*British Journal of Surgery* 1996, **83**, 1494–1504

## Review

# Desmoids in familial adenomatous polyposis

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**Clinical desmoid disease affects approximately 10 per cent of patients with familial adenomatous polyposis (FAP); the subclinical rate is unknown. Desmoids are probably neoplastic rather than regenerative in origin and may arise in association with germline or somatic mutations at or beyond codon 1444 of the *APC* gene. Intra-abdominal desmoids behave unpredictably but are an important cause of death in those with FAP. Signal intensity on magnetic resonance imaging reflects tumour cellularity, which in part determines progression, and this may help management. Surgical treatment of advanced desmoids is hazardous, but medical treatments have limited success. Chemotherapy with doxorubicin and dacarbazine is currently under evaluation.**

Desmoid tumours are a heterogeneous group of benign fibrous masses, at times clinically aggressive and even life threatening. They are classified as fibromatoses, a group of pathologies[1] resulting from proliferation of well differentiated fibroblasts that infiltrate and show repeated local recurrence but are neither unequivocally malignant nor inflammatory. Other fibromatoses include palmar, plantar and penile fibromatosis, keloids and low-grade fibrosarcoma.

The nomenclature and classification of desmoids is complex and confusing. Terms including aggressive fibromatosis, mesenteric fibromatosis and fibrosis are used to refer to these lesions. Classifications used by different authors vary subtly, making comparison difficult. Desmoids occur in association with familial adenomatous polyposis (FAP) or sporadically, and may be subdivided by site into extra-abdominal, abdominal wall or intra-abdominal[2]. There are differences in behaviour between FAP-associated and sporadic desmoids. Unfortunately, the literature often mixes desmoids and other fibromatoses, and includes FAP-associated with sporadic desmoids, making no distinction between these, and sometimes failing even to mention FAP.

## Epidemiology

Desmoids are rare, accounting for less than 0·1 per cent of all tumours[3,4], with an annual incidence of 2–4 per million[5]. About 2 per cent of desmoids are FAP associated and patients with FAP are at about 1000-fold increased risk of developing desmoids compared with the general population[6]. Incidences from 3·6[7] to 13[8] per cent have been reported by various polyposis registries; 10 per cent of patients with FAP attending the Cleveland Clinic are actually being treated for desmoid tumours[9]. Both sporadic and FAP-associated desmoids have a peak incidence between 28 and 31 years of age, the reported range being from 5 months to 80 years. Sporadic desmoids are significantly more common in women, with a female:male ratio ranging from 2:1 to 5:1, but in FAP any sex difference is less marked[6,8,10–12], non-existent[13,14] or even reversed[15,16].

Paper accepted 12 June 1996

Desmoid disease is an important cause of morbidity and mortality in FAP, life-table analysis of patients with intra-abdominal desmoids at St Mark's Hospital revealing an overall 10-year survival rate of 63 (95 per cent confidence interval 44–82) per cent (*Fig. 1*). Desmoid-associated mortality rate in FAP ranges from 10 to 50 per cent[11,16,18,19], with a mean interval from diagnosis to death of 4[20] to 6[21] years. In one large study[21], desmoid disease was the second commonest cause of death overall in patients with FAP (10·9 per cent), after colorectal carcinoma (58·2 per cent). In patients who had prophylactic colectomy, desmoid disease was the commonest cause of death (30·6 per cent), periampullary carcinoma being second (22·2 per cent), with desmoid-related death occurring significantly sooner after colectomy and at a significantly younger age than death from other causes. Other studies have confirmed desmoid disease as either the commonest[22,23] or second commonest[24,25] cause of death overall after colorectal cancer in patients with FAP, and either the commonest or second commonest[24,26] single cause of death after prophylactic colectomy. Desmoids can also contribute to death from other causes by making surgery for rectal or

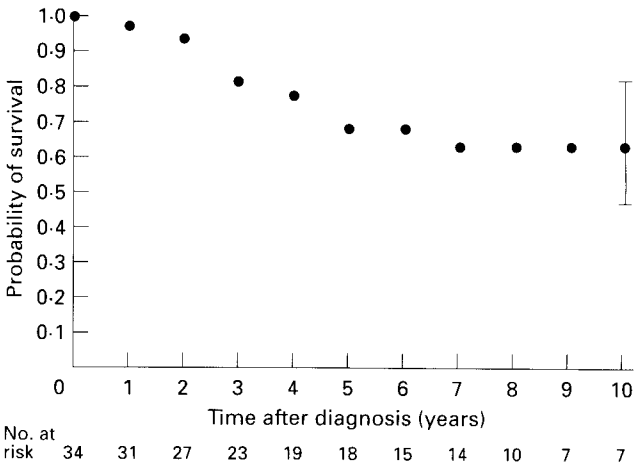


Fig. 1 Life-table analysis of survival of patients with intra-abdominal desmoid disease at St Mark's Hospital. Error bar shows 95 per cent confidence interval. From Farmer *et al.*[17], by permission of Edward Arnold (Publishers) Limited

upper gastrointestinal malignancy difficult or even impossible[15,27].

