New Therapeutic Strategies for Soft Tissue Sarcomas

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Opinion statement

The treatment of patients with metastatic soft tissue sarcomas (STS) is complex. There are limited agents available and many are associated with significant toxicity. When evaluating a patient with metastatic disease, physicians should ask themselves whether there is a role for surgery to render the patient free of disease. Combination chemotherapy in patients who have not received chemotherapy in the adjuvant setting is one option, particularly in a young patient with a good performance status. Sequential single-agent therapy for patients who are more elderly or debilitated by their disease may be more appropriate. Gemcitabine appears to be an agent with activity, particularly in patients with leiomyosarcomas. The data regarding prolonged gemcitabine infusions suggest improved activity that was predicted based on prolonged intracellular gemcitabine levels. Because of these data, the prolonged infusion schedule should be used. In addition, because of the paucity of effective agents, consideration of clinical trial participation for patients with newly diagnosed metastatic disease is appropriate, particularly in chemotherapy-insensitive histologies. The role of the newer agents (*eg*, ecteinascidin-743, epothilones, and mammalian target of rapamycin) is undefined. Ecteinascidin-743 has been the most extensively tested agent, and its ability to slow growth kinetics of a tumor and stabilize it clinically is intriguing. