Familial Cancer (2006) 5:275–285
DOI 10.1007/s10689-005-5675-1

Current ideas in desmoid tumours

N. Julian H. Sturt[1] and Susan K. Clark[2]
[1]*Clinical Research Fellow,* [2]*Consultant Surgeon, Polyposis Registry, Cancer Research UK Colorectal Cancer Unit, St Mark's Hospital, HA1 3UJ, Harrow, UK*

Key words: desmoid tumour, familial adenomatous polyposis

Abstract

Desmoid tumours are rare neoplasms of fibroblastic origin which arise with disproportionate frequency in patients with familial adenomatous polyposis (FAP). They are thought to develop in about 10–25% of FAP patients and may be the leading cause of death amongst those who have undergone colectomy. Risk factors include trauma, having a distal germline APC mutation, having a family history of desmoids, and probably oestrogens. In very high-risk individuals there may be a case for delay of colectomy or chemoprophylaxis at the time of surgery. Desmoids are now known to be true neoplasms but with normal telomere length and telomerase activity. FAP-associated tumours seem to carry biallelic APC mutations, one of which lies in the distal part of the gene. Such loss of wild-type APC seems to occur relatively late in tumour development. It is likely that β-catenin plays an important role in tumourigenesis. FAP-associated desmoids tend to arise in the abdomen or abdominal wall. CT scanning gives the best information on tumour anatomy whilst T2-weighted MRI indicates likely behaviour. Treatment may simply consist of observation. Otherwise, usual first-line therapy is with sulindac with or without an anti-oestrogen. Cytotoxic chemotherapy is an option in unresectable tumours. Surgery is a reasonable first-line treatment in abdominal wall tumours but is risky for intra-abdominal tumours and may necessitate massive small bowel resection. Desmoids are the greatest remaining challenge in the management of FAP and further research into their aetiology needs to be combined with multicentre clinical trials of new treatments in order to improve management of the disease.

Introduction

Desmoid tumours are rare soft tissue tumours which can arise sporadically or in association with familial adenomatous polyposis (FAP). Despite their inability to metastasise, desmoids are frequently locally invasive and may compress surrounding structures. In contrast with sporadic tumours, FAP-associated desmoids usually arise in the abdomen (Figure 1), and are a major cause of morbidity and mortality in patients who have undergone prophylactic colonic surgery. Despite recent research they remain a poorly understood entity and current treatments generally lack evidence of efficacy.

The purpose of this review is to assess recent research into the aetiology, pathology and treatment of FAP-associated desmoids and to determine how future studies might usefully advance the management of this challenging condition.

Epidemiology of FAP-associated desmoids

Desmoid tumours are rare, with an estimated annual incidence of 2–5 per million population [1]. While FAP-associated desmoids account for only 2% or so of all cases, the incidence in FAP patients is approximately 850 times that of the general population [2]. The prevalence of desmoid tumours in FAP is probably between 10 and 25% [3–6]. Series with a higher prevalence may reflect the fact that FAP patients with desmoids are more likely to be referred to the specialist centres where most of these studies have been carried out.

Desmoids undoubtedly represent a major cause of morbidity and mortality in FAP. In a variety of studies in FAP patients, desmoids have ranged from being the third equal most common cause of death after metastases of unknown primary and duodenal cancer (in the St Mark's series of patients who had undergone colec-

Correspondence to: Susan K. Clark, Consultant Surgeon, Polyposis Registry, St Mark's Hospital, Harrow HA1 3UJ, UK. E-mail: sclark@racoon.demon.co.uk

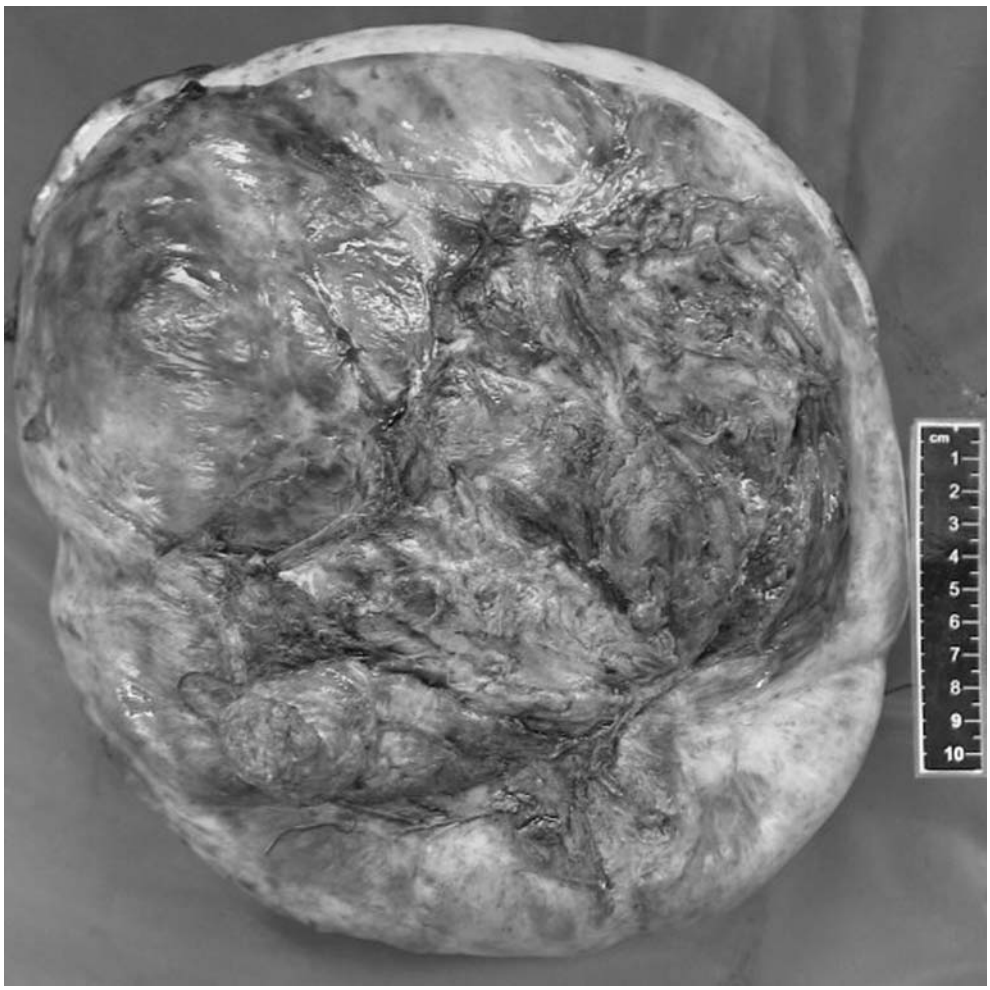

Figure 1. Surgical specimen of massive intra-abdominal desmoid tumour excised without significant small bowel loss.

tomy and ileorectal anastomosis) [7] to the second commonest cause of death, after colorectal cancer, in both Cleveland and Italian series [8, 9]. In Cleveland, they were noted to be the commonest cause of death in those who had undergone subtotal or total colectomy [8]. Additionally, they affect patients at a young age, with an average age of death of 35 years in this study.

