Detection of guanylyl cyclase C mRNA in lymph nodes of resected stage II colorectal cancer is highly correlated with the risk of tumor recurrence. If validated, these results could have significant implications for the selection of patients for adjuvant therapy in this disease. Clin Cancer Res; 17(10); 1–3. ©2011 AACR.
that are involved in the process of metastasis cannot be underestimated. The data raise the question as to whether distant metastases can develop without any lymphatic involvement, that is, without leaving a molecular trace of metastasis in regional lymph nodes behind (Fig. 1). The outcomes for patients with low GUCY2C mRNA levels in the Hyslop analysis are remarkably good, with a very low risk of tumor recurrence in the low-single-digit percentage range, whereas in almost all patients who developed distant metastases, intermediate or high mRNA levels could be identified in resected lymph nodes. The results therefore call into question the relevance of a hematologic (and not lymphatic) tumor spread in early-stage colorectal cancer. It could very well be that the prognosis for a truly lymph node-negative colorectal cancer, when analyzed with novel molecular detection methods for occult tumor cells, is much better than previously assumed. This notion is supported by recent data from the Adjuvant Colon Cancer Endpoints Group, which show that patients with stage II (but not stage III) disease diagnosed in 1996–2007 had a significantly longer time to recurrence than patients whose disease was diagnosed in 1978–1995, suggesting a refined and improved definition of “lymph node negativity” in the modern era (11).

Is GUCY2C RT-PCR of resected lymph nodes ready for use in clinical practice at this point? Unfortunately, the current study has certain limitations that will need to be addressed in future trials before this assay can be established in routine practice. The study was conducted over a period of >5 years in an oligo-center setting, which means that the actual accrual rate was quite low over time. The specific quantitative RT-PCR technique used in the study requires fresh-frozen tissue, which is not established for routine surgery, although this issue could likely be addressed. The study combined rectal and colon cancers, which express different metastatic patterns (for example, more lung metastases are found in rectal cancer patients); however, the authors specifically break out the colon cancer group in their analysis.

Eventually, a prospective validation study of this assay will be essential to establish GUCY2C as a marker for occult lymph node involvement with prognostic implications in colon and rectal cancer. Such a multicenter study is currently being conducted in a more selected group of patients with colon cancers only, at least 10 lymph nodes identified, and no previous treatment with adjuvant chemotherapy. In addition, this validation study is being performed on formalin-fixed tissue. Recently presented preliminary data show the feasibility of this approach and suggest that detection of GUCY2C mRNA in lymph nodes is associated with risk of disease recurrence in stage II colon cancer (12). If confirmed, these results could have significant implications for the selection of patients with stage II colorectal cancer for adjuvant therapy.

Figure 1. GUCY2C is a receptor for the gastrointestinal hormones guanylin and uroguanylin and is found exclusively in the luminal side of intestinal epithelial cells. The high specificity of GUCY2C as an intestinal marker forms the basis for its utility as a marker for occult lymph node metastases in colorectal cancer. Very few (if any) patients develop distant metastasis without detectable GUCY2C mRNA levels in regional lymph nodes.
Disclosure of Potential Conflicts of Interest

Axel Grothey is a consultant for Genentech, Bayer, and Pfizer.

References

Does Stage II Colorectal Cancer Need to Be Redefined?
Axel Grothey

Clin Cancer Res  Published OnlineFirst April 15, 2011.

Updated version  Access the most recent version of this article at:
doi:10.1158/1078-0432.CCR-11-0574

Supplementary Material  Access the most recent supplemental material at:
http://clincancerres.aacrjournals.org/content/suppl/2011/05/09/1078-0432.CCR-11-0574.DC1

E-mail alerts  Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions  To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions  To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.