## Aetiology and genetics

Three factors, initiation by trauma, the influence of sex steroids and an underlying inherited defect, have been implicated in the aetiology of desmoids, although their precise role is unclear.

### *Trauma*

Of intra-abdominal and abdominal wall desmoids in FAP, 68–86 per cent occur after abdominal surgery, the majority (55–75 per cent) within the first 5 years[6,8,11,15,16,28,29]. The average interval between surgery and the diagnosis of desmoid is 2–3 years, the reported range being 4 months to 28 years. The suggestion that the more extensive dissection in restorative proctocolectomy compared with ileorectal anastomosis might result in a higher incidence of subsequent desmoids is not borne out in the literature[15]. Despite the strong association with previous surgery, intra-abdominal desmoids can occur spontaneously in FAP[28], being found in 4 per cent of patients at the first laparotomy[15]. Only 30 per cent of sporadic abdominal wall desmoids occur after trauma[29] and these frequently arise in surgical scars[30].

### *Sex steroids*

Oestrogens seem to stimulate the growth of sporadic desmoids in particular and abnormal oestrogen metabolism is also implicated in the pathogenesis of palmar fibromatosis, a related condition[31]. There is a higher incidence of desmoids in females, particularly those of reproductive age, and an apparent tendency for them to develop, especially in the abdominal wall, during or soon after pregnancy[3,4,32–34] or while taking combined oral contraceptives[14,31,35,36]. Any relationship between intra-abdominal desmoid and pregnancy has been questioned however[12,37]. The fastest growth rate is observed in young women[29], who also have the highest rate of recurrence of extra-abdominal desmoid after excision[38]. There have been reports of regression after the menopause[5,36,39] and after oophorectomy[40]. A case report has described an abdominal wall desmoid developing in a man treated with oestrogen for carcinoma of the prostate[41] which regressed after treatment was stopped. Desmoid-like lesions also occur in laboratory animals given oestrogens[42–44] and these can be suppressed with progestogens[42].

Oestrogen binding sites have been identified in 25–75 per cent[29,45,46] of mixed desmoids. Some desmoid cell cultures grow and produce collagen in response to oestrogen and are inhibited by the antioestrogen tamoxifen[47]. Recently, extra-abdominal desmoids have been found to express platelet-derived growth factor $\beta$, a potent mitogen for mesenchymal cells not normally produced by fibroblasts. This expression was increased by oestrogens[48].

### *Genetics*

Sporadic desmoids do not seem to have a familial tendency, but Reitamo[49] found another abnormality of connective tissue (e.g. dental abnormalities, exostoses, incomplete spinal segmentation) on radiography in 80 per cent of patients with sporadic desmoid, compared with 7 per cent of normal controls, suggesting a basic functional inherited defect in connective tissue formation. Some familial clustering of desmoids in patients with FAP has been noted[8,10,20,32,50–53] and an increased risk of developing desmoids in first-degree relatives has been identified[6].

FAP, an autosomal dominant condition, can be considered to be a generalized disorder of tissue growth regulation caused by germline mutation in one copy of the *APC* gene. The *APC* gene has been localized to chromosome 5q22[54,55], cloned and sequenced[56–58], and mutations have been identified. It is estimated that about 10 per cent of cases of FAP arise as a result of a new mutation[59]. *APC* is a large gene consisting of 15 exons; exons 1–14 are small and exon 15 contributes 77 per cent of the coding region (codons 653–2843). The APC protein product localizes to the cytoplasm in epithelial cells[60]. Although its precise function is not known, this protein associates with $\alpha$ and $\beta$ catenins, which bind to cell-surface E cadherin and contribute to its role in cell adhesion and interaction[61,62]. APC protein is also thought to be important in formation of microtubules[63,64], which anchor the cytoskeleton and play a part in cell division. Most *APC* mutations occur between codons 900 and 1600, and almost always give rise to premature stop codons, resulting in a truncated protein product.

There is evidence of genotype–phenotype correlation in FAP: mutation at codon 1309 and large numbers of colonic polyps[65]; mutation at codons 1250–1464 and earlier death from colorectal cancer[66]; mutation 5′ of codon 160 and attenuated colonic polyposis[67]; mutation 3′ to a boundary in exon 9 and congenital hypertrophy of the retinal pigment epithelium[68]. Desmoids have been reported to occur more frequently in patients with mutation 3′ to codon 1444[69,70].