Current thinking on the aetiology of FAP-associated desmoids

Aetiological factors which are thought to be of importance in the development of FAP-associated desmoids include trauma, female sex, oestrogens and the position of the APC germline mutation.

Trauma

Trauma, often surgical, has long been implicated in the aetiology of FAP-associated desmoids. A review of studies by Clark and Phillips [10] noted that 68–86% of cases of abdominal wall and intra-abdominal desmoids occur after abdominal surgery, the majority within 5 years [10]. This is corroborated by a more recent finding by Bertario et al. that 84% of cases of FAP-associated desmoids developed within 5 years of abdominal surgery [4], and further evidence comes from the recording of desmoid development in laparascopic port sites [11].

Despite these data, a study looking for the presence of possible desmoid precursor lesions in the mesentery in FAP patients undergoing laparotomy showed many patients with such lesions had no prior history of abdominal surgery. In the same study, however, it was found that patients who had more advanced mesenteric fibrosis at laparotomy were more likely to have undergone previous surgery than those with smaller plaques, suggesting that the trauma of surgery may have caused a precursor lesion to advance forward in stages to becoming a true tumour [12].

Oestrogens and female sex

Oestrogens have been implicated in the pathogenesis of sporadic desmoid tumours because females have a higher incidence, particularly those of childbearing age [13]. Additionally, the growth of tumours in this group

has been noted to be significantly faster than in males or post- or premenopausal women [1, 14], and one of these studies directly correlated the rate of growth of tumours to the level of endogenous oestrogens [1].

Studies looking at the incidence of desmoids in FAP according to sex have differed in their findings, with some studies showing increased incidence in females [3, 4, 15, 16], while others found no significant gender difference [2, 17].

Some studies have looked for oestrodiol receptors in the cytosol of desmoid tumour cells. Lim et al. looked for oestrogen receptors and anti-oestrogen binding sites in 15 desmoid tumours, finding oestrogen receptor positivity in one third and anti-oestrogen binding sites in the majority of those who were oestrogen receptor negative [18]. Tonelli et al. cultured desmoid tumour cells from 4 FAP-associated tumours and noted that proliferation was stimulated by the addition of oestrogenic compounds and inhibited by tamoxifen in all cases, with oestrogen receptor positivity being demonstrated [19]. Such evidence does suggest that many desmoids are sensitive to the effects of oestrogens, although studies are again relatively small, and whether FAP-associated and sporadic tumours differ in this respect is not absolutely clear.

APC germline mutation

Genotype–phenotype correlation is now a well-documented phenomenon in patients with FAP, perhaps the best known being the dense and aggressive colonic phenotype seen in patients with germline *APC* mutations at codon 1309 [20, 21]. Additionally, there is now good evidence that the position of the *APC* germline mutation affects the likelihood of developing desmoids.

The association between a distal (or 3′) germline mutation and an increased propensity to desmoids was first noted by Caspari et al. [22] and Davies et al. [23] in 1995, and has been corroborated by several studies since [4, 24–28]. Caspari originally stated that it was patients with a germline mutation 3′ of codon 1444 who had a greater likelihood of developing desmoids and this delineation has largely been used since, although this is probably an arbitrary point which does not correspond to any functional domain of the APC protein. Nevertheless, having a germline mutation 3′ of codon 1444 (which is uncommon, accounting for 7% of all germline mutations in one study [4]) does undoubtedly increase desmoid risk greatly. For example in an Italian series, Bertario et al. found a 12-fold increased risk of desmoid development in those patients with such a mutation [4].

Other genetic influences

There is also evidence from studies of penetrance that other genes have a role in the development of desmoids independent of the *APC* germline mutation. Again this is analogous to the situation in the colorectum where modifier genes have been sought to explain marked differences in phenotype between individuals with the same germline mutation [29].

For example, Eccles et al. describe a family with a far 3′ *APC* mutation and complete penetrance of desmoid disease through the proband [25]. They argue that other families with 3′ mutations rarely show total penetrance and the inheritance of another modifier in this family may be the explanation. Additionally, a number of authors described FAP-associated desmoids clustered in families [2, 4, 16, 30]. Earlier studies which noted this phenomenon did not examine the germline mutation, and in these cases family history could be explained by the presence of 3′ germline *APC* mutations. However, multivariate analyses by Bertario et al. [4] and a recent study at St Mark's [16] indicate that family history is a risk factor independent of germline *APC* mutation and that families exist with 5′ germline mutations and a high proportion of members affected with desmoids. This strongly suggests the involvement of modifier genes; their characterisation would potentially allow predictive testing before colonic surgery, and perhaps in the future provide a target for gene therapy.

Clues to aetiology and modifier genes from the Apc1638N mouse model

Research into the aetiology and pathology of FAP-associated desmoids has been facilitated by the development of the Apc1638N mouse by Fodde et al. [31–33]. This mouse carries a targeted germline mutation at codon 1638 of one copy of the *APC* gene. This is a far 3′ mutation, and animals develop multiple desmoid tumours, cutaneous cysts and upper gastrointestinal tumours but sparse distal small bowel polyps compared with the Min/+ mouse (which carries a much more 5′ germline *APC* mutation).

In contrast to humans, the desmoids in the Apc 1638N mouse are largely extra-abdominal, being found mainly in the skeletal muscle. Also, males have a higher incidence than females, although tumours have been found to stain positive for mouse progesterone and oestrogen receptor α [32].

The Apc1638N mouse has enabled researchers to investigate the effect of mutation of other genes on desmoid multiplicity. Smits et al. showed that crossing this animal with p53 null animals caused a phenotype developing, on average, a seven-fold increase in desmoid numbers [32]. More recently, a Canadian group noted that aggressive fibromatoses in humans overexpress the hyaluronan receptor Rhamm [34]. Rhamm is known to be overexpressed in mesenchymal cells involved in wound healing and in many human neoplasms, and is a regulator of mesenchymal cell behaviour. This group found that Apc1638N mice which were deficient in Rhamm developed significantly fewer desmoids than mice with normal Rhamm showing that other genes can indeed modify desmoid phenotype.

Can aetiological risk factors guide patient management?

