Introduction

Desmoid tumor, also known as aggressive fibromatosis, is a rare, deep-seated, mesenchymal fibroblastic tumor. Such tumors do not metastasize, but are locally highly invasive, and exhibit a propensity to recur even after aggressive surgery with free operative margin [1]. Surgical treatment has been the mainstay for desmoid tumors. However, there has been controversy about the association between the microscopic margin status and recurrence rate, [2-9] and so no definitive conclusion has been reached regarding the significance of the histological margin status.

Recently, a few studies have investigated the predictive value of catenin β-1 (CTNNB1) mutation, which is harbored by most sporadic desmoid tumors, for the outcome of surgical treatment. The results of these studies, however, have been controversial possibly because they focused on retrospective cohorts with inhomogeneous treatment modality (i.e., with or without radiotherapy) and mixture of different margin status of surgery (R0 and R1). [10-12]. We have prospectively, and consecutively treated patients with extra-peritoneal desmoid tumors with meloxicam, a COX-2 inhibitor [13,14], and a significant predictive value of CTNNB1 for this conservative treatment was demonstrated [15].

We hypothesized that simple resections with positive surgical margins could be applicable to patients with truncal desmoid tumors, and the outcomes of surgical treatment would be correlated with mutational status of CTNNB1. In this study, we analyzed the outcome of surgical treatment in patients with extra-peritoneal desmoid tumors, who were mainly treated with meloxicam followed by planned simple resection, and clarify the mutational status of these tumors.

Patients and Methods

Treatment modality for patients with extra-peritoneal desmoid tumors

Until 2003, our patients with extra-peritoneal desmoid tumors were surgically treated with wide

surgical margins. However, an unsatisfactory recurrence rate even with microscopically negative margins [9] prompted us to change the treatment modalilty from 2003 to meloxicam, a COX-2 inhibitor, based on a study using genetically modified mice [16]. Meloxicam treatment for patients with extra-peritoneal desmoid tumors was approved by the Institutional Review Board of the Center for Advanced Medicine and Clinical Research, Nagoya University. Favorable short-term results were reported initially [14,17]; however, not a few patients exhibited resistance to meloxicam treatment subsequently [18]. We have formally organized the treatment modality with low dose chemotherapy (methotrexate and vinblastine) or planned simple surgery for patients with desmoid tumors refractory to or stable to meloxicam treatment since 2009. Selection criteria for planned simple resection surgery were as follows. Functional impairment was not anticipated after surgical treatment, which exhibited a tendency to include truncal desmoid tumors, and exclude extremity desmoid ones. Since 2010, mutational status has been considered as one of the selection criteria. Informed consent for simple resection and anonymized use of the samples for research was obtained from all patients in this cohort. The study protocol including analyzing mutational status of CTNNB1 was approved by the institutional review board of our institution.

Mutation analyses for CTNNB1 gene

In all patients enrolled in this study, desmoid tumors were histologically diagnosed using specimens obtained by incisional biopsy at the time of referral to our institution. Part of the obtained specimen was snap-frozen, and stored at -80 °C for mutation analyses as described previously [15]. Briefly, DNA was extracted from frozen tissue or 5-μm-thick formalin-fixed, paraffin-embedded tissue using the High Pure PCR Template Preparation Kit (Roche Molecular Diagnostics, Mannheim, Germany), according to the manufacturer's instructions. The extracted DNA was subjected to polymerase chain reaction (PCR) analyses to determine the existence of point mutations in codons

41 or 45 of CTNNB1 exon 3 using 2 pairs of primers spanning these mutation sites, as previously reported [15]. Amplified PCR products were subjected to direct sequencing. All sequencing results were compared with β-catenin sequences in the databases of NCBI-BLAST to evaluate the mutational status. This protocol of DNA analyses was approved by the Institutional Review Board of the Center for Advanced Medicine and Clinical Research, Nagoya University.

Planned simple resection

Simple resection was planned to minimize the extent of resection for surrounding normal tissues including muscles, fascia, and other connective tissues, which reduced the rate of soft tissue reconstruction. Major nerve injury did not occur with this simple resection. Practically, desmoid tumors were excised without the cuff of surrounding tissues. Muscles were partially excised with tumors when difficult to detach. Excised specimens were all subjected to pathological evaluation. Two-directional surfaces through the midline of excised specimens were examined for microscopic margin status by our experienced pathologists. Patients with planned simple resection were routinely evaluated for local recurrence with CT and/or MRI every 3 months until 1 year after surgery, and every 6 months thereafter.