Wild-type APC protein is believed to form active oligomers, interaction between normal and mutant APC perhaps blocking function[71] to an extent related to the structure of the truncated protein. Proximal (5′) mutations result in severely truncated protein that may fail to oligomerize with the wild-type product of the remaining normal gene and thus have little effect on its function. More distal (3′) mutations result in a less truncated protein, which could interact significantly thereby impairing function. This 'dominant negative' effect may be further complicated by varying stability of the truncated APC protein in different tissues and subnormal levels of wild-type protein produced by the single remaining normal *APC* gene[66,72].

Identical mutations may be associated with diverse phenotypes[56,73], so genetic modifiers are probably involved in determining phenotype, as in the Min mouse[74]. Environment also influences phenotype, evidenced by polyp regression after colectomy[75].

Fibroblasts cultured from skin biopsies from patients with FAP[76–78] show similar defects in organization of cytoplasmic actin to those of tumour fibroblasts[79], abnormalities of growth pattern, and increased susceptibility to viral transformation, supporting the view that desmoid tumours are a phenotypic variant of FAP due to an abnormal fibroblastic response caused by the effects of the germline mutation.

An important step in the adenoma–carcinoma sequence is a somatic mutation ('second hit') in the remaining normal *APC* gene in the colonic epithelium[80,81]. A clonal deletion of 5q bearing the normal copy of *APC* has been identified in an intra-abdominal desmoid in FAP[82]. Loss

of heterozygosity in 5q21–22, indicating loss of wild-type *APC*, has also been demonstrated[83,84]. Bridge *et al.*[85] described frequent clonal chromosomal rearrangements, especially 5q deletion, in fibroblasts from sporadic and FAP-associated desmoids. Almost all reported somatic mutations in desmoid tumours are deletions in exon 15[86,87] and lead to a downstream premature stop codon. Other abnormalities identified in sporadic desmoids include loss of chromosome 4[85] and trisomy 8[88,89], both of which have also been described in palmar and penile fibromatosis, and multiple complex chromosomal abnormalities[90]. There is thus some evidence that desmoids may result from a 'second hit' mutation followed by clonal expansion and therefore are true neoplasms.

A recent study[86] suggested that one of the two *APC* mutations in desmoids occurs at or beyond codon 1444, producing APC protein product of at least a certain length. This is irrespective of whether the mutation was inherited in the germline and is, therefore, present in all cells of the body, or was the result of a somatic mutation and clonal expansion.

## Pathology

Desmoid tumour pathogenesis is not clearly understood. Desmoids may occur in any musculoaponeurotic structure, but the distribution varies markedly between those occurring in FAP, of which about 70 per cent are intra-abdominal, 15 per cent in the abdominal wall and 15 per cent extra-abdominal[6,11,14,28], and others where the abdominal wall (about 50 per cent) and extra-abdominal sites (40 per cent) predominate and only a minority are intra-abdominal (10 per cent)[91,92]. About 80 per cent of intra-abdominal desmoids are in the small bowel mesentery. Other sites documented include the transverse mesocolon, ligamentum teres and retroperitoneum[93]. In 5–38 per cent of cases multiple sites are involved[6,14,92,94]. Intra-abdominal desmoids most often give rise to life-threatening complications and are most difficult to treat, which explains why desmoids pose such a problem in FAP.

Mesenteric desmoids probably arise as flat white plaques and strands which contract, tethering the bowel and causing thickening and puckering of the mesentery. Further progression results in a discrete lobulated mass[8,95] (*Fig. 2*). There is no true capsule and the desmoid grows, compressing and infiltrating surrounding tissues such that the infiltrative margin may extend several centimetres beyond the palpable tumour edge. Eventually small bowel, ureters and mesenteric blood vessels may become encased and obstructed. Desmoids range in size from a nodule a few millimetres in diameter to a large mass. The cut surface is usually pinkish-white, often whorled, and may show evidence of cystic degeneration or haemorrhage, especially in large tumours.

Desmoids usually grow slowly but the rate varies during the course of the disease and they may behave somewhat more aggressively when associated with FAP[96]. Church[95] has suggested that 10 per cent of intra-abdominal desmoids in FAP disappear spontaneously, 29 per cent undergo cycles of growth and resolution, 47 per cent remain stable after diagnosis and 10 per cent grow rapidly. They do not metastasize and the only reliable report of malignant change occurred after radiotherapy[97]. Spontaneous regression has been documented in 4–17 per cent[11,49,98].