Of all risk factors for desmoid development in FAP, the position of the APC germline mutation and the presence of a strong family history seem to be the most potent. It is noteworthy that 3′ germline mutations are associated with a low-density colonic phenotype [21, 35, 36]. Given the very high penetrance of desmoids in this group, and their probable association with abdominal surgery, it has been suggested that these individuals might be best managed with close colonoscopic surveillance and perhaps celecoxib prophylaxis against the development of colorectal polyps, with colectomy being delayed as long as possible [6, 16]. Patients with a strong family history and a more 5′ germline mutation present a more difficult problem as they are likely to have a classical colonic phenotype and it is therefore unlikely that colectomy can be safely delayed. The concept of giving these patients prophylaxis against desmoid development at the time of colonic surgery (for example using a non-steroidal drug and an anti-oestrogen) is attractive, but whether or not this is an effective means of preventing desmoid development and progression is currently unclear.

Pathology and molecular biology

Desmoid tumours are proliferations of mesenchymal cells which can arise in any musculoaponeurotic structure. They lack a true capsule and frequently infiltrate surrounding structures, but there are no convincing reports of any ability to metastasise. The exact nature of the cell involved is unclear, but cells exhibit fibroblast morphology and may be of myofibroblast origin. Telomerase length and activity are normal [37], nuclei are small and regular and mitoses are infrequent, providing further evidence that desmoids are histologically benign.

Desmoids are monoclonal proliferations

For a long time there was debate as to whether desmoids were true tumours (i.e. of monoclonal origin) or reactive processes. However, recent studies using molecular profiling of tumours have now showed unequivocally that desmoids do arise from a single clonal origin [38, 39], and are thus true neoplasms.

An equivalent process to the adenoma–carcinoma sequence

There is now good evidence that desmoids arise from well-defined precursor lesions and progress through stages before becoming mature tumours [12]. As described below, each stage probably represents an accumulation of genetic mutations somewhat akin to the adenoma-carcinoma sequence in the colorectum.

The presence of plaque-like lesions termed desmoid precursor lesions (DPL), histologically indistinguishable from desmoids and arising in the mesentery, has been described in FAP patients undergoing their first laparotomy [12]. However, it is noteworthy that more FAP patients have DPL's at laparotomy than go on to develop clinical tumours, so only a certain proportion of such lesions will progress.

Another entity termed mesenteric fibrosis (MF), consisting of mesenteric thickening and puckering but not amounting to a mass, is also described [3]. MF is a more advanced lesion than DPL both radiologically and at laparotomy, but lacks the space-occupying character of a true desmoid tumour. It thus probably represents the intermediate stage of desmoid development, but once again not all patients with MF will go on to develop true desmoids, rather as in the non-FAP population where not all patients with colorectal adenomas will go on to develop colorectal cancer.

A limited number of studies have examined the *APC* status of both mature desmoids and DPLs. Studies by three groups [40–42] consistently showed both germline and somatic *APC* mutations in FAP-associated desmoids. Interestingly, in patients who had a 5′ germline *APC* mutation (before codon 1444 or so), the 'second hit' was always in the 3′ region of the gene while in patients with 3′ germline mutations the somatic event was almost invariably loss of heterozygosity (LOH). It thus seems likely that desmoid development is dependent on at least one of the two APC mutations lying in the 3′ region of the gene. This helps to explain why the incidence of desmoids is so high in patients with 3′ germline mutations, since any second hit in vulnerable cells will allow the development of a tumour. In patients with 5′ germline mutations desmoids would be expected to be less common since it is necessary for a rare second hit in the 3′ region of the gene to occur in order for desmoid development (with this region lying at the far end of and beyond the mutation cluster region). This does not, however, explain the previously mentioned high incidence in certain families with 5′ mutations, and also the fact that certain individuals with 5′ mutations develop multiple tumours with an unexpectedly high frequency [16]. This lends further weight to the hypothesis that mutations in other genes are also necessary for, or to at least facilitate, desmoid development.

When DPLs have been examined in a similar way, there has been no evidence of there being a second hit in the APC gene [43]. In contrast to colorectal adenomas, it would thus appear that loss of normal APC is a relatively late event.

The role of aberrant β-catenin

β-catenin is an intracellular protein increasingly recognised as having a central role in colorectal carcinogenesis. It is known that loss of normal APC allows excess β-catenin to travel to the nucleus and upregulate the transcription of key genes involved in the cell cycle.

Compared with its role in colorectal carcinogenesis, the role of β-catenin in FAP-associated desmoids is less

clear. Very few studies have examined β-catenin expression specifically in FAP-associated tumours, although those that have noted upregulation [26]. However, clues to its role can be gained from sporadic desmoids, where a number of studies have noted β-catenin mutations in tumours [44, 45] which may prevent normal APC binding and subsequent degradation. Additionally, one study has noted that β-catenin overexpression in desmoids (not clearly divided into sporadic or FAP-associated) is so ubiquitous that the authors suggest using it as a marker to distinguish desmoids from other histologically similar tumours [46].

There is good evidence that β-catenin dysregulation does cause abnormal behaviour in mesenchymal cells, lending further weight to the hypothesis that β-catenin plays a key role in desmoid pathology. Cheon et al. showed that β-catenin is overexpressed in fibroblasts in the proliferating phase of healing. Additionally, fibroblasts from transgenic mice with a targeted β-catenin mutation exhibited increased proliferation, motility and invasiveness compared with controls and the mice developed aggressive fibromatoses and healed with hyperplastic cutaneous wounds [47].

Other molecular changes in desmoids

Some studies have examined the karyotype of desmoids and found that sporadic tumours in an extra-abdominal location may show cytogenetic abnormalities (such as trisomy 8 or gain of chromosome band 1q21), while abdominal tumours and FAP-associated tumours tend to be karyotypically normal [48, 49].

Presentation, clinical features and natural history

The clinical spectrum of desmoid disease ranges from incidental small, stable lesions to rapidly-growing, huge abdominal masses causing death in a matter of a few years or even months. It is quite common for an asymptomatic desmoid to be noted at routine clinical examination of an FAP patient. Other patients may note the mass themselves or present with pain or the sequelae of compression of surrounding structures such as the ureters or small bowel. Rapidly growing tumours may cause weight loss, cachexia and malaise. Symptoms can also result from compression of the ureters causing obstructive renal failure or compression of the small bowel causing bowel obstruction. Occasionally a desmoid can perforate into bowel resulting in localised or generalised peritonitis.

The anatomical location of desmoids in FAP differs quite markedly from the location of sporadic tumours, being much more likely to be intra-abdominal or in the anterior abdominal wall than in extra-abdominal sites. Whether this is related to the fact that FAP patients are more likely to have undergone previous abdominal surgery is not clear. There is no doubt that intra-abdominal tumours carry much the highest morbidity and mortality since they frequently involve vital abdominal structures and surgery is more hazardous.

