Author’s response to reviews

Title: Adjuvant chemoradiation in pancreatic cancer: impact of radiotherapy dose on survival

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REVIEWER #1:
Michael Back:
This is a well-structured manuscript originating from a large longstanding international database collaboration in pancreatic cancer. The data that is provided gives further evidence towards radiation dose response, and potential survival advantages of dose escalation above 45Gy, and potentially to beyond 55Gy. There is a well-defined population, results are presented with clarity and the discussion provides a sound overview of issues relating to adjuvant therapy. The manuscript is likely to be eventually suitable for publication but should be improved by addressing the following aspects with further analysis from their database.

Comment 1:
The timeframe of the study extend from 1995-2008 over which period staging investigations and more conformal RT techniques improved significantly. The more recently managed patients may have not only been more likely to receive doses beyond 55Gy but also may have had more effective staging procedures excluding the presence of previously occult metastatic disease. The authors should provide the RT doses in relation to year of treatment. The year of treatment can also be include in statistical analysis to determine whether it is an independent prognostic factor.

Answer 1:
Thank you very much for the suggestion. In fact, the patients were treated over a fairly long period of time, in which the evolution of imaging techniques could have penalized patients who underwent earlier therapy. For this reason we have divided the patients as suggested into 4 groups (1995-1998, 1999-2002, 2003-2005, 2006-2008) and we studied the correlation between:

1) administered dose and treatment period
2) overall survival and treatment period.

The analysis showed that dividing patients into 4 groups, treated with resection in the years 1995-1998 (54 patients), 1999-2002 (89 patients), 2003-2005 (187 patients), and 2006-2008 (184 patients), respectively, the mean postoperative RT dose underwent a slight but statistically significant increase (50.6 +/- 4.9 Gy, 50.0 +/- 3.2 Gy, 51.2 +/- 3.9 Gy, 52.6 +/- 4.9 Gy, respectively; p < 0.001). This could indicate as you suspected that patients who received higher doses were more recently irradiated. Therefore, thanks to the higher sensitivity of imaging techniques, they could have been favoured in terms of selection of truly non-metastatic and resectable patients, independently of the chemoradiation dose. Overall survival was also significantly improved in patients treated in more recent periods. Indeed, in the 4 groups, median survival was 14, 20, 26, and 24 months, respectively (p: 0.034). Therefore, we added the following sentences to the manuscript:

Results section, line 22-41, page 11: "Moreover, considering that patients were treated over a fairly long period of time, in which the evolution of imaging techniques could have penalized patients treated in an earlier period, we divided them into 4 groups based on the year of resection: 1995-1998 (54 patients), 1999-2002 (89 patients), 2003-2005 (187 patients), and 2006-2008 (184 patients) and we
analysed the correlation between treatment period and administered dose and survival. In the 4 groups, the mean postoperative RT dose underwent a slight but statistically significant increase (50.6 +/- 4.9 Gy, 50.0 +/- 3.2 Gy, 51.2 +/- 3.9 Gy, 52.6 +/- 4.9 Gy, respectively; p < 0.001). Furthermore, OS was also significantly improved in patients treated in more recent periods. Indeed, in the 4 groups, median survival was 14, 20, 26, and 24 months, respectively (p: 0.034). However, also this difference was not confirmed at multivariate analysis.

Comment 2:
The favorable dose response described in multivariate analysis is related to 45Gy dose level. As a dose of 50.4Gy is now become more standard the results could detail the analysis performed on the dose level of 55Gy as the reference dose, especially at 2-year survival. The numbers of patients in this >55Gy cohort should be adequate for this calculation, especially against the 50-55Gy cohort.

Answer 2:
Thank you for this comment. In fact, an interesting aspect of our analysis is to evaluate whether doses higher than "standard" (> 55 Gy) produce a significant advantage compared to "standard" doses. For this reason, we performed a univariate analysis (logrank) including only the 50-55 Gy and > 55 Gy groups. We also repeated the multivariate analysis including only these same subgroups and considering the group > 55 Gy as a reference. The results of these analyses were added to the manuscript as follows:

Results section, line 42-52, page 11: “Furthermore, to assess more specifically whether doses higher compared to doses now considered as standard (50 Gy) are actually more effective, we repeated the univariate and multivariate analysis including only the two subgroups of 50-55 Gy and > 55 Gy. Univariate analysis confirmed the advantage in the cohort receiving > 55 Gy compared to patients treated with 50-55 Gy (2-year OS: 60.0% vs 45.0%, respectively; p: 0.033). Multivariate analysis, considering the group > 55 as a reference, confirmed a trend in terms of higher risk of death in the 50-55 Gy group (HR: 1.31; 95% CI: 0.98-1.74; p: 0.066)

Discussion section, line 32-47, page 12: “We should admit that the comparison in terms of survival, including only the two groups treated with the highest doses (50-55 Gy and > 55 Gy), showed a statistically significant improvement in the second group at univariate analysis but with only a trend at multivariate analysis. However, it should be noted that the possibility of detecting a statistically significant difference was limited by the presence in the first group of 79/336 (23.5%) patients receiving a dose of 54.0-55.0 Gy and in the second group of 6/80 patients (7.5%) receiving a dose < 56 Gy. In other words, more than 30% of the patients included in this sub-analysis received a dose between 54 and 56 Gy, practically equivalent from the clinical point of view.”

Comment 3:
The discussion can be broadened by describing some of the issues related to potential morbidity from dose escalation, especially in relation to current protocols that deliver neoadjuvant chemotherapy prior to surgical procedures. Will the morbidity of 55 Gy be heightened significantly when patients have more extensive definitive management? Perhaps the paper by Morganti, referred to in the text (reference 35) could be expanded upon in the discussion.

Answer 3:
Thank you for your suggestion. Accordingly, we changed the discussion section, line 25-39, page 15 as follows: “Furthermore, with the use of conformal techniques (3D-conformal or IMRT), it is possible to administer even higher doses. A dose escalation study showed the possibility to deliver 55 Gy with slightly accelerated fractionation (2.2 Gy/fraction) without significant toxicity [35].”
doses or to intensify the treatment with accelerated regimens. For example, in a dose escalation study based on the 3D-conformal technique with a concomitant boost on the tumor bed, a dose of 55 Gy was reached with a slightly accelerated fractionation (2.2 Gy/fraction) and with concurrent capecitabine. Although this regimen is equivalent to a dose of 57.2 Gy in 2 Gy/fraction ($\alpha/\beta$ ratio: 3) and despite the administration of two cycles of gemcitabine before CRT, no patient showed grade $> 2$ toxicity. [35]

Moreover we added the following sentence to the discussion section, line 7-11, page 16: “However, higher than standard doses should be prescribed with caution in patients previously treated with neoadjuvant or adjuvant multiple-drug CT, being that the impact of intensified systemic treatments on tolerance to subsequent CRT is not known.”

Comment 4:
The proportion of patients receiving chemotherapy was far greater in the $> 55Gy$ subgroup. However chemotherapy presumably was not associated with survival on multivariate analysis. This could be more detailed in the results and discussion.

Answer 4:
Thank you for this correct observation. In fact, the group of patients who received a dose $> 55$ Gy differed significantly from others both for more unfavourable prognostic characteristics (higher percentage of patients with positive margins, with tumor diameter $\geq 30$ mm, with pT4 and pN+ stage) and for an increased use of adjuvant chemotherapy (Table 1). How these factors influenced the final result of the analysis is not easy to interpret. However, it should be emphasized that in the multivariate analysis, the lymph node involvement was statistically correlated to survival while the same did not happen for adjuvant chemotherapy. Therefore, as a whole, it is not possible to state that this subgroup of patients presented more favourable characteristics compared to the others.

Accordingly, as suggested, we added to the results section, line 42-50, page 9 the following sentence: “In particular, the cohort of patients who received a dose $> 55$ Gy differed significantly from the other groups both for more unfavourable prognostic characteristics (higher percentage of patients with positive margins, with tumor diameter $\geq 30$ mm, with pT4 and pN+ stage) and for an increased use of adjuvant CT (Table 1).” and to the discussion section, line 42-50, page 14 the following paragraph: “How the different disease (higher T and N stage, higher rate of R1 resection, larger tumors) and treatment (increased the use of CT) characteristics in the group treated with $> 55$ Gy influenced the final result of the analysis is not easy to interpret. However, it should be emphasized that in the multivariate analysis, the lymph node involvement was statistically correlated to survival while the same did not happen for adjuvant CT. Therefore, as a whole, it is not possible to state that this subgroup of patients presented more favourable characteristics compared to others.”