Histologically, desmoids consist of mature, highly differentiated fibroblasts in an abundant collagen matrix[99] (*Fig. 3*). Aggregates of lymphocytes are frequently located at the margins. There is a wide range of cellularity, often with acellular areas towards the centre of the tumour and a densely cellular periphery which can be mistaken for fibrosarcoma. Many of these cells are myofibroblasts[100,101], which are also found in repair tissue and malignant tumour stroma[102]. The cells have ill defined cytoplasm and pale nuclei. Mitoses are rare and nuclear atypia is absent. Electron microscopy has shown extensive intracellular collagen fibrillogenesis in the Golgi complexes of desmoid cells. This process usually occurs outside cells where collagen is formed from precursors secreted by the cells[103,104].

## Presentation and complications

Desmoids are often asymptomatic and an incidental finding on examination or at laparotomy. They can be

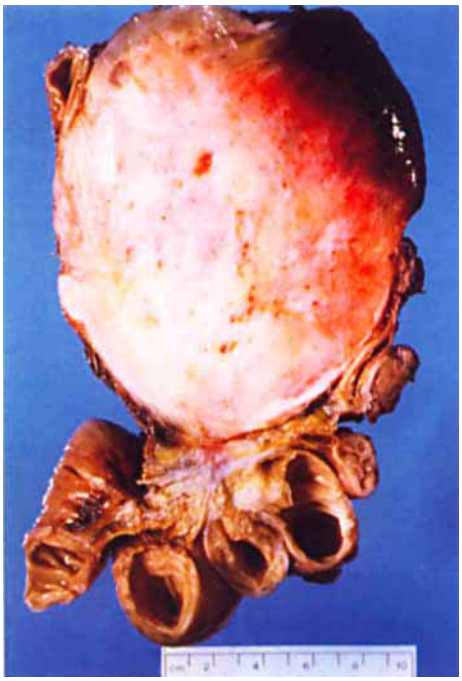

**Fig. 2** Operative specimen of a desmoid arising within the small bowel mesentery

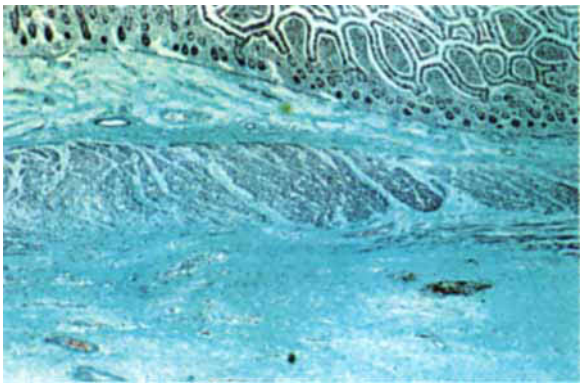

**Fig. 3** Desmoid infiltrating the muscle of the small bowel (Masson trichrome, original magnification × 100)

very large before causing symptoms and may present simply as a mass. About one-third of intra-abdominal desmoids cause pain. Tethering and compression of the small bowel can cause obstruction, so progressive cachexia is a frequent problem. The mesenteric blood vessels may become occluded causing small bowel ischaemia[31], and central necrosis sometimes occurs within the desmoid. Fistula and sepsis may supervene[105,106] and are important causes of mortality.

Compression of large veins results in deep venous thrombosis; nerve compression can cause pain and sensory and motor deficits. Ureteric obstruction is common and respiratory failure[31], upper gastrointestinal bleeding[107] and aortic rupture[21] have been reported. Penna *et al.*[15] reported that 27 per cent of intra-abdominal desmoids cause hydronephrosis, perforation, impaired pouch function or obstruction requiring laparotomy. Desmoids found at laparotomy may interfere with planned surgery, preventing restorative surgery[108] or even resection of malignancy[109]. Some patients with FAP present with a desmoid before the colonic polyposis is detected[8,14,110], making investigation of the large bowel essential when an apparently sporadic desmoid is diagnosed.

## Investigation

Laparoscopy caused bowel perforation in one study of chemotherapy for intra-abdominal desmoids[111] and cannot be recommended. Biopsy anecdotally has been implicated in accelerating tumour growth, but desmoid progression is notoriously variable and series in which several were biopsied do not support this[8]. Fine-needle aspiration cytology may be used, but histological confirmation is recommended, particularly to differentiate desmoid from low-grade fibrosarcoma[112,113].

Desmoids do not calcify, appearing on plain radiographs as a soft tissue mass displacing bowel loops. Intravenous urography and barium studies have been superseded by contrast-enhanced computed tomography (CT), which images the desmoid itself, although the former have some limited use in follow-up after surgery for bowel or ureteric obstruction. Angiography outlines neighbouring major blood vessels while also showing the usually sparse tumour vasculature, which contrasts with the extensive neovascularization of poorly differentiated sarcomas[114], but this investigation has also been largely replaced by enhanced CT.