As far as clinical course is concerned, desmoids can be divided into four groups, as reported in a study by Church [50]. Here he described how 10% of tumours resolve spontaneously, 30% undergo cycles of progression and resolution, 50% remain stable after diagnosis and 10% progress rapidly. This natural history should be borne in mind when assessing the efficacy of therapy, as some tumours in clinical trials which showed complete or partial regression may have done so anyway in the absence of any treatment.

Diagnosis

Diagnosis is often clinical, at least initially, and should be one of the first differentials in the case of an FAP patient presenting with an abdominal or abdominal wall mass. CT is the best imaging modality for making the diagnosis and establishing the relation of the tumour to surrounding structures (Figure 2). Additionally, a CT scoring system has been developed, characterising the appearances of DPL, MF and true tumours on CT and providing further evidence for a stepwise progression in desmoid development [51]. MRI scanning using T2 weighted imaging may give an indication as to how the tumour is likely to behave, with a bright signal indicating high water content and association with rapid growth (Figure 3) [52]. Biopsy is not usually necessary but does not seem to induce further growth, if performed.

Management

Given the problems with the treatment of desmoids, there is a good case for simple observation of many tumours, particularly if asymptomatic. Following diagnosis, a small tumour which is not encroaching on any nearby structures may be followed up by regular clinical examination (perhaps every 6 months) with or without imaging, usually by CT. It is wise to image all intra-abdominal tumours to ensure they are not causing ureteric compression.

Rapidly growing tumours, or those which are symptomatic, usually warrant treatment. Symptoms need to be managed as they occur with appropriate analgesia, stenting of obstructed ureters and management of bowel obstruction or peritonitis. It may be necessary to perform laparotomy in order to bypass obstructed bowel or manage perforation without attempting to remove the tumour itself.

Pharmacological therapies

Given the problems with surgery for desmoids, pharmacological agents are usually the initial agents of choice when managing desmoids in FAP. Unfortunately

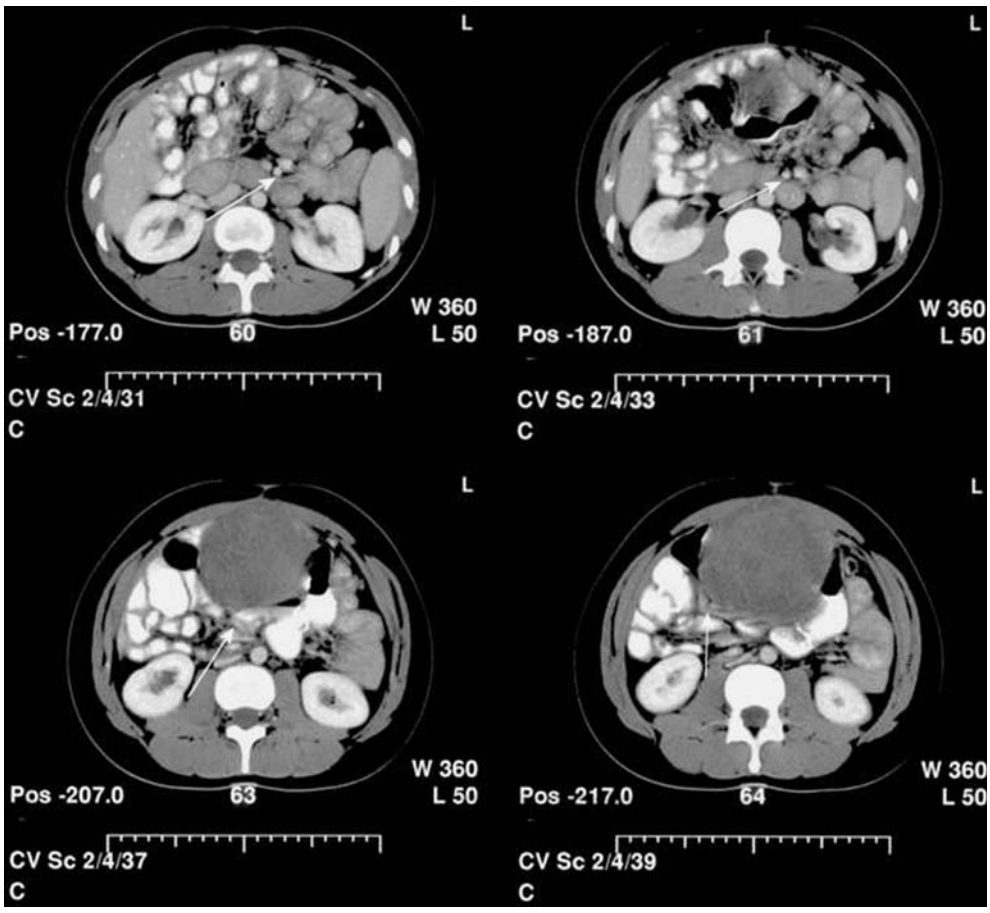

Figure 2. CT scan of intra-abdominal tumour showing relationship with superior mesenteric artery (highlighted with arrows). In this case the proximal SMA is free from tumour, making the lesion potentially resectable.

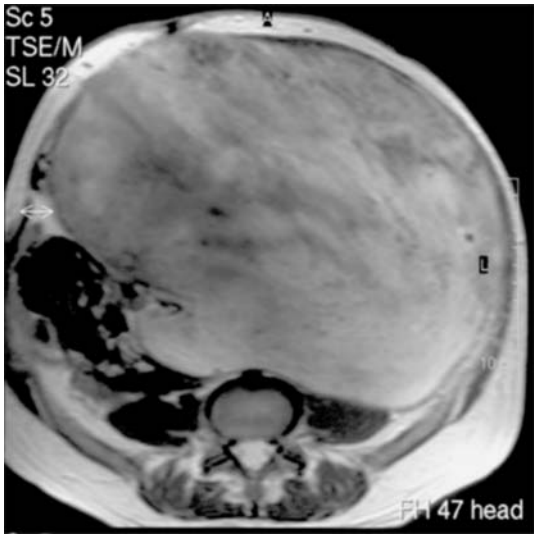

Figure 3. T2-weighted MRI of intra-abdominal tumour showing high (bright) signal indicative of rapid future growth.

the rarity of this condition, particularly when associated with FAP, has largely precluded meaningful randomised trials. Coupled with the variable natural history of desmoids (with some tumours appearing to show spontaneous regression even in the absence of treatment), interpretation of the efficacy of pharmacological treatments is extremely difficult. Non-steroidal anti-inflammatory drugs (NSAIDs) and anti-oestrogens are considered first-line therapies, with cytotoxic chemotherapy being used for specific indications, usually the failure of non-cytotoxic therapy in an irresectable tumour.