Statistical evaluation

Data were analyzed using the Fisher's exact test for dichotomous variables to determine correlations between the mutational status of CTNNB1 and clinicopathological characteristics. Continuous variables of age and tumor size were compared between the two groups using student-T test. All statistical analyses were performed using SPSS version 20. $P<0.05$ was considered significant.

Results

Patient demographics

Since 2003, there were 60 consecutive cases with extra-abdominal or abdominal wall desmoid tumors histologically diagnosed in our institution and affiliated hospitals. Patients treated with meloxicam (10mg/body daily) have been followed with MRI and/or CT at the outpatient unit of our department of orthopaedic surgery every 3-6 months. According to Response Evaluation Criteria in Solid Tumors (RECIST), 9 patients with progressive disease (PD) with meloxicam treatment, and 4 who refused meloxicam treatment were subjected to planned simple resection since 2009. Two of nine patients with PD were initially treated with methotrexate and vinblastine, and followed by planned simple resection. Eleven were female, and two male. Mean age of patients was 39 years ranging from 19 to 70. Six tumors occurred in the abdominal wall, four in the chest wall, two in the posterior neck, and one in the anterior neck region. Mean largest diameter of tumors was 9.9 cm (ranging from 4.5 to 18). Mean follow up period after planned simple resection surgery was 30 months (median: 26, ranging from 6-63) (Table 1).

Mutational status of CTNNB1 gene

Point mutations of CTNNB1 exon 3 were confirmed in 7 of 13 cases (54%), and 2 patterns of mutations were identified. Replacement of threonine by alanine (T41A) in codon 41 and serine by phenylalanine (S45F) in codon 45 was detected in 6 and 1 cases, respectively (Table 1). In 3 of 6 cases with desmoid tumor arising in the abdominal wall, mutation was not detected in exon 3 (wild type), 2 had codon 41 mutation (T41A) and one had codon 45 mutation (S45F). There was no significant difference ($p=0.91$) in tumor site between wild type and mutation group. There were no significant differences either in gender ($p=1$), age ($p=0.97$), or tumor size ($p=0.76$) between the groups.

Outcome of surgical treatment and mutational status

All thirteen patients underwent simple excision of desmoid tumors. Soft tissue reconstruction after resection was required in 2 of 10 cases. Both cases had abdominal wall desmoid tumors, and a small portion of an iliotibial band was used to patch a rectus sheath defect. No patients had surgery-related complications. Histological examination of excised specimens revealed the surgical margin to be microscopic positive in all thirteen cases. Only one of thirteen cases (8%) experienced recurrence 16 months after surgery, and this case had S45F mutation (Figure 1). Twelve cases with no recurrence had T41A mutation or wild type (Figure 2). There was a trend ($p=0.077$) of recurrence in patients with S45F mutation.

Discussion

The present study demonstrated the feasibility of simple resection in a cohort of truncal desmoid tumors prospectively treated with meloxicam. Intriguingly, although tumor sites of the present cohort were limited in trunk region (abdominal wall, chest wall and neck), 12 tumors with wild type and T41A mutation did not recur with microscopic positive margins. Several recent studies investigated the relationship of CTNNB1 mutational status and clinical outcome of surgery [19,10,20,21,11,12]. Lazar et al revealed with a single institution based study that desmoid tumors with S45F mutation had worse recurrence-free survival after surgical treatment [11]. Subsequently, Colombo et al reported their multicenter retrospective study [10] including Lazar's study cohort. Results of their study based on 179 cases with surgical treatment indicated that tumors with S45F mutation had a significantly higher recurrence rate compared with those with other mutations or wild type. However, of 166 patients with evaluable margin status, 98 (59%) had R0 resection and 68 (41%) had R1 resection, indicating the margin status was not identical in their cohort, making it difficult to draw any definitive conclusions regarding the relationship between recurrence and

mutational status and/or margin status. Contrary to the results of these studies, Mullen et al reported a slightly worse 5-year recurrence-free survival for patients with CTNNB1 mutated tumors (58%) than for those with wild type tumors in 115 cases treated with curative-intent surgical resection [12]. In their study, radiation therapy was delivered in an adjuvant fashion at the decision of the surgeon and radiation oncologist when a higher risk for recurrence was predicted on clinical grounds, which may have masked the correlation of CTNNB1 mutational status with local recurrence. Domont et al demonstrated a significant correlation ($p=0.02$) between higher risk of recurrence and CTNNB1 mutated tumors, but did not find any significant differences among mutation types. Interestingly, focusing on patients with R0 (microscopic negative margins) resection analyzed, the recurrence rate was significantly higher ($p=0.02$) in patients with mutated tumors than wild type tumors [20]. Considering that R0 resection seems to be more associated with functional impairment in patients with desmoid tumors, the significance of a specific genotype including wild type in patients with R1 (microscopic positive margins) resection should be investigated. The present study could suggest the possible favorable prognostic value of wild-type and T41A mutation in patients with R1 resection.

There are some limitations in this study. Although of prospectively treated patients with identical cohort (microscopic positive margins and no radiotherapy), only a small number of cases could be enrolled in this study. Desmoid tumors arising in the extremities were not included in the present study. Given that a previous study indicated a significantly higher incidence of the S45F mutation of desmoid tumors in the extremities ($p=0.005$) among extra-abdominal sites [22], simple microscopic positive resection could not be applied for most patients with extremity desmoid tumors.

In conclusion, we reported a successful case series of simple resection, even with microscopic positive margins, to reduce the functional impairment in patients with truncal desmoid tumors with wild type or T41A mutated tumors. Accumulating larger numbers of patients will help to clarify the significance of the results of the present study more precisely with prospectively treated cohorts.

Compliance of ethical standard

The authors declare that they have no conflict of interest.

Informed consent for simple resection and anonymized use of the samples for research was obtained from all patients in this cohort. The study protocol including analyzing mutational status of CTNNB1 was approved by the institutional review board of our institution.

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Conflict of interest

The authors declare that they have no conflict of interest.

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Figure legends

Figure 1. Nineteen year-old female with a desmoid tumor arising in abdominal wall. T2-weighted axial image (a) of magnetic resonance indicated desmoid tumor (arrows). CTNNB1 genotyping showed this tumor was to be S45F mutation of exon 3 (b). Sagittal surface (c) and axial surface of resected tumor were subjected to histological examination. Surgical margin was microscopic positive (R1). Sixteen months after R1 resection, Recurrence of desmoid tumor (arrow heads) was confirmed with T2-weighted axial image (d).

Figure 2. Thirty year-old female with a desmoid tumor arising in the right abdominal wall. T2-weighted axial image (a) of magnetic resonance indicated desmoid tumor (arrows). CTNNB1 genotyping showed this tumor was to be wild type of exon 3 (b). Tumor with simple resection (c) and a sagittal surface (d) and axial surface of resected tumor were subjected to histological examination. Surgical margin was microscopic positive (R1).

Table 1. Demographic data of 13 patients prospectively treated with simple resection

Age	Gender	Tumor site	Tumor size	F/U duration	Antecedent treatment	Rec	Mutation
30	F	Abd.	18	63 Mo.	Meloxicam	−	WT
19	F	Abd.	13	54	Meloxicam	+	S45F
25	F	Back	5.0	48	No	−	T41A
45	M	Back	5.0	38	No	−	T41A
29	F	Neck	7.1	38	Meloxicam	−	WT
39	F	Abd.	8.4	45	Meloxicam	−	WT
70	F	Neck	8.7	26	Meloxicam, Chemo	−	T41A
36	F	Neck	4.5	26	No	−	WT
39	F	Back	17	14	Meloxicam, Chemo	−	T41A
35	F	Abd.	14	13	Meloxicam	−	T41A
40	F	Abd.	12	10	Meloxicam	−	WT
62	M	C.W.	12	9	Meloxicam	−	WT
36	F	Abd.	4.5	6	No	−	T41A

F; female, M; male, Abd; abdominal wall, C.W.; chest wall, F/U; follow up, Mo.; months, Chemo; MTX (methotrexate) + VBL (vinblastine), Rec; recurrence, WT; wild type

