available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejconline.com

Multimodality treatment of mesenteric desmoid tumours

Monica M. Bertagnolli[a], *Jeffrey A. Morgan*[b], *Christopher D.M. Fletcher*[c], *Chandrajit P. Raut*[a], *Palma Dileo*[b], *Ritu R. Gill*[d], *George D. Demetri*[b,e], *Suzanne George*[b,*]

[a]*Department of Surgery, Brigham and Women's Hospital and Dana-Farber Cancer Institute, Harvard Medical School, 44 Binney Street, Boston, MA 02115, United States*

[b]*Department of Medical Oncology, Brigham and Women's Hospital and Dana-Farber Cancer Institute, Harvard Medical School, 44 Binney Street, Boston, MA 02115, United States*

[c]*Department of Pathology, Brigham and Women's Hospital and Dana-Farber Cancer Institute, Harvard Medical School, 44 Binney Street, Boston, MA 02115, United States*

[d]*Department of Radiology, Brigham and Women's Hospital and Dana-Farber Cancer Institute, Harvard Medical School, 44 Binney Street, Boston, MA 02115, United States*

[e]*Ludwig Center at Dana-Farber/Harvard Cancer Center, Boston, MA 02115, United States*

ARTICLE INFO

Article history:
Received 17 May 2008
Received in revised form 19 May 2008
Accepted 16 June 2008
Available online 14 August 2008

Keywords:
Desmoid tumours
Familial adenomatous polyposis
Fibromatoses

ABSTRACT

Background: Desmoid tumours are rare neoplasms characterised by clonal proliferation of myofibroblasts that do not metastasise, but often exhibit an infiltrative pattern and functional impairment. When desmoids arise in the intestinal mesentery, surgical resection is seldom possible without life-altering loss of intestinal function.

Methods: Retrospective review of the clinical management of 52 consecutive patients treated for desmoids of the intestinal mesentery from January 2001 to August 2006. A multidisciplinary treatment plan was developed based on primary disease extent, tumour behaviour and resectability. Patients with stable but unresectable disease were observed without treatment. Patients with resectable disease underwent surgery, and patients with unresectable progressing disease received chemotherapy, most commonly liposomal doxorubicin, followed by surgery if chemotherapy rendered the disease resectable.

Results: At a median follow-up of 50.0 months (range 4.6–212), 50 patients (96%) have either no recurrence or radiographically stable disease. No patient requires total parenteral nutrition.

Conclusion: These data indicate that the extent of disease; tumour behaviour and resectability are the important factors when defining a treatment plan for mesenteric desmoid tumours. A multidisciplinary approach of surgery combined with chemotherapy is an effective and function-sparing strategy for managing this disease.

1. Background and aims

Desmoid tumours, also known as desmoid fibromatoses, are uncommon soft tissue neoplasms. Although they do not metastasise, desmoids often exhibit an infiltrative pattern of spread in an abundant collagen matrix, giving them a dense, fibrotic character.[1] As a result, these tumours can produce local tissue destruction leading to significant morbidity and

* *Corresponding author:* Tel.: +1 617 632 5204; fax: +1 617 632 3704.
E-mail address: sgeorge2@partners.org (S. George).

0959-8049/$ - see front matter
doi:10.1016/j.ejca.2008.06.038

functional loss. Desmoid tumours are a relatively frequent complication of the hereditary cancer predisposition syndrome, Familial Adenomatous Polyposis (FAP), occurring in 10–20% of patients with this autosomal dominant disorder.[2] Sporadic desmoids are rare, with an estimated incidence of 2–5 per million persons per year.[3] Desmoids demonstrate a wide range of clinical behaviour, as they can remain stable for decades, but they can also rapidly grow to extremely large size. Desmoids can occur in any soft tissue location, although in FAP patients they tend to be present in the abdominal wall and intestinal mesentery, whereas sporadic tumours are most commonly found in the extremities.