Ultrasonographic scanning to investigate abdominal wall[115] and intra-abdominal desmoids[116,117] can localize a mass, but CT is required to demonstrate soft tissue density. Mesenteric desmoids appear as well demarcated solid masses with varying degrees of echogenicity due to mesenteric fat, blood vessels and cystic degeneration, but changes are not specific and cannot be used to distinguish a desmoid from mesenteric lymphadenopathy, lipoma or sarcoma.

Several radionuclides are taken up by desmoids. [$^{99m}$Tc(V)]dimercaptosuccinic acid is taken up more reliably than gallium-67 citrate and has the advantage that scanning can be done hours rather than days after injection[118]. This type of imaging may be useful in follow-up after treatment as it has greater sensitivity than CT in the differentiation of residual scarring from active disease[119,120].

CT is now the best choice for investigating intra-abdominal desmoids; the appearances have been well

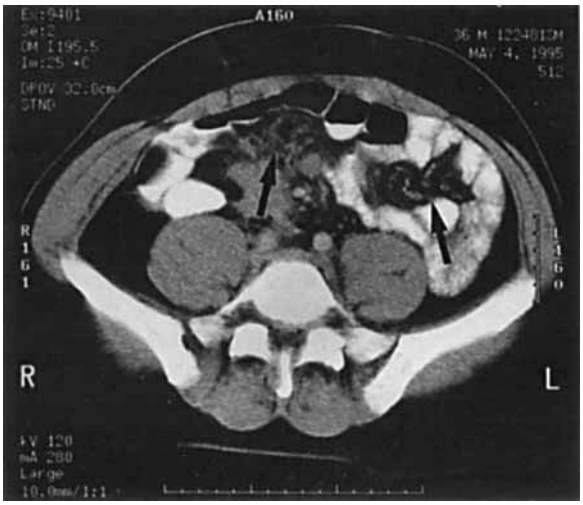


**Fig. 4** Computed tomogram showing early desmoid in the small bowel mesentery

described[94,116,121–123]. Early mesenteric lesions appear as ill defined soft tissue infiltration of mesenteric fat (*Fig. 4*). Later, a mass (as small as 2–3 cm) may be seen, with displacement, infiltration (with the appearance of 'whiskers' extending into the mesenteric fat), tethering and encasement of small bowel loops. Desmoids show mixed attenuation and variable enhancement. Computed tomographic appearances correlate poorly with symptoms in intra-abdominal desmoids, but tumour diameter greater than 10 cm, multiple mesenteric tumours, bilateral hydronephrosis and extensive small bowel involvement are poor prognostic markers[123]. Abdominal CT may show regression of bulky tumours, but small bowel matting and adhesions following colectomy may be difficult to distinguish from residual or recurrent desmoid[111].

Magnetic resonance imaging (MRI) has advantages when investigating extra-abdominal desmoids[124–127]. Not only does it have multiplanar imaging capabilities, but contrast resolution is superior to that of CT, particularly in the presence of postoperative or radiotherapy changes[127]. The MRI features of both extra-abdominal[128,129] and abdominal wall[130] desmoids have been documented. The image intensities are heterogeneous, but overall there is low or similar signal intensity relative to muscle on $T_1$-weighted images and variable signal intensity on $T_2$-weighted images. There is good delineation of vascular involvement and variable enhancement with gadolinium–diethylenetriamine penta-acetate[131]. $T_2$-weighted sequences correlate best with histological findings[129,132,133]; high signal intensity is associated with increased cellularity, and low intensity is due to parallel orientation of abundant collagen and decreased density of mobile proteins in relatively acellular areas. Perhaps active cellular areas within desmoids might be detected by means of $T_2$-weighted sequences, thereby aiding prediction of tumour growth.

## Treatment

Treatment is controversial, empirical and difficult. It is based largely on anecdotal reports and small, poorly controlled studies of predominantly sporadic desmoids, most of which are retrospective, encompassing long time

spans, changing techniques and varying in follow-up. Many lack detailed information on desmoid site or FAP status.

*Surgery*

Surgery is widely accepted as the first-line treatment for extra-abdominal and abdominal wall desmoids, despite recurrence being common (20–80 per cent)[2,11,18,34,49,134]. The infiltrative nature of the lesion makes completeness of excision difficult to judge clinically, but there is controversy over the importance of excision margins. Some series[19] show a higher recurrence rate after incomplete or marginal excision compared with wide excision, but even without wide excision there may be no recurrence. Abdominal wall reconstruction with polypropylene mesh, polytetrafluoroethylene sheet or a myocutaneous flap may be required[135–137].