REVIEWER#2:
James Bates:
This manuscript is addresses an important question in the field of radiation oncology and will be directly useful in the day-to-day practice of those who treat pancreatic cancer. The question of RT dose-response in the adjuvant treatment of pancreatic cancer is vital, especially given the low RT doses and split course techniques used by prior randomized studies. The authors show that the highest doses are associated with the greatest overall survival and do so with alacrity and rigorous methodology. However, there are several small changes that would improve the value of the manuscript.

Comment 1:
The authors mention that "some centers [had] equipment able to deliver higher doses." Elaboration of these techniques is vital and the selection criteria for the use of these techniques important. Are these techniques methods that are readily available to most modern RT centers (IMRT/VMAT) or are the
techniques more specialized such as proton therapy? An alternative consideration that needs to be discussed is the selection criteria for higher doses - it appears that patients treated with >55 Gy were more likely to have positive margins, T3/4 disease, and N+ status compared to those treated with 45 - 55 Gy. All of these factors may have played a greater role in dose selection that technical ability to dose escalate.

Answer 1:
Thank you very much for these comments. First of all, we realized that we referred to previous publications but did not specify that the patients had been treated in most cases with 3D-conformal technique and not with IMRT or VMAT. Therefore, we added the following sentence to the material and method section, line 25-27, page 8. "Most patients underwent 3D-conformal therapy while no patient received treatment based on Intensity Modulated RT or Volumetric Arc Therapy.

Secondly we have softened the statement about the ability in the deliver higher dose in the methods section, line 52, page 7 and line 7-11, page 8 as follows "The third cut-off of 55 Gy was selected because some centers with equipment able to deliver higher doses with advanced technique participated in this study.” ◊ "The third cut-off of 55 Gy was selected because a substantial number of patients received higher doses based on the personal experience of radiation oncologists, their technological equipment, and due to the higher risk of local recurrence.”

Comment 2:
The authors state that their results are in line with a previous retrospective analysis from Hall (page 12, lines 5 - 12, reference 25). This is inaccurate as that prior analysis showed inferior survival with doses beyond 55 Gy. The authors need to better elucidate the differences between their manuscript and the previously published results.

Answer 2:
Thank you for this correct clarification. In fact, Hall and colleagues recorded a lower survival in patients receiving doses > 55 Gy compared to those receiving 50-55 Gy. The authors hypothesized that patients who underwent higher doses were at least in part those with greater suspicion (for example on CT-simulation) of residual macroscopic disease or that lower survival was caused by more serious toxic effects after high-dose radiotherapy. Furthermore, it should be emphasized that our study involved patients treated in a small number of centers (all academic and research centers with extensive experience in the treatment of pancreatic cancer) while the analysis of Hall et al. was performed on data from the National Cancer Data Base and only about one third of the patients had been treated in academic/research cancer programs facilities. Finally, we can observe that all patients analysed in the Hall study had been treated from 1998 to 2002, while 72.2% of our patients were treated in a subsequent period when conformal radiotherapy techniques were probably more developed.

For these reasons we changed the discussion section, line 46-52, page 13 and line 7-24, page 14 as follows: “The results of our study differ from those of the Hall’s analysis with regard to patients treated with doses > 55 Gy. In fact, the survival of these patients was significantly improved and worsened in our analysis and in that of Hall and colleagues, respectively. The authors of the cited study hypothesized that patients who underwent higher doses were at least in part those with greater suspicion (for example on CT-simulation) of residual macroscopic disease or that lower survival was due to more serious toxic effects after high-dose radiotherapy. The reasons for the opposite result we observed may be due to the following reasons: i) our study involved patients treated in a small number of centers (all academic and research centers with extensive experience in the treatment of PDAC) while the analysis of Hall et al. was performed on data from the National Cancer Data Base and only about one third of the patients had been treated in academic/research cancer programs facilities; ii) all patients included in the Hall’s study were treated from 1998 to 2002, while 72.2% of our patients were
treated later when the experience in treating PDAC patients with conformal radiotherapy techniques was probably improved”.

Comment 3:  
Please state the organization names for the relevant cooperative groups that are discussed (EORTC, GITSG, etc).

Answer 3:  
Thank you. We have described in full the definitions of the cited cooperative groups (GITSG, EORTC, ESPAC) in background section, line 30-33, 37, page 6.

Comment 4:  
Please add "The" as the first word of the discussion section (page 10, line 58).

Answer 4:  
Thank you for your suggestion. The correction was done.