The standard treatment for desmoid tumours is surgical resection with histologically negative margins. Unfortunately, multifocal or central disease involvement is common in patients with desmoid tumours of the mesentery, making resection with negative margins (R0) impossible. Several small studies indicate a benefit from systemic therapy in patients with desmoid tumours. Multiple small case series report objective responses to cytotoxic chemotherapy in severe desmoid disease. These include doxorubicin and dacarbazine,[4–6] doxorubicin and dacarbazine followed by carboplatin and dacarbazine,[7,8] the vinca alkaloids vincristine, vinblastine and vinorelbine,[9] and the combination of vinblastine with methorexate.[10]

We report the results of a consecutive series of 52 patients with desmoid tumours of the intestinal mesentery, managed with a combination of surgery and chemotherapy with the goal of effectively controlling the disease whilst minimising treatment morbidity.

2. Methods

2.1. *Patient selection and pre-treatment assessment*

In a study, approved by the Institutional Review Boards of Brigham and Women's Hospital (BWH) and Dana-Farber Cancer Institute (DFCI), we reviewed a consecutive series of

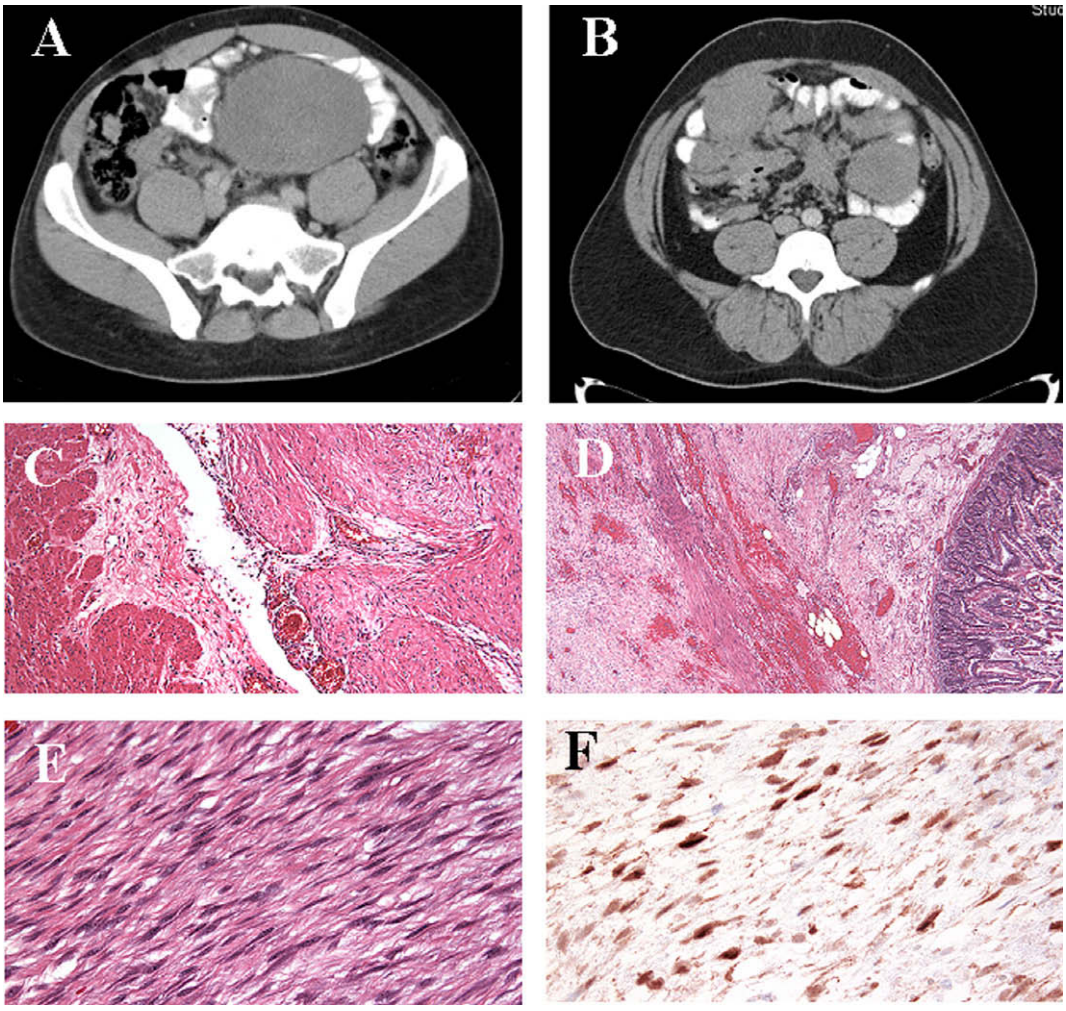

Fig. 1 – Radiographic and histologic characteristics of mesenteric desmoid tumours. (A) CT image showing single localised mesenteric desmoid tumour; (B) infiltrative desmoid disease with extensive involvement of small bowel mesentery; (C) histology of localised desmoid tumour showing a well-circumscribed tumour (right) abutting muscle (left); (D) infiltrative desmoid demonstrating tracking of tumour cells through the muscularis propria of the small bowel; (E) high power view of a typical desmoid fibromatosis showing fascicles of uniform fibroblasts/myofibroblasts.

patients with desmoid tumours of the intestinal mesentery that were referred to the Sarcoma Service at BWH/DFCI between January 2001 and October 2006. These patients were evaluated and treated by a multidisciplinary team including three medical oncologists (JAM, SG and GDD) and two surgical oncologists (MMB and CPR). A total of 21 patients carried a diagnosis of FAP (ages 20–50, median 31 years, and 31 patients had sporadic desmoid tumours (ages 24–67, median 41 years). Each patient's diagnosis was confirmed by review of tumour pathology by a single pathologist with an expertise in soft tissue tumours (CDMF).