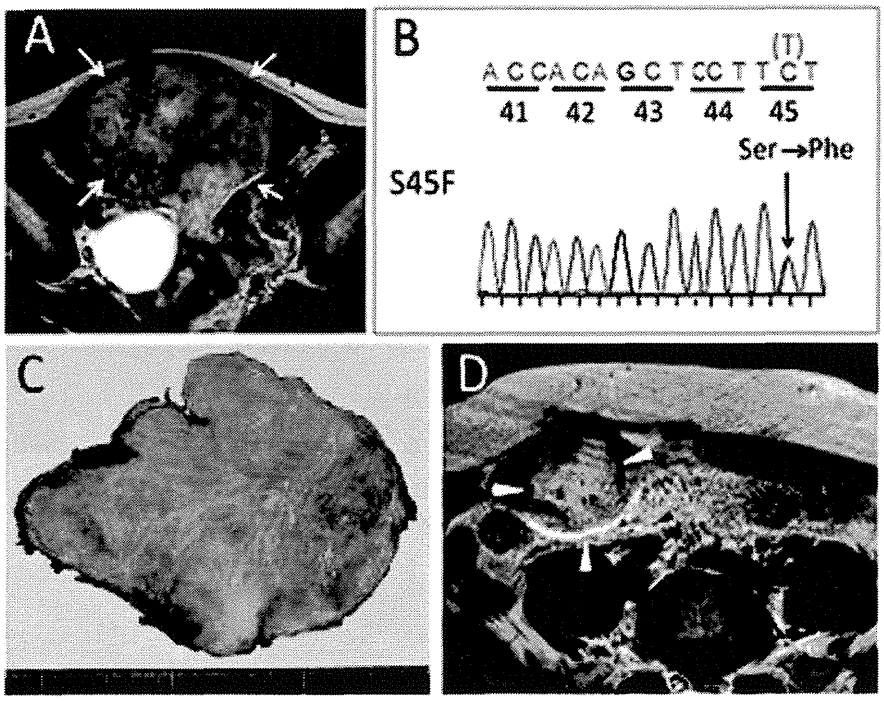

Figure 1.

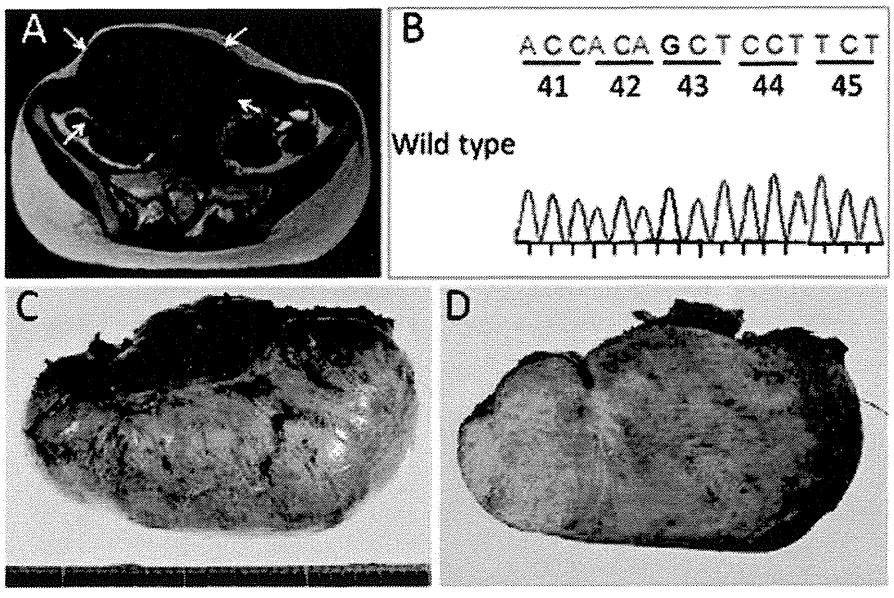

Figure 2.

6 デスモイド
desmoid

デスモイドに対する薬物療法・補助療法

1. デスモイドに対する各種治療法の位置づけ

●デスモイドは，線維芽細胞の増殖を特徴とする，局所浸潤性は強いが遠隔転移を起こさない腫瘍で WHO 分類において intermediate に分類される．断端陰性の適切な切除を実施しても術後再発がたかいため，手術を治療の中心とするのか否かは現在意見の分かれるところである．

●① 初回治療として，wait & see（経過観察），各種薬物治療，手術治療，放射線治療の中からどれを選択するのか，② 難治例（手術後の再発例，切除困難例）に対してどの治療法を選択するのか，で対応が異なる．

●最近は，wait & see や非細胞毒性薬剤を使用した治療を初回治療として選択する施設が増えている．初回治療に抵抗性の症例に対して，抗がん剤，放射線治療，将来的には分子標的治療薬の使用を考慮することになろう（図 6-1）．

