patients, are currently treated with separate international protocols, such as Interfant and EsPhALL.

Measuring minimal residual disease (MRD) during the first weeks or months of therapy is used for risk stratification in many protocols because it is the strongest predictor of relapse risk in childhood ALL. MRD is a powerful tool to predict relapse because it measures overall therapy response, irrespective of underlying genetic abnormality. However, the disadvantage of using MRD is that adaptations in therapy can not be made in the first weeks or months of therapy. Because details of genetic abnormalities are readily available in the first few days after diagnosis, these can be used, for instance, to determine in which patients the use of anthracyclines can be reduced in the induction course—especially relevant since a large proportion of patients can be cured without this class of drugs, thus avoiding their cardiotoxic side-effects.[8]

One should note that the strongest predictive factor for relapse in patients with ALL is the administered treatment itself. If low intensive treatment is given, many abnormalities have prognostic relevance, whereas intensification of therapy over-rides many of the differences in outcome associated with genetic abnormalities. With increasing therapy, the number of relapses have—fortunately—decreased and the survival of children with ALL has increased from less than 10% in the early 1960s to more than 80% now. It is inevitable that new genetic abnormalities with predictive value will continue to be discovered. Genome-wide techniques recently identified a new type of very high-risk ALL characterised by a *BCR–ABL*-like gene expression profile and showed abnormalities in the Ikaros gene as a poor prognostic factor.[9,10] However, long-term follow-up and large numbers of patients are necessary to firmly establish which genetic abnormalities have independent prognostic value. As Moorman and colleagues[1] show here, genetic abnormalities are strong predictors of outcome in childhood ALL, and will be used increasingly in the stratification of children with ALL in current and future protocols. The findings of Moorman and colleagues[1] will contribute to further refinements of therapy so that every child with ALL receives the most appropriate intensity of therapy.

Rob Pieters
Department of Pediatric Oncology/Hematology,
Erasmus MC—Sophia Childrens Hospital, Rotterdam, Netherlands
rob.pieters@erasmusmc.nl

The author declared no conflicts of interest.

1 Moorman AV, Ensor HM, Richards SM, et al. Prognostic effect of chromosomal abnormalities in childhood B-cell precursor acute lymphoblastic leukaemia: results from the UK Medical Research Council ALL97/99 randomised trial. Lancet Oncol 2010; published online Apr 20. DOI:10.1016/S1470-2045(10)70066-8.
2 Stams WA, den Boer ML, Holleman A, et al. Asparagine synthetase expression is linked with L-asparaginase resistance in TEL-AML1-negative but not TEL-AML1-positive pediatric acute lymphoblastic leukemia. *Blood* 2005; **105:** 4223–25.
3 Kaspers GJ, Smets LA, Pieters R, et al. Favorable prognosis of hyperdiploid common acute lymphoblastic leukemia may be explained by sensitivity to antimetabolites and other drugs: results of an in vitro study. *Blood* 1995; **85:** 751–56.
4 Aricò M, Valsecchi MG, Camitta B, et al. Outcome of treatment in children with Philadelphia chromosome-positive acute lymphoblastic leukemia. *N Engl J Med* 2000; **342:** 998–1006.
5 Schultz KR, Bowman WP, Aledo A, et al. Improved early event free survival with imatinib in Philadelphia chromosome positive acute lymphoblastic leukaemia: a Childrens Oncology Group study. *J Clin Oncol* 2009; **27:** 5121–23.
6 Pui CH, Gaynon PS, Boyett JM, et al. Outcome of treatment in childhood acute lymphoblastic leukaemia with rearrangements of the 11q23 chromosomal region. *Lancet* 2002; **359:** 1909–15.
7 Pieters R, Schrappe M, De Lorenzo P, et al. A treatment protocol for infants younger than 1 year with acute lymphoblastic leukaemia (Interfant-99): an observational study and a multicentre randomised trial. *Lancet* 2007; **370:** 240–50.
8 Childhood Acute Lymphoblastic Leukaemia Collaborative Group. Beneficial and harmful effects of anthracyclines in the treatment of childhood acute lymphoblastic leukaemia: a systematic review and meta-analysis. *Br J Haematol* 2009; **145:** 376–88.
9 den Boer ML, van Slegtenhorst M, De Menezes RX, et al. A subtype of childhood acute lymphoblastic leukaemia with poor treatment outcome: a genome-wide classification study. *Lancet Oncol* 2009; **10:** 125–34.
10 Mullighan CG, Su X, Zhang J, et al. Deletion of IKZF1 and prognosis in acute lymphoblastic leukaemia. *New Engl J Med* 2009; **360:** 470–80.

Extended follow-up after extended lymphadenectomy for gastric cancer: was it worth the wait?