The patient's extent of disease was evaluated by CT scanning using oral and intravenous contrast. Based upon CT scan characteristics, the mesenteric tumours were classified as either localised or infiltrative (Fig. 1). Localised tumours were solitary masses with well-circumscribed borders, and with no evidence of direct invasion of the surrounding structures. Infiltrative tumours exhibited poorly defined margins, and commonly produced multiple tumour masses that were bridged by tumour projections interspersed with mesenteric fat. Using these definitions, 16 patients (31%) presented with localised mesenteric disease and 36 patients (69%) had infiltrative tumours. All but one of the 21 patients with FAP presented with an infiltrative tumour type. Three patients, all with sporadic disease, were diagnosed with their tumours during pregnancy.

Most of the patients referred to the BWH/DFCI Sarcoma Center had already received treatment with non-steroidal anti-inflammatory drugs, such as sulindac or celecoxib, or anti-estrogens including tamoxifen. This was the case in all the patients with FAP, and in ~30% of the patients with sporadic desmoid tumours. A small subset of patients (12%) had received imatinib mesylate. None of these treatments achieved a clinically significant disease response. Three patients with FAP and one patient with sporadic disease received cytotoxic chemotherapy prior to referral to the BWH/DFCI Sarcoma Center. Two of these patients received single agent doxorubicin, one received ifosfamide and etoposide and one received methotrexate. None of these patients received additional cytotoxic chemotherapy. At presentation, 12 (23%) patients had radiographically stable disease and 40 (78%) exhibited disease progression (Fig. 2).

2.2. *Treatment planning*

All the patients were evaluated by one of the surgical oncologists associated with the Sarcoma Program to determine whether surgery should be the first treatment modality. Patients were considered candidates for surgery if, in the opinion of the treating surgeon, all the grossly visible tumour could be removed without sacrificing the small bowel function. By this definition, 34 patients (65%) were recommended for surgery as their first treatment modality (Fig. 2). Patients whose disease was considered unresectable without major morbidity were evaluated by one or more of the medical oncologists affiliated with the Sarcoma Program. For patients with unresectable tumours, treatment decisions were based upon the natural history of the patient's disease. All the patients were evaluated by CT scan at 2–3 month intervals. Those who demonstrated unresectable disease that was radiographically stable and asymptomatic were observed without additional treatment ($n = 4$, 8%). In 27% of cases