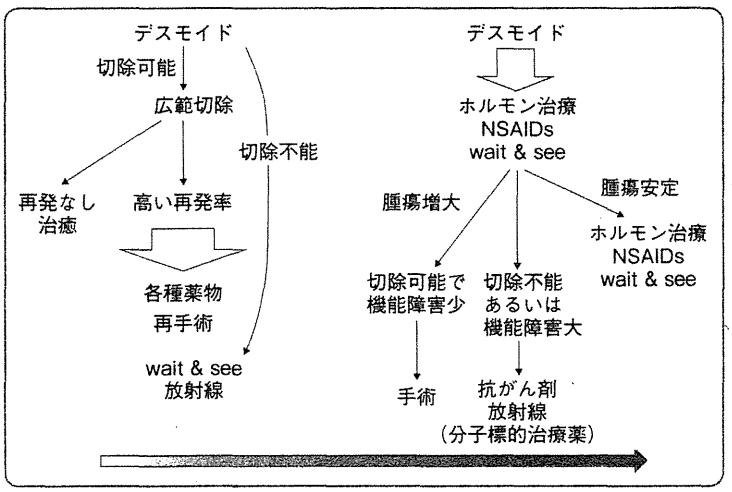

図 6-1 デスモイド治療の変遷

●デスモイドはまれな腫瘍，いわゆる orphan disease であるため，各種薬物治療は保険適用となっていない．各種薬物の使用には保険適用のハードルがある．

2. 各種薬物治療（表6-1）

a) ホルモン治療

●女性患者で女性ホルモン分泌期にデスモイド腫瘍が増大することの経験やデスモイド腫瘍にエストロゲン受容体が発現しているとの報告から抗エストロゲン治療が実施されている．最も多く使用されてきたのはタモキシフェン（tamoxifen；TAM）であるが，多くが症例報告であり，確実な結論には至っていない．

●トレミフェン（toremifene）を単剤 200 mg/day で使用した 20 例の報告がある[1]．初回治療として実施した 12 例中 1 例が CR，5 例が PR，5 例が SD を示し，20 例全体では CR 1 例，10 例 PR，6 例 SD であった．最近は後述する非ステロイド抗炎症薬（NSAIDs）との併用療法に関する報告が多い．

表6-1 デスモイドに対する有効性が報告されている主な薬剤

ホルモン療法	タモキシフェン トレミフェン プロゲステロン
NSAIDs	インドメタシン スリンダク メロキシカム セレコキシブ
抗がん剤	MTX＋VBL MTX＋VNR ADR＋DTIC VAC
分子標的治療薬	イマチニブ ソラフェニブ スニチニブ

NSAIDs：non-steroidal anti-inflammatory drugs, MTX：methotrexate, VBL：vinblastine, VNR：vinorelbine, ADR：doxorubicin, DTIC：dacarvazine, VAC：vincristine＋actinomycin-D＋cyclophosphamide

b) NSAIDs

●デスモイドに対するインドメタシン（indometacin）の著効例に関する報告や動物実験でのインドメタシンの示す抗腫瘍効果から，インドメタシン，スリンダク（sulindac）の使用例が報告されている．

●家族性大腸腺腫症（FAP）に合併するデスモイド 14 例に対するスリンダク 300 mg/day の使用成績は，CR 1 例，PR 7 例，SD 4 例であった[2]．

●TAM とスリンダクを併用した報告がある．25 例に対して TAM 120 mg/day とスリンダク 300 mg/day を使用し，FAP 関連発症デスモイドに対する初回治療として実施した 13 例中 10 例が PR または CR を示し，再発例に対して使用するよりも良好な成績であったと報告している[3]．

●本併用治療を 19 歳未満の小児 59 例に使用した報告では奏効率が 8 %（CR 1 例，PR 4 例），2 年の progression-free survival（PFS）が 36 % であり，小児への有効性は低いと思われる[4]．

●最近は COX-2 阻害薬の有効性も報告されている．メロキシカム（meloxicam）10 mg/day 単独使用での有効性を筆者らが報告している．当初 20 例の報告では，1 例が CR，7 例

が PR，11 例が SD，1 例が PD であった[5]．最近の 33 例の報告では 1 例が CR，7 例が PR，12 例が SD，13 例が PD であった[6]．副作用が少なく，忍容性の高い治療法といえる．

c) 抗がん剤治療

メトトレキサート（methotrexate；MTX）＋ビンブラスチン（vinblastine；VBL）治療とアントラサイクリン系抗がん剤を含めた治療に分けられる．

●**MTX＋VBL**：手術困難な 30 例に MTX（30 mg/m^2），VBL（6 mg/m^2）を 7～10 日に 1 回投与し，28 人に grade 3 の白血球減少，grade 1 の脱毛が 6 人（20 %）にみられた．12 人が PR，18 人が SD，5 年の PFS が 67 %であった[7]．