Published Online
April 20, 2010
DOI:10.1016/S1470-2045(10)70098-X
See Articles page 439

Studies show that D2 (extended) lymphadenectomy improves the accuracy of locoregional staging and might reduce disease recurrence in patients with advanced gastric adenocarcinoma.[1,2] When expert surgeons perform D2 lymphadenectomy and avoid routine distal pancreatectomy and splenectomy, perioperative morbidity and mortality can be kept to a minimum.[3] At present, surgical resection is seldom the only treatment for patients with advanced disease. The use of multimodal therapies is supported by a series of trials substantiating

their efficacy and positive effect on recurrence and survival.[4–6] In this issue of *The Lancet Oncology*, Songun and colleagues[7] report on 15-year follow-up data of the nationwide Dutch trial of D1 (limited) versus D2 lymphadenectomy for treatment of gastric cancer. We commend the group's ability to undertake a nationwide trial with such extended follow-up and hope that this effort will be an example for other cooperative groups to follow. Although skeptics have argued that neither the 5-year nor 11-year results of the Dutch trial showed a significant improvement in overall survival for patients randomised to D2 lymphadenectomy compared with D1, we believe that D2 resection has clinical relevance in most treatment algorithms.[1,8] The benefits of standardisation of surgical procedures for cancer should not be underestimated. Surgery remains the only non-standardised therapy in the context of clinical trials, which hinders our ability to interpret study results and inform patients of the best available treatment. Furthermore, most cancer surgery is done by surgeons who have not been consistently exposed to appropriate oncological surgical techniques during their training, so performance improvement through education, and the documenting of quality control, should be future goals. This trial provides a strong foundation on which to build.

Although we support most of the study's conclusions, several controversial issues should be addressed. First, although the D2 group had significant improvement in disease-specific survival compared with D1 patients, several issues limit the value of the analyses. Recurrent disease was diagnosed in most patients, but not all recurrences were documented by tissue biopsies or postmortem autopsies. After recurrence, only the date of death was registered; therefore, death was assumed to be a direct result of gastric-cancer recurrence, although recurrence might not have been the cause. Furthermore, after a documented recurrence, no data are given on the use of non-curative surgical interventions, chemotherapy, biological therapy, radiation, or a combination of therapies that might have affected disease-specific survival. Second, it has been suggested that a significant improvement in overall survival could be achieved if the early disadvantage associated with D2 lymphadenectomy (secondary to the prohibitive morbidity) could be avoided.[3] Although this concept is intriguing, even in the randomised trial by Wu and colleagues[3] where there were no perioperative deaths with extended lymphadenectomy, the survival curves show an early benefit for D1 patients and do not favour the D2–D3 group until 2–3 years after surgery. Likewise, the current study did not show an increase in gastric-cancer deaths until several years after the procedures. If we assumed that most of these recurrences were secondary to metastatic nodal disease that was not resected with D1 lymphadenectomy, why would the disease remain clinically quiescent for several years in the absence of adjuvant chemotherapy? Finally, the absence of a significant difference in overall survival between lymph-node positive and negative patients, or between N2 patients who had a D2 versus D1 lymphadenectomy, highlights the uncertain benefit of extended lymphadenectomy on survival.

The optimum treatment for gastric cancer is still the subject of considerable debate. Most of us agree that D2 lymphadenectomy is an appropriate and potentially beneficial staging and treatment approach that is just one aspect of effective treatment. Like any vital therapy, surgery must be done safely and correctly by skilled clinicians and should be individualised to the patient and biology of the disease. Further debate on the absolute value of extended lymphadenectomy will likely detract from a needed emphasis on defining the optimum timing, choice of drugs, and ordering of chemotherapies in patients with gastric cancer.

Life In View/Science Photo Library

Kevin K Roggin, Josh Hemmerich, Mitchell C Posner*
Department of Surgery, Section of General Surgery and Surgical Oncology (KKR, MCP); and Department of Internal Medicine, Section of Geriatrics, University of Chicago Medical Center, Chicago, IL, USA (JH)
kroggin@surgery.bsd.uchicago.edu

The authors declared no conflicts of interest.

1 Bonenkamp JJ, Hermans J, Sasako M, et al. Extended lymph-node dissection for gastric cancer. *N Engl J Med* 1999; **340:** 908–14.
2 Cuschieri A, Weeden S, Fielding J, et al. Patient survival after D1 and D2 resections for gastric cancer: long-term results of the MRC randomized surgical trial. Surgical Co-operative Group. *Br J Cancer* 1999; **79:** 1522–30.
3 Wu CW, Hsiung CA, Lo SS, et al. Nodal dissection for patients with gastric cancer: a randomised controlled trial. *Lancet Oncol* 2006; **7:** 309–15.
4 Cunningham D, Allum WH, Stenning SP, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *N Engl J Med* 2006; **355:** 11–20.
5 Macdonald JS, Smalley SR, Benedetti J, et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. *N Engl J Med* 2001; **345:** 725–30.
6 Sakuramoto S, Sasako M, Yamaguchi T, et al. Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. *N Engl J Med* 2007; **357:** 1810–20.
7 Songun I, Putter H, Kranenbarg E M-K, Sasako M, van de Velde CJH. Surgical treatment of gastric cancer: 15-year follow-up results of the randomised nationwide Dutch D1D2 trial. *Lancet Oncol* 2010; pulished online Apr 20. DOI: 10:1016/51470-2045(10)70070-x.
8 Hartgrink HH, van de Velde CJ, Putter H, et al. Extended lymph node dissection for gastric cancer: who may benefit? Final results of the randomized Dutch gastric cancer group trial. *J Clin Oncol* 2004; **22:** 2069–77.