Non-cytotoxic chemotherapy

The mainstays of non-cytotoxic chemotherapy in desmoid disease are NSAIDs (usually sulindac) and anti-oestrogens (tamoxifen or toremifene), used alone or in combination.

NSAIDs

Non-steroidal anti-inflammatories have been shown to reduce the incidence of both upper [53] and lower [54] GI tract polyps in FAP, and it is thus logical that other tumours arising from similar molecular mechanisms will be similarly sensitive.

A study by Poon et al. showed that desmoids from Apc1638N mice had elevated levels of cyclo-oxygenase 2 (an enzyme inhibited by NSAIDs). When these mice

were crossed on to a Cox-2 deficient background, the average tumour size was smaller, although the number of tumours remained unchanged. Additionally, in cell cultures derived from human sporadic desmoids, Cox-2 blockade resulted in reduced cell proliferation [55].

The drug which has been used most in FAP-associated desmoids is sulindac, as it is the agent with which most clinicians have the greatest experience. As with all therapies, evidence for efficacy is based on small case series, with most showing variable response. Since such studies are non-randomised it is rarely clear what the behaviour of the tumour would have been if there had been no treatment. For example, Tsukada et al. noted a 57% overall response rate to sulindac therapy in 14 FAP patients with desmoids, although the effect was typically delayed [56].

Given that the role of cyclo-oxygenase in desmoids seems to be mediated via a Cox-2 specific mechanism, it is probable that Cox-2 specific NSAIDs such as celecoxib will have the same efficacy as drugs like sulindac with fewer of the gastrointestinal side-effects. These drugs may therefore be an option in patients who have suffered side-effects from the traditional drugs.

Anti-oestrogens

As discussed in the section on the aetiology of desmoids, there is good evidence that desmoid tumours are sensitive to the effect of oestrogens, based on observations of increased incidence and growth rates in women (with highest growth rates in pregnancy), and *in vitro* studies of oestrogen receptor status and the effects of anti-oestrogens on cell proliferation in cultures of desmoid tumour cells. Anti-oestrogen therapy has therefore been a mainstay in the management of desmoids, both FAP-associated and sporadic.

Evidence for the efficacy of anti-oestrogens is based on a number of non placebo-controlled trials, many of which have reported disease stabilisation or regression (reviewed by Janinis et al. [57]). Drugs used include the oestrogen receptor antagonists tamoxifen or toremifene. Tamoxifen has traditionally been given at doses equivalent to that used for breast cancer (i.e. 20 mg per day), but there are anecdotal reports that there is additional efficacy when it is given in higher doses (e.g. 120 mg per day). Collaborative multicentre trials may help to elucidate whether this is the case.

Recently, an Italian study investigated the effects of raloxifene on 13 patients with FAP-associated desmoids [58]. Raloxifene is an oestrogen receptor modulator, with either oestrogenic or anti-oestrogenic activity, depending on the tissue. In this small series, 5 patients showed complete remission of their tumours and 8 patients partial remission, with no significant side-effects. On the basis of this study, further trials of this compound may well be warranted.

Other non-cytotoxic agents

Other drugs have been used in desmoid disease in the past including cyclic AMP inhibitors and interferon α, but are now rarely used (if at all) in FAP-associated tumours. Recent small trials have investigated the efficacy of the oral anti-fibrinolytic agent pirfenidone [59], and the tyrosine kinase inhibitor imantinib mesylate [60], although in the latter case the patients involved did not have FAP. Due to small patient numbers interpretation of results is difficult and further evaluation is necessary to decide whether formal clinical trials of these compounds would be worthwhile.

Cytotoxic chemotherapy

Again, there are no randomised trials of cytotoxic chemotherapy for desmoids in FAP, with regimens being based largely on single arm retrospective studies.

Single agents have been used rarely, although there are case reports of tumour response to doxorubicin alone [61, 62]. More commonly, doxorubicin has been combined with another agent such as dacarbazine or cyclophosphamide and vincristine (reviewed by Janinis et al. [57]). The overall response rate to doxorubicin-based chemotherapy is 50%, but at the expense of severe side-effects (especially nausea and vomiting) and acute and delayed toxicity, with cardiotoxicity being a particular concern. Alternatively, so-called low dose chemotherapy using a vinca alkaloid in combination with methotrexate has been used with apparently good efficacy in non-FAP related desmoids [63, 64]. Toxicity is less severe than with doxorubicin-based therapies but some patients experience myelotoxicity. For this reason, cytotoxic chemotherapy is probably best reserved for inoperable tumours which are progressing despite treatment with a combination of a non-steroidal and an anti-oestrogen.

Radiotherapy

Radiotherapy has been used in combination with surgery in the treatment of sporadic desmoids occurring on the extremities. However, since FAP-related desmoids are much more likely to occur in the abdomen, radiotherapy is rarely useful due to the resultant small bowel toxicity.

Surgery

Surgery remains a useful modality of therapy for desmoids, albeit with defined indications. Surgery of abdominal wall desmoids is generally safe; in a series at St Mark's, 51 abdominal wall desmoids were excised with no mortality or significant morbidity, but 41% recurred. Surgery for mesenteric desmoids is more contentious; in the same series, 36% of patients operated on for mesenteric tumours died in the perioperative

