

Letter to the Editor

P53 abnormalities and outcomes in colorectal cancer: a systematic review

FM Smith^{*,1}, RB Stephens¹, MJ Kennedy¹ and JV Reynolds¹

¹University Department of Surgery and The Department of Clinical and Molecular Oncology, St James's Hospital, Dublin 8, Ireland

British Journal of Cancer (2005) 92, 1813. doi:10.1038/sj.bjc.6602589 www.bjcancer.com

Published online 26 April 2005

© 2005 Cancer Research UK

Sir,

We would like to make comment on the above article, which as its main conclusion found that abnormal p53 was associated with failure of response to radiotherapy in patients with rectal cancer. Our department has recently conducted a similar analysis focusing purely on rectal cancer undergoing neoadjuvant treatment and the conclusions that we drew were somewhat different.

In total, we sourced 22 studies that assessed p53 status in this setting. Of these, 18 used immunohistochemistry (IHC) and only four (18%) showed that it could predict response. A further six studies assessed the p53 gene directly, four using single-strand conformational polymorphism analysis (ssCP) (Sakakura *et al*, 1998; Elsaleh *et al*, 2000; Rau *et al*, 2003; Saw *et al*, 2003) and two using direct p53 gene sequencing (DGS) (Kandioler *et al*, 2002; Rebischung *et al*, 2002). No study (0%) where ssCP was used could predict response. While both the studies where DGS was used showed that tumours manifesting mutations in p53 were less likely to respond, we feel that these results should be interpreted with caution for several reasons.

Firstly, patients in both DGS studies underwent short-course radiotherapy, whereas there is an increasing use of long-course

neoadjuvant radiochemotherapy (RCT) as standard of care in many institutions (Sauer *et al*, 2004). Also, the pathological end point used in both studies was a decrease in T stage determined by comparison of pretreatment transrectal ultrasound (TRUS) and postoperative pathological staging, which may be unreliable. For example, a recently published study of 1184 patients undergoing pretreatment staging by TRUS found that it had an overall staging accuracy of 69% due to its limited depth of acoustic penetration preventing accurate staging of locally advanced tumours (Garcia-Aguilar *et al*, 2002). In addition, specific analyses of tumours that have undergone a decrease in T stage post-RCT showed that up to 41% of these may harbour residual tumour deposits in the lymph nodes (Medich *et al*, 2001; Zmora *et al*, 2004).

We therefore feel that the conclusion of this study, based principally on the results of two papers, is a little premature. What does seem apparent, however, is that IHC and ssCP analysis of p53 yield unreliable and heterogeneous results. While DGS may hold promise, the question of whether such an expensive and labour-intensive technique will become useful in the clinical setting still remains to be answered.

REFERENCES

- Elsaleh H, Robbins P, Joseph D, Powell B, Grieu F, Menso L, Iacopetta B (2000) Can p53 alterations be used to predict tumour response to preoperative chemo-radiotherapy in locally advanced rectal cancer? *Radiation Oncology* 56: 239
- Garcia-Aguilar J, Pollack J, Lee SH, Hernandez de Anda E, Mellgren A, Wong WD, Finne CO, Rothenberger DA, Madoff RD (2002) Accuracy of endorectal ultrasonography in preoperative staging of rectal tumors. *Dis Colon Rectum* 45: 10
- Kandioler D, Zwrtek R, Ludwig C, Janschek E, Ploner M, Hofbauer F, Kuhrer I, Kappel S, Wrba F, Horvath M, Karner J, Renner K, Bergmann M, Karner-Hanusch J, Potter R, Jakesz R, Teleky B, Herbst F (2002) TP53 genotype but not p53 immunohistochemical result predicts response to preoperative short-term radiotherapy in rectal cancer. *Ann Surg* 235: 493
- Medich D, McGinty J, Parda D, Karlovits S, Davis C, Caushaj P, Lembersky B (2001) Preoperative chemoradiotherapy and radical surgery for locally advanced distal rectal adenocarcinoma: pathological findings and clinical implications. *Dis Colon Rectum* 44: 1123
- Rau B, Sturm I, Lage H, Berger S, Schneider U, Hauptmann S, Wust P, Riess H, Schlag PM, Dorken B, Daniel PT (2003) Dynamic expression profile of p21WAF1/CIP1 and Ki-67 predicts survival in rectal carcinoma treated with preoperative radiochemotherapy. *J Clin Oncol* 21: 3391
- Rebischung C, Gerard JP, Gayet J, Thomas G, Hamelin R, Laurent-Puig P (2002) Prognostic value of P53 mutations in rectal carcinoma. *Int J Cancer* 100: 131
- Sakakura C, Koide K, Ichikawa D, Wakasa T, Shirasu M, Kimura A, Taniguchi H, Hagiwara A, Yamaguchi T, Inazawa J, Abe T, Takahashi T, Otsuji E (1998) Analysis of histological therapeutic effect, apoptosis rate and p53 status after combined treatment with radiation, hyperthermia and 5-fluorouracil suppositories for advanced rectal cancers. *Br J Cancer* 77: 159
- Sauer R, Becker H, Hohenberger W, Rodel C, Wittekind C, Fietkau R, Martus P, Tschmelitsch J, Hager E, Hess CF, Karstens JH, Liersch T, Schmidberger H, Raab R (2004) Preoperative versus postoperative chemoradiotherapy for rectal cancer. *N Engl J Med* 351: 1731
- Saw RP, Morgan M, Koorey D, Painter D, Findlay M, Stevens G, Clarke S, Chapuis P, Solomon MJ (2003) p53, deleted in colorectal cancer gene, and thymidylate synthase as predictors of histopathologic response and survival in low, locally advanced rectal cancer treated with preoperative adjuvant therapy. *Dis Colon Rectum* 46: 192
- Zmora O, Dasilva GM, Gurland B, Pfeffer R, Koller M, Noguera JJ, Wexner SD (2004) Does rectal wall tumor eradication with preoperative chemoradiation permit a change in the operative strategy? *Dis Colon Rectum* 47: 1607

*Correspondence: Dr FM Smith; E-mail: fassiefem@hotmail.com

Published online 26 April 2005