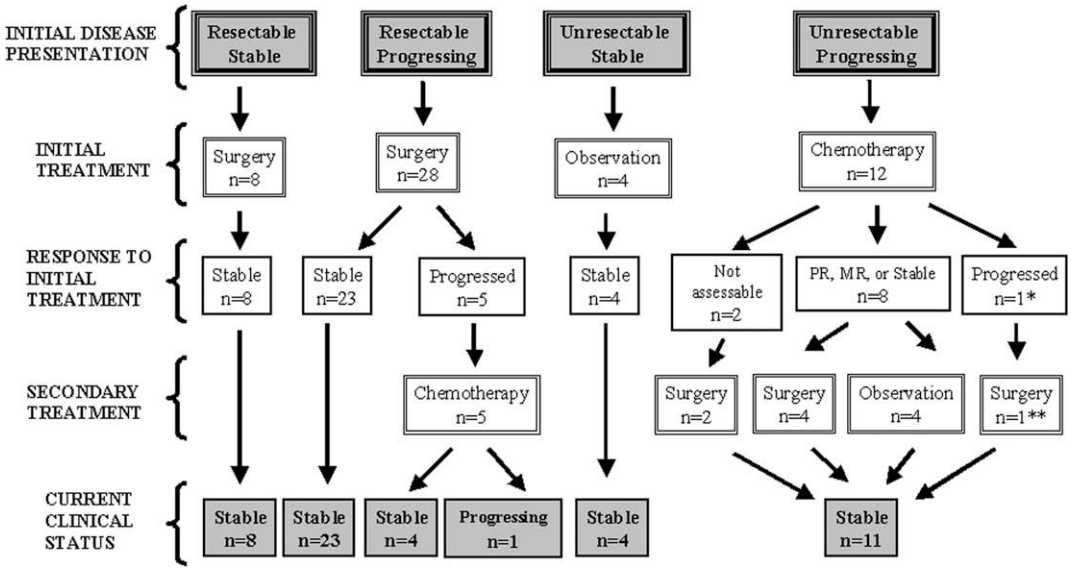

Fig. 2 – Multimodality management of mesenteric desmoid tumours. Treatment and outcome for a consecutive series of 52 patients with desmoid tumours of the intestinal mesentery managed with surgery and/or chemotherapy. Surgery was the first modality of treatment for 36 patients, and 5 (16%) of these received chemotherapy for post-operative progression. A total of 12 patients were recommended to receive cytotoxic chemotherapy as initial treatment, however, one patient with unresectable progressing disease died before treatment could be administered, and two patients were unable to tolerate chemotherapy due to infectious complications. *this patient received liposomal doxorubicin, then debulking surgery, then vinorelbine produced MR when administered for post-operative progression, followed by another debulking surgery.

($n = 14$), chemotherapy was recommended as the first treatment due to the presence of unresectable disease with radiographically documented progression. The systemic drug of choice was liposomal doxorubicin, with vinorelbine used as a second-line.

2.3. Treatment

For patients managed by surgery, the objective was to obtain tumour-free margins of resection (R0) without significant loss of the small intestinal function. In cases where this was not possible, resection of all the grossly visible tumour (R1) was attempted. Every effort was made to preserve as much bowel as possible, including, when necessary, creation of multiple intestinal anastomoses. Chemotherapy consisted of liposomal doxorubicin, administered at 40 mg/m^2 every 28 d. Dose reductions occurred at the discretion of the treating physician. Vinorelbine, administered at 25–30 mg/m^2 weekly, was utilised as the first-line therapy for patients unable to tolerate liposomal doxorubicin, or as the second-line therapy if liposomal doxorubicin proved ineffective.

2.4. Post-treatment evaluation

Serial CT scanning was used to assess the disease status. Patients on active chemotherapy were imaged every 2 months, and patients in observation were reviewed at intervals of 2–6 months, depending upon the natural history of their disease. For this report, on-treatment images were re-reviewed by a single radiologist (RRG) to determine response by RECIST metrics, defining partial response (PR) as a reduction in the sum of maximal tumour diameter of target lesions of $\geqslant$30%.[11] Because desmoids grow slowly, small changes in the mesenteric tumour size can be clinically significant when tumours are in close proximity to major vessels. We therefore also assigned a category of minor response (MR) to subcategorise stable disease as defined by RECIST. Minor response was defined as reduction in the sum of maximal tumour diameter of target lesions of 10–29%.