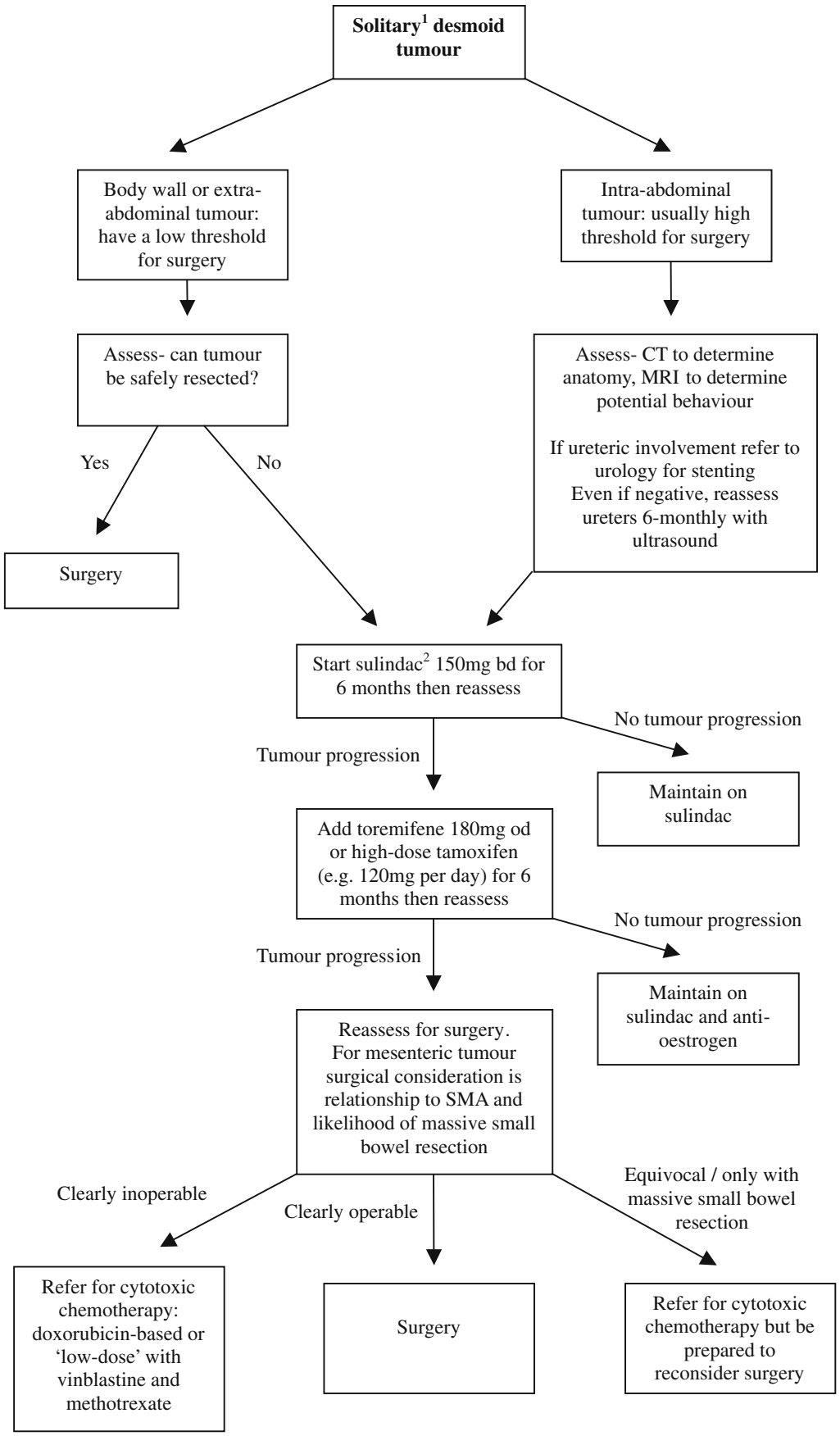

Figure 4. Treatment algorithm for FAP-associated desmoid tumours as used at St Mark's hospital. (1) This algorithm applies to solitary desmoid tumours. In the case of multiple tumours the balance of treatment needs to be adjusted towards pharmacological management and away from surgery, particularly in individuals at known high-risk of developing further or recurrent tumours (e.g. 3′ germline APC mutation, strong family history). (2) In individuals unable to tolerate sulindac consider celecoxib 400 mg bd.

period from haemorrhagic complications and nearly half of the survivors needed extensive enough enterectomy (due to small bowel involvement) to require long-term parenteral nutrition. In addition, the tumour recurred in 71% of these patients [65]. Other series report similar rates of recurrence and risk for surgery on intra-abdominal tumours.

It would thus seem that surgery is a reasonable first-line treatment for abdominal wall tumours, but should only be used for intra-abdominal tumours in specific circumstances. These would include tumours which do not appear to involve vital organs and vessels on pre-operative imaging, those resistant to drug treatment and in cases where a risky operation is the only possible option in the case of a rapidly growing, life-threatening tumour. High rates of recurrence should be expected and patients must be counselled pre-operatively about the risks of death and the possibility of needing long-term TPN afterwards. Such cases should only be attempted in specialist centres with sufficiently experienced staff.

In certain circumstances, small bowel transplantation may be an alternative to lifelong TPN after extensive bowel resection. One centre has also reported a technique where the tumour and small bowel are removed en bloc, perfused and cooled, and the tumour resected on the bench in a bloodless field with subsequent autotransplantation of the small bowel back in to the patient [66].

Interventional radiology

One report has recently been published where two desmoids (one intra-abdominal) were treated with percutaneous chemical ablation with acetic acid under radiological guidance [67]. In both cases there was substantial regression of the tumours within a few months. Radiologically-guided targeting of large tumours would seem to be relatively straightforward, and even temporary shrinkage may be a useful measure in otherwise untreatable cases.

Possible future therapy: Gene therapy

Gene therapy involves the administration of genetic material to human cells for therapeutic purposes. A great deal of preclinical and clinical research has been conducted on gene therapy over the last few years, generally with disappointing results in human trials. However, as gene delivery vectors improve it is likely to provide another useful modality of therapy in the future since tumours can be targeted on a cellular level.

One paper has been published looking at the feasibility of reintroduction of the *APC* gene into human fibroblasts *in vitro*, and into mouse mesenchymal cells *in vivo*, using liposomes as vectors [68]. Given the molecular pathology in FAP-associated desmoids of *APC* loss, this would seem to represent one possible gene therapy strategy. It was shown that the gene could be reintroduced successfully into fibroblasts in cell cultures, and into mouse peritoneum and mesentery when the therapy was given intraperitoneally. Given that gene expression was verified by PCR, it could have been at very low levels. However, this does, at least in principle, demonstrate that gene therapy represents a potential future form of treatment for desmoids.

An algorithm for treatment

Figure 4 shows the current algorithm used for treatment of FAP-associated desmoids at the St Mark's hospital polyposis registry.

Conclusions

As the management of the large bowel and duodenum have improved, desmoid disease has become the most challenging clinical manifestation of FAP.

Current treatments are not based on properly randomised trials and evidence for efficacy is lacking. There is thus a need for international collaboration between different centres specialising in FAP in order to gain the necessary numbers to conduct meaningful trials. In addition, there is a need for further studies to better our understanding of the aetiology and pathology of this poorly characterised disease. Hopefully the results of such studies will eventually lead to more targeted interventions and effective treatments for this difficult condition.

Acknowledgements

The authors would like to acknowledge the help of Dr Amir Sadat (Department of Histopathology, St Mark's Hospital) for photography of the surgical specimen, Dr Michelle Marshall (Consultant Radiologist, St Mark's Hospital) for advice and interpretation of CT and MRI scans, and Professor Robin Phillips (Director, Polyposis Registry at St Mark's Hospital) for the design of the treatment algorithm.

