part of diagnostic biomarker analysis. Circulating DNA analysis is promising and convenient, but uniformity of circulating DNA collection and analysis remains insufficient, making additional validation necessary. Furthermore, its use is still deemed to be exploratory and is not financially approved by insurance providers. Nonetheless, Tabernero and colleagues' results do lend support to the use of circulating DNA to identify existing tumour mutation status in patients with metastatic colorectal cancer.

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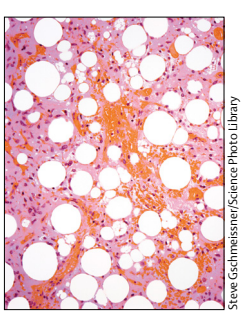
The growing problem of benign connective tissue tumours

Medical oncology has traditionally focused on malignant tumours of the connective tissue, which represent a major burden of disease in most communities. Although few public registries mandate reporting, evidence suggests that benign tumours of the soft tissue could be 100 times more common than are malignant tumours.[1,2] Moreover, the prevalence of benign tumours could be much higher than the incidence, because they are less lethal. For the most part, benign connective tissue tumours are managed surgically, usually curatively. However, an uncertain proportion might not be treatable by surgery, usually because of the site or size of the tumour. The definition of unresectability is inherently vague, and reflects a balance between the permanent morbidity of surgery, alternative therapeutic options, and the effect of the tumour on health—a balance usually decided by the patient and their doctor. As with the overall incidence of these diseases, the proportion of benign tumours that are not amenable to definitive local therapy is not clear.

Those involved in the multidisciplinary management of connective tissue tumours have long known that unresectable benign tumours—most commonly aggressive fibromatoses, giant cell tumours of bone, and tenosynovial giant cell tumours of the soft tissue—represent a substantial burden of disease. Until recently, systemic therapies have had an unclear role in these disorders, and the available data have typically been based on small institutional series with equivocal results. This situation is changing, with the application of targeted therapies developed on the basis of biological insights into tumour development. In the past 5 years, we have seen the emergence of the RANKL inhibitor denosumab for the treatment of giant cell tumour of bone.[3,4] This systemic therapy has transformed the management of patients with unresectable disease. In *The Lancet Oncology*, Philippe Cassier and colleagues[5] expand this portfolio with the first report of an effective systemic therapy for tenosynovial giant cell tumour.

Cassier and colleagues report a phase 1 study of a CSF-1 receptor inhibitor, emactuzumab, in locally advanced diffuse-type tenosynovial giant cell tumour (dt-GCT). The rationale for this treatment is that dt-GCT seems to be driven by overexpression of CSF1 as a result of a translocation involving *CSF1* and *COL6A3*.[6] Unresectable dt-GCT is rarely, if ever, a lethal disease, but rather a debilitating chronic illness, frequently associated with several surgical procedures. Cassier and colleagues report that 24 (86%) of the 28 patients treated with the drug had an objective response, including two (7%) complete responses. In this short-term study, emactuzumab was reported to be fairly well tolerated, although it is interesting to note that autoimmune phenomena resembling systemic lupus erythematosus and dermohypodermitis were reported.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The emergence of systemic therapies for benign tumors raises important questions for oncology trials. As with denosumab, the duration of treatment of dt-GCT with emactuzumab is not yet clear. These drugs are highly specific and potent inhibitors of pathways with important physiological roles, and the consequences of long-term treatment are not known. This has not been an issue commonly faced in oncology because treatment with systemic therapies is usually restricted by the lifespan of the target population with malignant tumours, which is also frequently an elderly population. Both giant cell tumour of bone and dt-GCT affect a substantially younger population (the median age in Cassier and colleagues' study is 42 years), and are rarely lethal. In principle, treatment could be given for years. A specific issue for younger patients is reproductive decision-making, because we do not know the effects on the developing foetus of these targeted therapies. Another interesting issue to consider is the effect of administering new treatments on specialist connective tissue tumour services, because of the duration of treatment and because it is difficult to predict the numbers of benign tumours that might be increasingly referred for therapy. It seems likely that rapid advances in our understanding of tumour biology will increase the number of patients with benign tumours who could receive treatment, so these questions will be important in years to come.

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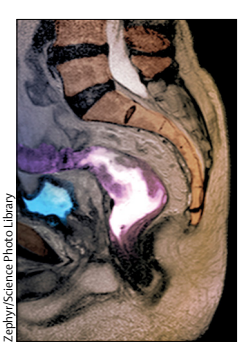
Extending neoadjuvant chemotherapy in rectal cancer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Preoperative chemoradiation or short-course radiotherapy improves outcomes in rectal cancer.[1–3] It diminishes local relapses and increases progression-free survival and, therefore, is regarded as standard of care. However, its effect on reducing metastatic disease or increasing survival has not been proven. Postoperative chemotherapy is of limited value in patients who initially received neoadjuvant chemoradiation or short-course radiation.[4] Many physicians believe that better systemic treatment is needed to improve survival in these patients.

In the past decade, we have learned that local staging with pelvic MRI can be used to predict with high accuracy those individuals at risk of circumferential margin involvement. This feature, along with extramural vascular invasion and involvement of several nodes, can also predict aggressive clinical behaviour and a high risk for metastatic disease.[5] A more selective approach for intensification of treatment in patients with more aggressive findings is recommended. Another important point is that those individuals who achieve a pathological complete response have better outcomes than those who do not. In fact, 5-year overall survival exceeds 87% among patients who achieve a pathological complete response.[6] However, in most reports, less than 15% of patients achieve this. Thus, increasing the proportion of patients who achieve a pathological complete response could lead to better outcomes.

In an exploratory phase 2 trial with four sequential groups of patients with stage II and III rectal cancer, Julio García-Aguilar and colleagues[7] show that adding up to six cycles of mFOLFOX6 chemotherapy between preoperative chemoradiation and definitive surgery increases the proportion of patients who achieve a pathological complete response. In their report, such a response was achieved by 11 (18%, 95% CI 10–30) of 60 patients who had no neoadjuvant chemotherapy (group 1) compared with 17 (25%, 16–37) of 67 who received two cycles of mFOLFOX6 (group 2), 20 (30%, 19–42) of 67 who received four (group 3), and 25 (38%, 27–51) of 65 who received six (group 4); the increased number of cycles was