3. Results

3.1. Description of initial treatment

Summaries of the treatment administered are provided in Fig. 2 and Table 1. Surgery was the first treatment modality for 94% of those with localised tumours, and for 45% of those with infiltrative tumours. Tumour resection with negative margins was achieved in only 7 of 34 (20%) cases for which surgery was used as the first treatment modality, and each of these patients had localised tumour type. In the remaining 27 patients with bulky or infiltrative disease, R1 resections were achieved. For the 34 patients receiving surgery as first treatment, 6 (17.6%) with infiltrative disease type developed post-operative disease progression at 2, 3, 4, 6, 12 and 25 months after surgery.

Chemotherapy was recommended for 14 patients. Three of these patients received both first- and second-line chemotherapy. All these patients had infiltrative disease with the exception of one. This case involved a very large tumour that arose during the first pregnancy of a woman with sporadic disease (Fig. 3). Following nine cycles of liposomal doxorubicin, this patient experienced a 35% reduction in the maximal tumour diameter, enabling tumour resection.

3.2. Chemotherapy response

Ten patients received liposomal doxorubicin. Nine (90%) achieved either MR or PR, with reductions in maximal tumour diameter of at least 10%. One patient progressed on this regimen. Two additional patients received one dose of liposomal doxorubicin each, but response could not be assessed for response due to the development of infectious complications, unrelated to chemotherapy, which required surgery. Four patients received vinorelbine. Two of these patients demostrated SD, and one patient achieved MR and one patient had disease progression. Of the 14 patients in this series who received chemotherapy for progressive disease and were assessable for response, two showed disease progression during their initial regimen, giving an initial disease control rate of 93%. Chemotherapy with liposomal doxorubicin was recommended in one patient, whose initial presentation with a sporadic desmoid tumour was characterised by tumour infiltration of the pancreatic head and proximal bile duct, associated with necrotising pancreatitis. This patient died shortly after diagnosis, before treatment could be administered.

3.3. Surgical results

A total of 44 patients (85%) underwent surgery at some point in their disease management (Table 2). The extent of surgery reflected the nature of the disease. For FAP patients, 95% of whom had infiltrative disease, the need for resection of multiple intestinal segments was common (57%), as was a requirement for multiple surgeries (38%). Only 50% of the patients with sporadic disease had infiltrative tumours, and as a result they required fewer bowel resections (23% with multiple segments removed) and fewer repeat surgeries (16%). There were no deaths due to surgery, although ~16% experienced serious peri-operative complications. These included 4 (10%) with

Table 1 – Treatment of disease according to CT characteristics

	Surgery	Surgery + chemotherapy[a]	Chemotherapy only	Observation only
Localised disease $n = 16$	15/16 (94%)	1/16 (6%)	0/16 (0%)	0/16 (0%)
Infiltrative disease $n = 36$[b]	16/36 (45%)	12/36 (33%)	3/36 (8%)	4/36 (11%)

a Includes use of liposomal doxorubicin or vinorelbine.
b One patient with infiltrative disease died of tumour-associated complications before recommended chemotherapy could be administered.