References

1. Reitamo JJ, Scheinin TM, Hayry P. The desmoid syndrome. New aspects in the cause, pathogenesis and treatment of the desmoid tumor. Am J Surg 1986; 151: 230–7.
2. Gurbuz AK, Giardello FM, Petersen GM et al. Desmoid tumours in familial adenomatous polyposis. Gut 1994; 35: 377–81.
3. Lofti AM, Dozois RR, Gordon H et al. Mesenteric fibromatosis complicating familial adenomatous polyposis: predisposing factors and results of treatment. Int J Colorectal Dis 1989; 4: 30–6.
4. Bertario L, Russo A, Sala P et al. Genotype and phenotype factors as determinants of desmoid tumours in patients with familial adenomatous polyposis. Int J Cancer 2001; 95: 102–7.
5. Heinimann K, Mullhaupt B, Weber W et al. Phenotypic differences in familial adenomatous polyposis based on APC germline mutation status. Gut 1998; 43: 675–679.
6. Friedl W, Caspari R, Sengteller M et al. Can APC mutation analysis contribute to therapeutic decisions in familial adenoma-

tous polyposis? Experience from 680 FAP families. Gut 2001; 48: 515–521.
7. Nugent KP, Spigelman AD, Phillips RKS. Life expectancy after colectomy and ileorectal anastomosis for familial adenomatous polyposis. Dis Colon Rectum 1993; 36: 1059–62.
8. Arvanitis ML, Jagelman DG, Fazio VW et al. Mortality in patients with familial adenomatous polyposis. Dis Colon Rectum 1990; 33: 639–42.
9. Bertario L, Presciuttini S, Sala P et al. Causes of death and postsurgical survival in familial adenomatous polyposis: results from the Italian registry of familial polyposis writing committee. Semin Surg Oncol 1994; 10: 225–34.
10. Clark SK, Phillips RKS. Desmoids in familial adenomatous polyposis. Br J Surg 1996; 83: 1494–504.
11. Lynch HT, Fitzgibbons R Jr. Surgery, desmoid tumors, and familial adenomatous polyposis: case report and literature review. Am J Gastroenterol 1996; 91: 2598–601.
12. Clark SK, Smith TG, Katz DE et al. Identification and progression of a desmoid precursor lesion in patients with familial adenomatous polyposis. Br J Surg 1998; 85: 970–3.
13. Reitamo JJ, Hayry P, Nykyri E et al. The desmoid tumor. I. Incidence, sex-, age- and anatomical distribution in the Finnish population. Am J Clin Pathol 1982; 77: 665–73.
14. Hayry P, Reitamo JJ, Totterman S et al. The desmoid tumor. II. Analysis of factors possibly contributing to the etiology and growth behavior. Am J Clin Pathol 1982; 77: 674–80.
15. Klemmer S, Pascoe L, Decosse J. Occurrence of desmoids in patients with familial adenomatous polyposis of the colon. Am J Med Genet 1987; 28: 385–92.
16. Sturt NJH, Gallagher MC, Bassett P et al., 2004 Evidence for genetic predisposition to desmoid tumours in familial adenomatous polyposis (FAP) independent of the APC germline mutation. Gut 2004; 53: 1832–6.
17. McAdam WA, Goligher JC. The occurrence of desmoids in patients with familial polyposis coli. Br J Surg 1970; 57: 618–31.
18. Lim CL, Walker MJ, Mehta RR et al. Estrogen and antiestrogen binding sites in desmoid tumors. Eur J Cancer Clin Oncol 1986; 22: 583–7.
19. Tonelli F, Valanzano R, Brandi ML. Pharmacologic treatment of desmoid tumors in familial adenomatous polyposis: results of an in vitro study. Surgery 1994; 115: 473–9.
20. Miyoshi Y, Ando H, Nagase H et al. Germ-line mutations of the APC gene in 53 familial adenomatous polyposis patients. Proc Natl Acad Sci USA 1992; 89: 4452–6.
21. Nagase H et al. Correlation between the location of germline mutations in the APC gene and the number of colorectal polyps in familial adenomatous polyposis patients. Cancer Res 1992; 52: 4055–7.
22. Caspari R, Olschwang S, Friedl W et al. Familial Adenomatous Polyposis: desmoid tumours and lack of opthalmic lesions (CHRPE) associated with APC mutations beyond codon 1444. Hum Mol Genet 1995; 4: 337–40.
23. Davies DR, Armstrong JG, Thakker N et al. Severe Gardner syndrome in families with mutations restricted to a specific region of the APC gene. Am J Hum Genet 1995; 57: 1151–8.
24. Scott RJ, Froggatt NJ, Trembath RC et al. Familial infiltrative fibromatosis (desmoid tumours) (MIM135290) caused by a recurrent 3′ APC gene mutation. Hum Mol Genet 1996; 5: 1921–4.
25. Eccles DM, van der Luijt R, Breukel C et al. Hereditary desmoid disease due to a frameshift mutation at codon 1924 of the APC gene. Am J Hum Genet 1996; 59: 1193–201.
26. Couture J, Mitri A, Lagace R et al. A germline mutation at the extreme 3′ end of the APC gene results in a severe desmoid phenotype and is associated with overexpression of beta-catenin in the desmoid tumour. Clin Genet 2000; 57: 205–12.
27. Bertario L, Russo A, Sala P et al. Multiple approach to the exploration of genotype–phenotype correlations in familial adenomatous polyposis. J Clin Oncol 2003; 21: 1698–707.
28. Dobbie Z, Spycher M, Mary J-L et al. Correlation between the development of extracolonic manifestations in FAP patients and mutations beyond codon 1403 in the APC gene. J Med Genet 1996; 33: 274–80.
29. Houlston R, Crabtree M, Phillips R et al. Explaining differences in the severity of familial adenomatous polyposis and the search for modifier genes. Gut 2000; 48: 1–5.
30. Soravia C, Berk T, McLeod RS et al. Desmoid disease in patients with familial adenomatous polyposis. Dis Colon Rectum 2000; 43: 363–9.
31. Fodde R, Edelmann W, Yang K et al. A targeted chain-termination mutation in the mouse Apc gene results in multiple intestinal tumors. Proc Natl Acad Sci USA 1994; 91: 8969–73.
32. Smits R, van der van Houven Oordt W, Luz A et al. Apc1638N: a mouse model for familial adenomatous polyposis-associated desmoid tumors and cutaneous cysts. Gastroenterology 1998; 114: 275–83.
33. Smits R, Kartheuser A, Jagmohan-Changur S et al. Loss of Apc and the entire chromosome 18 but absence of mutations at the Ras and Tp53 genes in intestinal tumors from Apc1638N, a mouse model for Apc-driven carcinogenesis. Carcinogenesis 1997; 18: 321–7.
34. Tolg C, Poon R, Fodde R et al. Genetic deletion of receptor for hyaluronan-mediated motility (Rhamm) attenuates the formation of aggressive fibromatosis (desmoid tumour). Oncogene 2003; 22: 6873–82.
35. van der Luijt RB, Meera Khan P, Vasen HFA et al. Germline mutations in the 3' part of APC exon 15 do not result in truncated proteins and are associated with attenuated adenomatous polyposis coli. Hum Genet 1996; 98: 727–34.
36. Soravia C, Berk T, Madlensky L et al. Genotype–phenotype correlations in attenuated adenomatous polyposis coli. Am J Hum Genet 1998; 62: 1290–301.
37. Middleton SB, Pack K, Phillips RK. Telomere length in familial adenomatous polyposis-associated desmoids. Dis Colon Rectum 2000; 43: 1535–9.
38. Li M, Cordon-Cardo C, Gerald WL et al. Desmoid fibromatosis is a clonal process. Hum Pathol 1996; 27: 939–43.
39. Middleton SB, Frayling IM, Phillips RK. Desmoids in familial adenomatous polyposis are monoclonal proliferations. Br J Cancer 2000; 82: 827–32.
40. Miyaki M, Konishi M, Kikuchi-Yanoshita R et al. Coexistence of somatic and germ-line mutations of APC gene in desmoid tumours from patients with familial adenomatous polyposis. Cancer Res 1993; 53: 5079–82.
41. Palmirotta R, Curia MC, Esposito DL et al. Novel mutations and inactivation of both alleles of the APC gene in desmoid tumours. Hum Mol Genet 1995; 4: 1979–81.
42. Lamlum H, Ilyas M, Rowan A et al. The type of somatic mutation at APC in familial adenomatous polyposis is determined by the site of germline mutation: a new facet to Knudson's 'two hit' hypothesis. Nat Med 1999; 5: 1071–5.
43. Clark SK. Studies in desmoid disease in familial adenomatous polyposis. MD thesis, University of Cambridge, 1998.
44. Miyoshi Y, Iwao K, Nawa G et al. Frequent mutations in the beta-catenin gene in desmoid tumours from patients without familial adenomatous polyposis. Oncol Res 1998; 10: 591–4.
45. Tejpar S, Nollet F, Li C et al. Predominance of beta-catenin mutations and beta-catenin dysregulation in sporadic aggressive fibromatosis. Oncogene 1999; 18: 6615–20.
46. Montgomery E, Torbenson MS, Kaushal M et al. Beta-catenin immunohistochemistry separates mesenteric fibromatosis from gastrointestinal stromal tumor and sclerosing mesenteritis. Am J Surg Pathol 2002; 26: 1296–301.
47. Cheon SS, Cheah AYL, Turley S et al. b-Catenin stabilization dysregulates mesenchymal cell proliferation, motility, and invasiveness and causes aggressive fibromatosis and hyperplastic cutaneous wounds. Proc Natl Acad Sci USA 2002; 99: 6973–8.
48. Larramendy ML, Virolainen M, Tukiainen E et al. Chromosome band 1q21 is recurrently gained in desmoid tumors. Genes Chromosomes Cancer 1998; 23: 183–6.