再発あるいは手術・放射線治療に適さない 28 人の小児例に対して MTX（30 mg/m^2）＋VBL（5 mg/m^2）を初めの 26 週は毎週，後半の 26 週は 2 週に 1 回投与した試験では，26 人が評価可能であり，best response として，CR 1 人，PR 4 人，MR（minor response）3 人，SD 10 人，PD 8 人であり[8]，成人例と比較すると有効性が低いと考えられる．

イタリアからの 21 歳以下のデスモイド患者 94 例の報告では MTX＋VBL 治療を実施した 19 人中 11 人で有効性が認められている[9]．

●**アントラサイクリン系を含めた抗がん剤治療**：ドキソルビシン（doxorubicin；ADR）＋ダカルバジン（dacarbazine；DTIC）の併用療法の有効性が報告されている．12 人の患者（年齢中央値が 29 歳）に対して ADR（60～90 mg/m^2）＋DTIC（750～1,000 mg/m^2）を投与し，効果判定可能であった 9 人中，2 人が CR，4 人 PR，1 人 MR，2 人 SD を示した[10]．

また FAP 患者に発生したデスモイド 7 例に 4～5 cycle の ADR 80 mg/m^2，DTIC 600 mg/m^2 投与し，効果判定では 3 人が CR，4 人が PR と非常に良好な結果が報告されている[11]．

62 例の再発あるいは切除不能例に対する各種薬物治療の効果を比較した研究では，アントラサイクリン系抗がん剤を含んだ治療の奏効率（54 %）が他治療（12 %）と比較して有意に良好であり（p＝0.0011），また PFS 中央値は 40.8 ヵ月であったと報告している．

Memorial Sloan Kettering Cancer Center からの NSAIDs を除いた薬物治療成績の報告がある．68 人について検討し，アントラサイクリン系抗がん剤の有効性を報告している[12]．

d) 分子標的治療薬

イマチニブ（imatinib，商品名グリベック®），ソラフェニブ（sorafenib，商品名ネクサバール®），スニチニブ（sunitinib，商品名スーテント®）の報告がある．

●**イマチニブ**：切除不能 40 例に対する第 II 相試験で，イマチニブを 400 mg/day で 1 年間投与，平均年齢 41 歳，経過観察期間中央値が 34 ヵ月において，評価可能 35 例中，CR 1 人，PR 3 人，PFS は 3 ヵ月で 91 %，6 ヵ月で 80 %，12 ヵ月で 67 %，2 年で 55 %，

grade 3 の副作用として発疹，腹痛，嘔気・嘔吐，下痢，筋痛が報告されている[13]．

19 人の患者に対する第Ⅱ相試験でイマチニブを 800 mg/day 投与し，3 人（15.7 %）が PR，4 人が SD，1-year control rate が 36.8 %（7/19 人）であったと報告している[14]．

切除不能あるいは手術を実施すると機能障害が予想される 10 歳以上の 51 例に対してイマチニブの投与量を体表面積に合わせて 600 mg/day，400 mg/day，200 mg/day とした試験では，PFS は 2 ヵ月で 94 %，4 ヵ月で 88 %，1 年で 66 %，客観的奏効率は 6 %（3/51 人）であった[15]．

●**ソラフェニブ**：26 人が対象，年齢の中央値が 31 歳であり，中央値 6 ヵ月の投与で，評価可能 24 例中，best response の評価で PR 6 例，SD 17 例であった．イマチニブと比較して，臨床症状の改善がみられたことが特徴的であった．副作用として手足症候群，皮疹，高血圧，軽度の脱毛，下痢がみられた[16]．

●**スニチニブ**：多施設前向き第Ⅱ相試験で，進行デスモイド 19 例に対して 37.5 mg/day のスニチニブを投与．年齢の中央値は 30 歳，FAP 関連デスモイドが 10 例．効果は PR 5 人（26.3 %），SD 8 人（42.1 %）であり，overall response rate は 26.3 %，2 年の PFS は 74.7 %であった．有害事象としては好中球減少，下痢，手足症候群があった[17]．

3. 放射線治療

●放射線治療は初回治療として単独で実施，手術と併用して実施，再発例に対して実施，など多様な場面で使用できる．しかし，デスモイドが良性であること，少なからず合併症が生ずることから，特に日本では放射線治療は慎重に検討してから使用される．

●手術単独，手術＋放射線治療，放射線治療単独の 3 群の治療成績を比較すると，手術単独と比較して，放射線単独，手術＋放射線はいずれも無局所再発率が有意に低かった[18]．

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