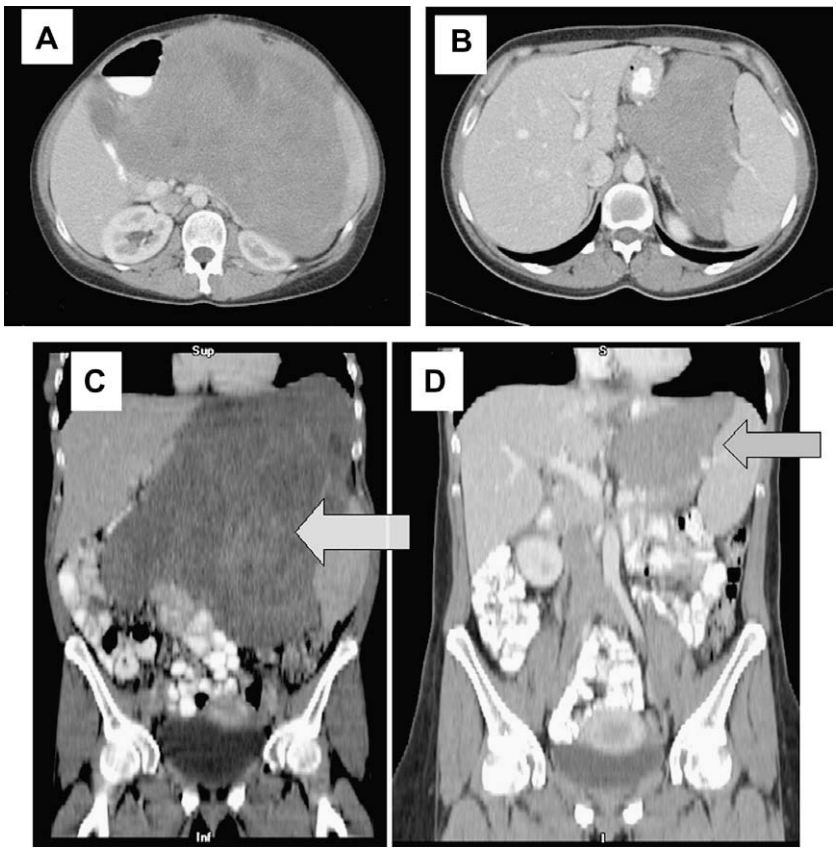

Fig. 3 – Response to liposomal doxorubicin. CT scan before (A, C) and after (B, D) nine cycles of liposomal doxorubicin for the treatment of a large localised sporadic desmoid tumour in a 31-year-old woman.

Table 2 – Extent of surgery for mesenteric desmoid tumours

Extent of surgery	FAP			Sporadic		
	All	Localised disease	Infiltrative disease	All	Localised disease	Infiltrative disease
Single small bowel segment	4	1	3	14	8	6
Multiple small bowel segments	12	0	12	4	1	3
Single colon segment	0	0	0	3	3	0
Ileocolectomy	0	0	0	4	3	1
Resection separate segments colon + small bowel	0	0	0	3	0	3
None	4	0	4	2	0	2
>1 operation for desmoid management	8	0	8	5	0	5

Localised disease: $n = 16$, average size 10.4 ± 5.5 cm range 2.8–21 cm.
Resected with negative margin $n = 13$ positive margin $n = 3$.

anastomotic leaks and/or enterocutaneous fistulae, 2 (4.5%) who required transfusion of >10 units PRBC during surgery and 1 (2.3%) who required percutaneous abscess drainage.

3.4. *Overall effectiveness of disease control*

At the time of this report, 50 patients (96%) have either no evidence of disease recurrence or radiographically stable disease. The median duration of the disease is 50.0 months, and the median duration of post-treatment follow-up for patients remaining stable following last treatment is 31.3 months (Table 3). Long-term treatment-related complications occurred in 3 patients, representing 6.4% of those who received surgery and/or chemotherapy. Two patients, both pre-menopausal women with intact menstrual function, have an intestinal iron absorption defect and require periodic infusions of intravenous ferric gluconate. Neither of these patients requires TPN to maintain normal nutritional status. A third patient developed cardiac dysfunction related to liposomal doxorubicin. In this 26-year-old male, chemotherapy was halted after eight cycles when his left ventricular ejection fraction (LVEF) fell to 35%. Three years later, his cardiac

Table 3 – Duration of follow-up

	All patients: duration of disease follow-up (months)		Duration of disease stability[a] (months)	
	Median	Range	Median	Range
FAP	61.5	5.1–128.4	38.8	1.9–75.4
Sporadic	36.9	4.6–212	28.6	5.2–111
Combined	50.0	4.6–212	31.3	1.89–111

a For FAP cohort, $n = 20$; excluding 1 patient with progressing disease at time of report; for sporadic cohort, $n = 30$; excluding 1 patient who died of disease.

function has normalised, LVEF of 55–60%, and he has normal exercise tolerance.

4. Discussion

The optimal management strategy for patients with mesenteric desmoid tumours balances the individual patient's disease risk with the risks and potential benefits of intervention. We found that addition of a relatively well-tolerated systemic chemotherapy, liposomal doxorubicin or vinorelbine, in selected patients with aggressive desmoids can achieve objective responses and disease stabilisation in cases where surgical risks are high. Our overall experience further indicates that some patients with aggressive disease benefit from a combination of surgery and chemotherapy.

