SELECTED ABSTRACTS

Independent Validation of a Prognostic Genomic Signature (ColoPrint) for Patients with Stage II Colon Cancer

Maa, M, Simon I, Nitsche U, Roepman P, Snel, M Glas A, Schuster T, Keller G, Zeestraten E, Goossens I, Janssen K, Friess H, Rosenberg R.

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Background

Adjuvant therapy is recommended for high-risk patients with stage II colon cancer, but better tools to assess patients' prognosis accurately are still required. The aim of this study was to independently validate a genomic signature developed both to assess recurrence risk in stage II patients and to assist in treatment decisions.

Methods

Previously, an 18-gene signature had been developed and validated on an independent cohort, using full genome microarrays. In this study, the gene signature was translated and validated as a robust diagnostic test (ColoPrint), using customized 8-pack arrays. In addition, clinical validation of the diagnostic ColoPrint assay was performed on 135 patients who underwent curative resection (R0) for colon cancer stage II in Munich. Fresh-frozen tissue, microsatellite instability status, clinical parameters, and follow-up data for all patients were available. The diagnostic ColoPrint readout was determined blindly from the clinical data.

Results

ColoPrint identified most stage II patients (73.3%) as at low risk. The 5-year distant-metastasis free survival was 94.9% for low-risk patients and 80.6% for high-risk patients. In multivariable analysis, ColoPrint was the only significant parameter to predict the development of distant metastasis with a hazard ratio of 4.28 (95% confidence interval, 1.36-13.50; P = 0.013). Clinical risk parameters from the American Society of Clinical Oncology (ASCO) recommendation did not add power to the ColoPrint classification. Technical validation of ColoPrint confirmed stability and reproducibility of the diagnostic platform.

Conclusions

ColoPrint is able to predict the development of distant metastasis of patients with stage II colon cancer and facilitates the identification of patients who may be safely managed without chemotherapy.

Commentary: Pramodh Chandrasinghe MS MRCS

Use of adjuvant chaemotherapy in stage II colon cancer remains controversial and lacks an objective risk assessor of tumour recurrence. Individualized genomic profiling is routinely used in breast cancer (Mammaprint/ Oncotype DX) to identify patients who would benefit from adjuvant systemic therapy. In this study, Maak et al have demonstrated that ColoPrint is the only significant predictor of distant recurrence in stage II colon cancer compared with traditional clinic-pathological predictors. While they showed high predictability in the low risk group, only 20% of the high risk population had developed distant recurrence in 5 years, implying that 80 % in this group would still be subjected to the side effects of chemotherapy. Although the study may be under-powered due to small numbers, this new tool has the potential to be used routinely in the management of colon cancer.

Optimal time interval between neoadjuvant chemoradiotherapy and surgery for rectal cancer

Sloothaak, D. A. M., Geijsen, D. E., van Leersum, N. J., Punt, C. J. A., Buskens, C. J., Bemelman, W. A., Tanis, P. J. and on behalf of the Dutch Surgical Colorectal Audit

British Journal of Surgery, 100: 933-39.

Background

Neoadjuvant chemoradiotherapy (CRT) has been proven to increase local control in rectal cancer, but the optimal interval between CRT and surgery is still unclear. The purpose of this study was to analyse the influence of variations in clinical practice regarding timing of surgery on pathological response at a population level.

Methods

All evaluable patients who underwent preoperative CRT for rectal cancer between 2009 and 2011 were selected from the Dutch Surgical Colorectal Audit. The interval between radiotherapy and surgery was calculated from the start of radiotherapy. The primary endpoint was pathological complete response (pCR; pathological status after chemoradiotherapy (yp) T0?N0).

Results

A total of 1593 patients were included. The median interval between radiotherapy and surgery was 14 (range 6-85, interquartile range 12-16) weeks. Outcome measures were calculated for intervals of less than 13?weeks (312 patients), 13-14?weeks (511 patients), 15-16?weeks (406 patients) and more than 16?weeks (364 patients). Age, tumour location and R0 resection rate were distributed equally between the four groups; significant differences were found for clinical tumour category (cT4: 17·3, 18·4, 24·5 and 26·6 per cent respectively; P?=?0·010) and clinical metastasis category (cM1: 4·4, 4·8, 8·9 and 14·9 per cent respectively; P?<?0·001). Resection 15-16?weeks after the start of CRT resulted in the highest pCR rate (18·0 per cent; P?=?0·013),

with an independent association (hazard ratio 1·63, 95 per cent confidence interval 1·20 to 2·23). Results for secondary endpoints in the group with an interval of 15-16?weeks were: tumour downstaging, 55·2 per cent (P?=?0·165); nodal downstaging, 58·6 per cent (P?=?0·036); and (near)-complete response, 23·2 per cent (P?=?0·124).