Mesenteric desmoids are rarely small enough or sufficiently localized to allow complete excision, and the most frequent site at the root of the small bowel mesentery and intimate relation to the mesenteric vessels means that often a considerable length of small bowel has to be sacrificed[93] when resection is possible. This surgery is hazardous, with a perioperative mortality rate of 10–60 per cent, usually from blood loss[11,12,17,37,138], and a major morbidity rate of 22–60 per cent. Recurrence here is more frequent than at other sites[8,11,20], occurring in 65–88 per cent. Sporadic desmoids and those associated with FAP behave differently, the latter having a higher recurrence rate even if excised completely[33,96]. Partial excision (but not biopsy) may accelerate growth[8]. There have been two reported cases of small bowel transplantation following enterectomy to excise large mesenteric desmoids[139,140]. Most authors[8,95] recommend that surgery should be avoided for mesenteric desmoids because of the risk of accelerated growth and high risk of recurrence. Nevertheless, operation may be needed to bypass bowel obstruction or relieve ureteric obstruction, either with stents or by ureteroureterostomy[17].

*Radiotherapy*

Radiotherapy by various techniques has been used; a total dose of 50–60 Gy by external-beam interoperative treatment[141] or brachytherapy[142,143] have yielded similar results. Radiotherapy was used primarily to avoid mutilating surgery, but more recently it has been employed as an adjunct to surgery when excision is incomplete or when recurrent disease has been resected. There is evidence that this may reduce recurrence rates both at extra-abdominal sites[19,134,144–147] and in the abdominal wall[148,149]. Recurrence rates of 40–70 per cent after surgery alone are reported to drop to 20–40 per cent when radiotherapy is added, leading some authors[38,144] to recommend its routine use when anything less than a wide excision is performed. Treatment with radiotherapy alone has been associated with local control rates similar to those after surgery alone[147], but tumour regression can be slow.

Intra-abdominal desmoids treated by radiotherapy behave differently, either not responding[11,37,150], or increasing in size[9], or showing a higher recurrence rate after adjuvant radiotherapy than after surgery alone[49]. Furthermore, the use of radiotherapy at this site is limited by radiosensitivity of surrounding intra-abdominal structures. Nevertheless, a handful of patients have been treated with some success[134,142,151–153]. Intra-abdominal desmoids may be less radiosensitive than those at other sites and any effect of radiotherapy may possibly be a byproduct of ovarian irradiation[3], explaining the better results in women than men in some reports[14,32].

*Pharmacological treatment*

Various medical treatments have been reported to give mixed success. Non-steroidal anti-inflammatory drugs (NSAIDs) and antioestrogens are the most frequently employed and most widely documented, but other modifiers of adenosine 3′,5′-cyclic monophosphate (cAMP) metabolism, corticosteroids, colchicine, interferon $\alpha$, interleukin 2 and warfarin have all been used. There have been reports of desmoid regression, sometimes dramatic, associated with some of these, but none is predictably efficacious and there are almost as many reports of failure as of success. There have been no prospective randomized trials and it is difficult to assess the value of different drugs because of the small numbers in each study. Again sporadic and FAP-associated desmoids, and tumours at different sites, are often reported together. This, coupled with the fact that drugs are often used in combination, can make the interpretation of results difficult.

Sulindac and indomethacin are the NSAIDs that have been used. They inhibit prostaglandin synthesis, which is thought to promote immunological attack on tumour cells, and also inhibit ornithine decarboxylase, an enzyme associated with tumour proliferation. In addition, they are known to cause a decrease in cAMP concentrations in tumour cells, which can lead to interruption of the cell cycle. There is evidence that NSAIDs can reduce tumour growth in experimental models[154] and polyp numbers in the rectal stump of patients with FAP following ileorectal anastomosis. Overall, the studies of NSAIDs alone[98,155,156] show an objective response rate of about 50 per cent (*Table 1*). There are also reports of their use in combination with antioestrogen[8,98,155,156] or ascorbic acid[157]. Most responses occurred at from 2 weeks to 3 months of treatment, but some were observed up to 2 years after the start of therapy. In a retrospective controlled study Tsukada *et al.*[98] showed significant benefit from tamoxifen, sulindac or indomethacin, alone or in combination, compared with controls not given any drug treatment, and of sulindac alone compared with these other drugs. There is evidence that sulindac, in particular, can be effective and, as NSAIDs are relatively non-toxic, it is often used as a first-line treatment.