Pre-treatment staging, based upon tumour location, size, symptoms and growth behaviour, is useful to characterise the disease severity, plan treatment, and compare results across institutions.[12] Treatment decisions are the most straightforward in patients with localised disease not involving the root of the mesentery, a clinical presentation that is more common in sporadic disease. This disease type can often be removed with negative resection margins, providing an opportunity for cure. Excellent surgical series from other institutions also show that long-term disease control can be achieved by surgical resection even with positive microscopic margins.[13–15] As a result, localised disease is best managed by resections that preserve bowel function, even if this requires marginal excision. Although follow-up of our series is less than that of other investigators who studied desmoids at all anatomical sites,[16,17,19] these early results support the conclusion that function-sparing surgery maximises patient benefit in cases of localised mesenteric desmoids.

The most challenging patients are those whose disease exhibits an infiltrative pattern of spread, making R0 or R1 resection impossible. Some patients develop extensive diffuse mesenteric disease, but then the tumour enters a stable state without symptoms or radiographic evidence of progression. In this situation, the most reasonable course of action is to delay treatment until evidence of tumour progression, as treatment risk outweighs tumour-associated morbidity. Only two patients in this series fit this clinical picture, likely reflecting our status as a referral centre for patients who have failed initial management elsewhere. Both of these patients are stable without symptoms or disease progression at 19 and 69 months of follow-up.

Patients with progressing infiltrative disease are at a greatest risk for complications caused by tumour encroachment of local structures. In this setting, most patients are treated first with non-cytotoxic therapies, including NSAIDs, such as sulindac, hormonal agents, such as tamoxifen or raloxifene, or investigational agents, such as imatinib mesylate. Clinical benefit for these agents is on the order of 50% or less.[18] In the current series, all patients with infiltrative disease had received one or more of these agents without success. Surgery has been attempted in this clinical setting, but carries a high complication rate due to mesenteric vascular involvement and inability to mobilise the bowel because of mesenteric tumour fixation. In a recent series of 24 patients undergoing surgery for intra-abdominal desmoid tumours, 18 patients had mesenteric tumours, and one-third of these patients had significant post-operative loss of bowel function.[19] Clark et al. also reported a series of 22 patients with FAP who underwent resection of a mesenteric desmoid tumour.[19] Serious operative complications occurred in two-thirds of these patients, with eight peri-operative deaths[19] and six of the surviving patients required long-term TPN. Both these reports are from institutions that are centres of excellence in management of complex gastrointestinal malignancies. These studies show that, for infiltrative mesenteric desmoid tumours, management by surgical resection alone has the potential to do more harm than good.

Several small series have indicated a benefit from anthracycline-based chemotherapy in both FAP-associated, and sporadic desmoid fibromatosis.[7,9,12] In the current series, 93% of patients with progressing tumours and unresectable disease achieved disease response or stability with the administration of cytotoxic chemotherapy. In the single patients with disease progression on first-line chemotherapy, disease control was achieved with a combination of surgery and second-line chemotherapy. In addition, chemotherapy reduced disease to an extent sufficient to allow R1 tumour resections without loss of bowel function in 8 of 12 patients originally deemed unresectable. At the time of this report, 96% of patients treated by our treatment approach have stable or radiographically undetectable disease. None of the patients require TPN, and none have serious long-term complications related to their chemotherapy. Although follow-up of this cohort is small, with a median duration of follow-up of 31.3 months, data from other large series of desmoids at all anatomic sites suggest that ~80% of disease recurrence occurs by 3 years following treatment,[18] suggesting that our early results are encouraging in this most challenging patient population.

In summary, we conclude that optimal multidisciplinary management of mesenteric desmoid fibromatosis requires assessment of disease location, local growth pattern and

natural history in each patient. In patients with progressive, infiltrative or bulky disease, cytotoxic chemotherapy contributes substantially to disease control and may permit successful function-sparing surgery in patients initially deemed unresectable.

Conflict of interest statement

Dr. Demetri serves as a member of the scientific advisory board of the Desmoid Tumour Research Foundation, as well as having received consulting fees and research support from Novartis, Pfizer, Ariad and Johnson and Johnson.

Dr. George has received consulting fees from Pfizer.

Acknowledgments

Research funded in part by the Virginia and Daniel K. Ludwig Trust for Cancer Research.

