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Response to: Comment on “The Impact of Positive Resection Margins on Survival and Recurrence Following Resection and Adjuvant Chemotherapy for Pancreatic Ductal Adenocarcinoma.” By Niccolo Petrucciani, MD, PhD, FACS, Laura Antolino, MD, Giovanni Moschetta, MD, Giovanni Ramacciato, MD, FACS.

Dear Editor,

We are grateful for the opportunity to respond to the comments made by Niccolo Petrucciani and his colleagues on our recent publication.1

Petrucciani et al state that the definition of R1 is still debated in pancreatic cancer surgery. Whilst there is some truth in this notion, our latest study and other recent findings now strongly indicate that we should we should always report three levels of R status defined microscopically as: (a) R0 clear of any tumor cells >1 mm from any margin, (b) R1 as any tumor cell <1mm of any margin, and (c) R1-direct where there are tumor cells at any margin. 1,2

Petrucciani et al have confused the changing definitions of, and differences between, the 7th and 8th Editions of the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC) TNM Classifications in saying that “the AJCC defines positive resection margins as direct microscopic involvement by the tumor, whereas the Union for International Cancer Control (UICC) defines R1 if tumor cells are ≤1 mm from the margin, as proposed by the Leeds Pathology Protocol.”

Previously, the respective 7th editions of both the AJCC and the UICC TNM Classifications had defined a positive resection (R1) margin as direct microscopic involvement by one or more malignant cells at any surface or margin (R1-direct) and a clear resection (R0) if not at the margin.3,4 In the current (8th edition) of the UICC, this definition remains unchanged.5 In contrast the 8th edition of the AJCC now defines R1 as cancer cells within 1mm of the margin.6

It is also quite incorrect to refer to R1<1mm as the “Leeds Pathology Protocol”, a study based on only 26 patients. This definition and methodology was originally introduced in 2002 by the Royal College of Pathologists (RCPath) led by Fiona Campbell in Liverpool, who became the lead pathologist for the ESPAC trials, and was subsequently reinforced in the 2010 and 2017 RCPath revisions.8-10 At an open ESPAC meeting in 2005 this definition was formally adopted and introduced into the ESPAC-4 trial.11

Petrucciani et al further state, “the majority of European institutions, and experts’ groups including the International Study Group of Pancreatic Surgery (ISGPS), adopted the latter definition, whereas US institutions generally adopted the former one.” The UK Guidelines along with the ISGPS have adopted the new R status, but the USA has also adopted this position (AJCC 8th edition), whilst the European UICC (8th edition) remains with the old definition.5, 6, 12,13,

Petrucciani et al pose a number of questions about the ESPAC-3 trial, which can be answered by reference to the paper itself, and online material.14 In brief the eligibility criteria only permitted patients who had had histologically proven ductal adenocarcinoma of pancreas, macroscopically resected (R0 or R1) and no previous neoadjuvant chemotherapy or other concomitant chemotherapy. Registration for the trial prior to randomization required the completion of a pathology proforma. The trial utilized the UICC 1997 Classification.15The first patient entered the trial on July 7 2000, two years before the publication of the RCPath Guidelines in 2002.8 As specified in the methods section all histopathological reports had to be transmitted centrally for registration and before randomization.14 Initial patient histology reports were reassessed retrospectively using a more detailed proforma, which was sent for on site completion by all contributing centers.1

Petrucciani et al ask that we “explain the high rate of R1 margin on the pancreatic, biliary, and gastric or duodenal margin, accounting collectively for one third of R1-direct.” How do Petrucciani et al know that this is a “high rate” when there are no comparable data? We are simply reporting empirical observations: these are the data.

Petrucciani et al add that “the majority of institutions perform frozen section to identify positive pancreatic margin and extend the pancreatectomy in the effort to obtain complete tumor clearance” and that it is “widely recommended”. There is no evidence that that undertaking an extended pancreatectomy following a positive frozen resection margin improves survival. An R1 margin cannot be converted into an R0 in this manner. In the absence of strong evidence it cannot be said to be widely recommended – and it is not clear whether Petrucciani et al propose undertaking frozen section biopsies on of all the six margins or just one of these margins.

For evidence to be credible it needs to be reproducible and this seems to be the case for the new R status.1,2 16-20 We recommended reporting R1, R1-direct and R1<1 mm in all studies. As for questions relating to primary borderline and unresectable cancers in the neoadjuvant setting these are addressed by Klaiber et al in the recent publication in the Annals of Surgery. 21

Yours sincerely,

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