Antioestrogens were used in logical response to the observations of the influence of sex hormones on desmoid growth. Some success has been achieved with progestogens, such as medroxyprogesterone acetate[158], and goserelin has also been used[159]. Testosterone use has shown no benefit[99]. Most attention has focused on the triphenylethylene, tamoxifen[32], and its chlorinated analogue, toremifene.

Oestrogen receptor blockade restricts RNA synthesis and alters the transcription of genes involved in tumour growth. However, not all desmoids are oestrogen receptor positive and, as is the case in carcinoma of the breast, alternative mechanisms of action have been suggested. Tamoxifen has an effect on prostaglandin metabolism and may also act via stromal–epithelial interactions[160], inducing transforming growth factor $\beta$ production in stromal fibroblasts, which inhibits fibroblast growth *in*

**Table 1** Treatment with non-steroidal anti-inflammatory drugs of intra-abdominal desmoids in patients with familial adenomatous polyposis

| Reference | No. of patients | Drug | Outcome | | | |
|---|---|---|---|---|---|---|
| | | | Complete regression | Partial regression | Static | Progression |
| Klein *et al.*[156] | 2 | Indomethacin | 0 | 0 | 0 | 2 |
| Tsukada *et al.*[98] | 14 | Sulindac | 1 | 7 | 4 | 2 |
| | 4 | Indomethacin | 1 | 0 | 1 | 2 |
| Waddell and Kirsch[155] | 4 | Sulindac | 0 | 2 | 1 | 1 |
| Total | 24 | | 2 | 9 | 6 | 7 |

**Table 2** Treatment with antioestrogens of intra-abdominal desmoids in patients with familial adenomatous polyposis

| Reference | No. of patients | Drug | Outcome | | | |
|---|---|---|---|---|---|---|
| | | | Complete regression | Partial regression | Static | Progression |
| Brooks *et al.*[51] | 9F, 3M | Toremifene | 1 | 5 | 3 | 3 |
| Tsukada *et al.*[98] | 3F | Tamoxifen | 0 | 1 | 1 | 1 |
| Total | 15 | | 1 | 6 | 4 | 4 |

*vitro*[161]. Antioestrogen binding sites distinct from oestrogen receptors have been identified in 79 per cent of desmoids[45].

Most patients treated with tamoxifen or toremifene have been women, who were often given NSAIDs or other treatments in addition[32,35,51,156,162–164]. Taken together, the studies (*Table 2*) show an objective response rate of about 50 per cent when treating intra-abdominal desmoids in FAP with antioestrogens alone[51,155]. Response can be variable, even between different tumours in the same patient, and the initial response occurs between 2 weeks and 6 months after the start of treatment.

Theophylline, testolactone and chlorothiazide synergize the action of adenosine 3′,5′-monophosphate and may inhibit adenosine 3′,5′-monophosphate diesterase[31]. This causes a rise in intracellular cAMP levels and has been shown to differentiate Chinese hamster ovary cells to mature fibroblasts *in vitro*. There have been a few reports of the use of these drugs to treat desmoids, with mixed results[8,31,33,165]. Ascorbic acid, which causes a fall in intracellular cAMP concentration, has also been used in a few patients, particularly in combination with NSAIDs[157]. Again, the results are mixed and on the whole unconvincing.

Glucocorticoids inhibit growth of desmoid fibroblasts in culture[166] and have been effective clinically in a few cases[167,168]. Colchicine disrupts microtubules, causing a decrease in intracellular collagen formation. It is used in the management of palmar and penile fibromatosis and there is a single report of its use in sporadic extra-abdominal desmoid disease, with good result[169]. Warfarin[155] and interleukin 2[170] have been tried with little benefit, but a single case report[171] of treatment with interferon α, which inhibits fibroblasts and stimulates collagenase *in vitro* and is used to treat keloids and systemic sclerosis, was promising.

### *Cytotoxic chemotherapy*

Cytotoxic chemotherapy was originally used as a last resort in recurrent, irresectable or aggressive desmoid disease because of the similarities between this and low-grade fibrosarcoma. In general, objective remissions of variable degree and duration have been noted with almost all agents, including actinomycin D, cyclophosphamide and vincristine[172], actinomycin D, vinblastine and methotrexate[173,174] and others[9,52,144], but the numbers reported are small.

There is increasing evidence that the antisarcoma regimen consisting of doxorubicin and dacarbazine is effective in the treatment of life-threatening intra-abdominal desmoid disease in FAP. Nine cases have been reported (*Table 3*)[111,175,176], with complete tumour regression in four and partial regression in five. In another case doxorubicin was used alone, with subsequent partial tumour regression[170]. These results have prompted the authors of the most recent report to recommend that this treatment should be considered for patients with FAP with symptomatic irresectable desmoid that is unresponsive to conventional medical therapy, and to suggest that it be used at an earlier stage in the management of such patients.