Delaying surgery until the 15th or 16th week after the start of CRT (10-11?weeks from the end of CRT) seemed to result in the highest chance of a pCR.

Commentary: Following the observations made in the Swedish, Dutch and German trials neoadjuvant chemoradiation (NCRT) has become the standard for locally advanced rectal cancer. Conventionally, timing of surgery following NCRT has been at or around 8 weeks (or 13 weeks from the time of commencement of neoadjuvant chemoradiation - the duration of long course chemoradiation is 5 weeks). Through our improved understanding of tumour biology, this study evaluated if a greater time interval after chemoradiation would facilitate tumour cell apoptosis resulting in rectal tumour shrinkage following NCRT. The investigators observed that the highest complete pathological response rate at 10 - 11 weeks after completion of NCRT.

Also worth noting is the significant rate of nodal down staging of 58.6%. Long term follow up studies to assess local recurrence rates in these patient groups would provide definitive evidence for a change in practice. Furthermore, whether waiting for this long after chemoradiation increases the incidence of liver and lung metastasis remains a hitherto unanswered question.

Pramodh Chandrasinghe MS MRCS

Intermittent versus continuous androgen deprivation in prostate cancer.

Hussain M, Tangen CM, Berry DL, Higano CS, Crawford ED, Liu G et al.

New England Journal of Medicine 2013;368:1314-25.

Background

Castration resistance occurs in most patients with metastatic hormone-sensitive prostate cancer who are receiving androgen-deprivation therapy. Replacing androgens before progression of the disease is hypothesized to prolong androgen dependence.

Methods

Men with newly diagnosed, metastatic, hormone-sensitive prostate cancer, a performance status of 0 to 2, and a prostate-specific antigen (PSA) level of 5 ng per milliliter or higher received a luteinizing hormone-releasing hormone analogue and an antiandrogen agent for 7 months. We then randomly assigned patients in whom the PSA level fell to 4 ng per milliliter or lower to continuous or intermittent androgen deprivation, with patients stratified according to prior or no prior hormonal therapy, performance status, and extent of disease (minimal or extensive). The coprimary objectives were to assess whether intermittent therapy was noninferior to continuous therapy with respect to survival, with a one-sided test with an upper boundary of the hazard ratio of 1.20, and whether quality of life differed between the groups 3 months after randomization.

Results

A total of 3040 patients were enrolled, of whom 1535 were included in the analysis: 765 randomly assigned to continuous androgen deprivation and 770 assigned to intermittent androgen deprivation. The median follow-up period was 9.8 years. Median survival was 5.8 years in the continuous-therapy group and 5.1 years in the intermittent-therapy group (hazard ratio for death with intermittent therapy, 1.10; 90% confidence interval, 0.99 to 1.23). Intermittent therapy was associated with better erectile function and mental health ($P<0.001$ and $P = 0.003$, respectively) at month 3 but not thereafter. There were no significant differences between the groups in the number of treatment-related high-grade adverse events.

Conclusions

Our findings were statistically inconclusive. In patients with metastatic hormone sensitive prostate cancer, the confidence interval for survival exceeded the upper boundary for noninferiority, suggesting that we cannot rule out a 20% greater risk of death with intermittent therapy than with continuous therapy, but too few events occurred to rule out significant inferiority of intermittent therapy. Intermittent therapy resulted in small improvements in quality of life. (Funded by the National Cancer Institute and others; ClinicalTrials.gov number, NCT00002651.)

Commentary - Ajith Malalasekera MBBS MS MRCS. Urological Surgeon

Progression to a castration resistant state is the final outcome in many patients presenting with metastatic prostate cancer. Whether intermittent androgen deprivation therapy (ADT) has advantages versus continuous ADT with regard to this issue has not been conclusively proven or disproved. The present study also makes no conclusions. However, it does indicate that intermittent ADT may have a survival disadvantage balanced by quality of life improvements in erectile function and mental health in the short term. Looking at the current practice in Sri Lanka, this would be somewhat reassuring, as the most commonly practiced ADT is bilateral orchidectomy, which lacks the ability for intermittency of androgen deprivation.