomized trial involving patients with locally advanced pancreatic cancer with disease controlled after 4 months of induction chemotherapy, there was no significant difference in overall survival with chemoradiotherapy compared with chemotherapy alone and there was no significant difference in overall survival with gemcitabine compared with gemcitabine plus erlotinib used as maintenance therapy.

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Comments

1. The role of chemoradiation (CR) in this setting is heatedly debated as five randomized studies have produced contradictory results [1—5]. Moreover, retrospective studies have suggested that induction chemotherapy could improve survival [6], avoiding administration of local CR in patients who have rapidly progressive disease.
2. This international phase III study, focused on this specific problem, is negative, and was unable to show any benefit of intensification chemotherapy with erlotinib; CR impacted local disease control but not survival.
3. Protocol deviations were not retained as a possible explanation for the absence of benefit from radiotherapy, because these deviations were major in only 18% of cases and did not influence survival. A radiotherapy quality assurance program had been instituted and tolerance was judged to be satisfactory.
4. While another randomized trial has shown a two-week difference in overall survival in favor of erlotinib, the current study definitively removes this molecule from the therapeutic arsenal for pancreatic cancer.
5. These results suggest that before thinking of intensifying local control, more efficient systemic treatments, aiming to eradicate micro-metastatic disease, should be used. Along these lines, Folfirinox and nab-paclitaxel seem to be promising options [7,8].

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■ Markar SR, Gronnier C, Duhamel A, et al. Significance of microscopically incomplete resection margin after esophagectomy for esophageal cancer. Ann Surg 2016;263:712—8. DOI: 10.1097/SLA.0000000000001325

OBJECTIVE: The objectives of this study were to establish if R1 resection margin after esophagectomy was (i) a poor prognostic factor independent of patient and tumor characteristics, (ii) a marker of tumor aggressiveness and (iii) to look at the impact of adjuvant treatment in this subpopulation.

METHODS: Data were collected from 30 European centers from 2000 to 2010. Patients with an R1 resection margin ($n = 242$) were compared with those with an R0 margin ($n = 2573$) in terms of short- and long-term outcomes. Propensity score matching and multivariable analyses were used to compensate for differences in baseline characteristics.

RESULTS: Independent factors significantly associated with an R1 resection margin included an upper third esophageal tumor location, preoperative malnutrition, and pathological stage III. There were significant differences between the groups in postoperative histology, with an increase in pathological stage III and TRG 4-5 in the R1 group. Total average lymph node harvests were similar between the groups; however, there was an increase in the number of positive lymph nodes seen in the R1 group. Propensity matched analysis confirmed that R1 resection margin was significantly associated with reduced overall survival and increased overall, locoregional, and mixed tumor recurrence. Similar observations were seen in the subgroup that received neoadjuvant chemoradiation. In R1 patients adjuvant therapy improved survival and reduced distant recurrence however failed to affect locoregional recurrence.

CONCLUSIONS: This large multicenter European study provides evidence to support the notion that R1 resection margin is a prognostic indication of aggressive tumor biology with a poor long-term prognosis.

Comments

1. This is the first large-scale study showing that R1 resection is a poor prognostic factor, independently of tumor or patient characteristics.
2. The other main importance of this study is to show that R1 resection is related more to tumor biology aggressiveness than to sub-optimal surgery. Even in well-trained teams, multimodal therapy is highlighted as being essential. This is in line with similar concepts published recently for surgery in patients with rectal, pancreatic and liver metastatic cancer [1—3].
3. Last, this study suggests that, unlike the use of adjuvant radiotherapy to limit the risk of locoregional recurrence after R1 resection, chemotherapy offers a better survival benefit for these patients, notably by decreasing the risk of metastasis. This makes sense if one admits that R1 resection attests to particularly aggressive tumor biology.

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■ Stenberg E, Szabo E, Ågren G, et al. Closure of mesenteric defects in laparoscopic gastric bypass: a multicentre, randomised, parallel, open-label trial. Lancet 2016;387:1397—404. DOI: 10.1016/S0140-6736(15)01126-5

BACKGROUND: Small bowel obstruction due to internal hernia is a common and potentially serious complication after laparoscopic gastric bypass surgery. Whether closure of surgically created mesenteric defects might reduce the incidence is unknown, so we did a large randomised trial to investigate.

METHOD: This study was a multicentre, randomised trial with a two-arm, parallel design done at 12 centres for bariatric surgery in Sweden. Patients planned for laparoscopic gastric bypass surgery at any of the participating centres were offered inclusion. During the operation, a concealed envelope was opened and the patient was randomly assigned to either closure of mesenteric defects beneath the jejunojejunostomy and at Petersen's space or non-closure. After surgery, assignment was open-label. The main outcomes were reoperation for small bowel obstruction and severe postoperative complications. Outcome data and safety were analysed in the intention-to-treat population. This trial is registered with ClinicalTrials.gov, number NCT01137201.

FINDINGS: Between May 1, 2010, and Nov 14, 2011, 2507 patients were recruited to the study and randomly assigned to closure of the mesenteric defects ($n = 1259$) or non-closure ($n = 1248$). A total of 2503 (99.8%) patients had follow-up for severe postoperative complications at day 30