### *Treatment recommendations*

Desmoids are pathologically benign, have a variable growth rate, and occasional examples of spontaneous regression have occurred. Surgery carries considerable risks in intra-abdominal disease and there is a lack of consistently effective alternatives. There is, however, substantial mortality and morbidity associated with desmoid tumours. Despite the fact that doxorubicin and dacarbazine are potentially toxic, they should be considered in some cases of clinically aggressive disease.

The treatment protocol developed at St Mark's Hospital after a comprehensive review of the literature recommends imaging by CT and initial treatment with sulindac 150 mg twice daily for 6 months. If growth continues, toremifene 180 mg daily is added. If the desmoid is still growing or is giving rise to significant symptoms after a further 6 months, MRI is performed to assess tumour cellularity, and doxorubicin and

**Table 3** Doxorubicin and dacarbazine chemotherapy for intra-abdominal desmoids in patients with familial adenomatous polyposis

| Reference | Centre | No. of patients | Failed prior treatment | Treatment regimen | Adverse effects | Outcome | |
|---|---|---|---|---|---|---|---|
| | | | | | | Complete regression | Partial regression |
| Hamilton *et al.*[175] | Toronto | 3 | Sulindac (3 patients)<br>Tamoxifen (3 patients)<br>Toremifene | Doxorubicin and dacarbazine (7 cycles), then carboplatin and dacarbazine | Febrile neutropenia (2 patients) | 0 | 3 |
| Lynch *et al.*[111] | Omaha, Nebraska | 2 | Sulindac<br>Tamoxifen (2 patients)<br>Partial resection<br>Radiotherapy<br>vincristine cyclophosphamide, azathioprine and prednisolone | Doxorubicin and dacarbazine (5–7 cycles), then carboplatin and dacarbazine | Cardiotoxicity (1 patient) | 2 | 0 |
| Patel *et al.*[176] | Houston, Texas | 4 | Partial resection (3 patients)<br>Complete resection<br>Tamoxifen | Doxorubicin and dacarbazine (8–10 cycles) and cyclophosphamide (1 patient), then ifosfamide (1 patient) | Probable cardiotoxicity (1 patient, who died) | 2 | 2 |
| Seiter and Kemeny[170] | New York | 1 | Resection (×3)<br>Indomethacin<br>Tamoxifen<br>Interleukin 2 | Doxorubicin | Febrile neutropenia (1 patient) | 1 | 0 |
| Total | | 10 | | | Febrile neutropenia (3 patients)<br>Cardiotoxicity (2 patients; 1 died) | 5 | 5 |

dacarbazine chemotherapy considered. Any patient presenting with a rapidly growing or severely symptomatic desmoid is started on both sulindac and toremifene at the above doses, and cytotoxic chemotherapy is considered immediately. Once a desmoid has stabilized or regressed, the doses of sulindac or toremifene can be reduced cautiously. If a desmoid is found at surgery that can be resected with a minimum of small bowel, this should be done. Otherwise, surgery is reserved for obstructive complications and abdominal wall desmoids.

## Conclusions

Desmoid tumours, particularly when intra-abdominal, are a serious and increasing problem in patients with FAP. It is not known whether they are, indeed, true neoplasms or the result of a generalized fibroblast abnormality; there is increasing evidence to support the former. Further study of the underlying genetics and molecular biology of desmoids may allow the identification of patients who are at particular risk of their development. This raises the prospect of modifying the management of this group, perhaps delaying colectomy slightly, employing minimally invasive techniques to reduce surgical trauma or opting for primary restorative proctocolectomy to avoid subsequent surgery. Recognition of high-risk patients may justify clinical trials of perioperative prophylaxis.

It has been proposed that the incidence of intra-abdominal desmoids may have been underestimated, as some never progress to become symptomatic[8]. It is known that desmoids are more likely to recur after surgery if large[2], and it has been suggested that treatment may be more effective when the tumour burden is small[156]. More intensive screening of those with FAP for intra-abdominal desmoid disease would establish the true incidence, improve knowledge of the natural history and allow early treatment. Although desmoid disease can run a severe course, prolonged periods of stability and even regression have been reported. There is a need to identify the minority of desmoids that grow rapidly, so that they can be treated aggressively. MRI may offer some prognostic information and may also be valuable in monitoring response to treatment. Finally, further studies of the treatment of intra-abdominal desmoids in patients with FAP are required to establish optimal protocols. These studies will probably need to involve several centres in order to overcome the problems caused by the rarity of this condition.

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