REFERENCES

1. Middleton SB, Frayling IF, Phillips RK. Desmoids in familial adenomatous polyposis are monoclonal proliferations. *Br J Cancer* 2000;**82**:827–32.
2. Sturt NJH, Gallagher MC, Bassett P, Philip CR, Neale KF, Tomlinson IPM, et al. Evidence for genetic predisposition to desmoid tumors in familial adenomatous polyposis independent of the germline APC mutation. *Gut* 2004;**53**:1832–6.
3. Fallen T, Wilson M, Morlan B, Lindor NM. Desmoid tumors – a characterization of patients seen at Mayo Clinic 1976–1999. *Fam Cancer* 2006;**5**:191–4.
4. Gega M, Yanagi H, Yoshikawa R, Noda M, Ikeuchi H, Tsukamoto K, et al. Successful chemotherapeutic modality of doxorubicin plus dacarbazine for the treatment of desmoid tumors in association with familial adenomatous polyposis. *J Clin Oncol* 2006;**24**:102–5.
5. Lynch HT, Fitzgibbons RJ, Chong S, Cavalieri J, Lynch J, Wallace F, et al. Use of doxorubicin and dacarbazine for the management of unresectable intra-abdominal desmoid tumors in Gardner's cyndrome. *Dis Colon Rectum* 1994;**37**:260–7.
6. Patel SR, Evans HL, Benjamin RS. Combination chemotherapy in adult desmoid tumors. *Cancer* 1993;**72**:3244–7.
7. Schnitzler M, Cohen Z, Blackstein M, Berk T, Gallinger S, Madlensky L, et al. Chemotherapy for desmoid tumors in association with familial adenomatous polyposis. *Dis Colon Rectum* 1997;**40**:798–801.
8. Portiz LS, Blackstein M, Berk T, Gallinger S, McLeod RS, Cohen Z. Extended follow-up of patients treated with cytotoxic chemotherapy for intraabdominal desmoid tumors. *Dis Colon Rectum* 2001;**44**:1268–73.
9. Weiss AJ, Horowitz S, Lackman RD. Therapy of desmoid tumors and fibromatosis using vinorelbine. *Am J Clin Oncol* 1999;**22**:193–5.
10. Azzarelli A, Gronchi A, Bertulli R, Tesoro JD, Baratti D, Pennacchioli E, Dileo P, Rasponi A, Ferrari A, Pilotti S, Casali PG. Low-dose chemotherapy with methotrexate and vinblastine for patients with advanced aggressive fibromatosis. *Cancer* 2001;**92**:1259–64.
11. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 2000;**92**:205–16.
12. Church JM, Berk T, Boman BM, Guillem J, Lynch C, Lynch P, et al. Staging intra-abdominal desmoid tumors in familial adenomatous polyposis: a search for a uniform approach to a troubling disease. *Dis Colon Rectum* 2005;**48**:1528–34.
13. Merchant NB, Lewis JJ, Woodruff JM, Leung DHY, Brennan MF. Expremity and trunk desmoid tumors: a multifactoral analysis of outcome. *Cancer* 1999:86.
14. Lewis JJ, Boland PJ, Leung DHY, Woodruff JM, Brennan MF. The enigma of desmoid tumors. *Ann Surg* 1999;**229**:866–73.
15. Ballo MT, Zagars GK, Pollack A, Pisters PTW, Pollock RA. Desmoid tumor: prognostic factors and outcome after surgery, radiation therapy, or combined surgery and radiation therapy. *J Clin Oncol* 1999;**17**:158–67.
16. Smith AJ, Lewis JJ, Merchant NB, Leung DHY, Woodruff JM, Brennan MF. Surgical management of intra-abdominal desmoid tumors. *Br J Surg* 2000;**87**:608–13.
17. Heiskanen I, Jarvinen HJ. Occurrence of desmoid tumours in familial adenomatous polyposis and results of treatment. *Int J Colorect Dis* 1996;**11**:157–62.
18. Patel SR, Benjamin RS. Desmoid tumors respond to chemotherapy: defying the dogma in oncology. *J Clin Oncol* 2006;**24**:11–2.
19. Clark SK, Neale KF, Landgrebe JC, Phillips RKS. Desmoid tumors complicating familial adenomatous polyposis. *Br J Surg* 1999;**86**:1185–9.