49. Brandal P, Micci F, Bjerkehagen B et al. Molecular cytogenetic characterization of desmoid tumors. Cancer Genet Cytogenet 2003; 146: 1–7.
50. Church JM. Desmoid tumours in patients with familial adenomatous polyposis. Semin Colon Rectal Surg 1995; 6: 29–32.
51. Middleton SB, Clark SK, Matravers P et al. Stepwise progression of familial adenomatous polyposis-associated desmoid precursor lesions demonstrated by a novel CT scoring system. Dis Colon Rectum 2003; 46: 481–5.
52. Healy JC, Reznek RH, Clark SK et al. MR appearances of desmoid tumors in familial adenomatous polyposis. AJR Am J Roentgenol 1997; 169: 465–72.
53. Phillips RKS, Wallace MH, Lynch PM et al. A randomised, double blind, placebo controlled study of celecoxib, a selective cyclooxygenase 2 inhibitor, on duodenal polyposis in familial adenomatous polyposis. Gut 2002; 50: 857–60.
54. Friend WG. Sulindac suppression of colorectal polyps in Gardener's syndrome. Am Fam Physician 1990; 41: 891–4.
55. Poon R, Smits R, Li C et al. Cyclooxygenase-two (COX-2) modulates proliferation in aggressive fibromatosis (desmoid tumor). Oncogene 2001; 20: 451–60.
56. Tsukada K, Church JM, Jagelman DG et al. Noncytotoxic drug therapy for intra-abdominal desmoid tumor in patients with familial adenomatous polyposis. Dis Colon Rectum 1992; 35: 29–33.
57. Janinis J, Patriki M, Vini L et al. The pharmacological treatment of aggressive fibromatosis: a systematic review. Ann Oncol 2003; 14: 181–90.
58. Tonelli F, Ficari F, Valanzano R et al. Treatment of desmoids and mesenteric fibromatosis in familial adenomatous polyposis with raloxifene. Tumori 2003; 89: 391–6.
59. Lindor NM, Dozois R, Nelson H et al. Desmoid tumors in familial adenomatous polyposis: a pilot project evaluating efficacy of treatment with pirfenidone. Am J Gastroenterol 2003; 98: 1868–74.
60. Mace J, Sybil Biermann J, Sondak V et al. Response of extraabdominal desmoid tumors to therapy with imatinib mesylate. Cancer 2002; 95: 2373–9.
61. Seiter K, Kemeny N. Successful treatment of a desmoid tumour with doxorubicin. Cancer 1993; 71: 2242–4.
62. Risum S, Bulow S. Doxorubicin treatment of an intra-abdominal desmoid tumour in a patient with familial adenomatous polyposis. Colorectal Dis 2003; 5: 585–6.
63. Weiss A, Lackman R. Low-dose chemotherapy of desmoid tumours. Cancer 1989; 64: 1192–4.
64. Azzarelli A, Gronchi A, Bertulli R et al. Low-dose chemotherapy with methotrexate and vinblastine for patients with advanced aggressive fibromatosis. Cancer 2001; 92: 1259–64.
65. Clark SK, Neale KF, Landgrebe JC et al. Desmoid tumours complicating familial adenomatous polyposis. Br J Surg 1999; 86: 1185–9.
66. Tzakis AG, Tryphonopoulos P, De Faria W et al. Partial abdominal evisceration, *ex vivo* resection, and intestinal autotransplantation for the treatment of pathologic lesions of the root of the mesentery. J Am Coll Surg 2003; 197: 770–6.
67. Clark TW. Percutaneous chemical ablation of desmoid tumors. J Vasc Interv Radiol 2003; 14: 629–34.
68. Bright-Thomas RM, Agrawal A, Hargest R. Preclinical studies of gene transfer for the treatment of desmoid disease in familial adenomatous polyposis. Br J Surg 2002; 89: 1563–9.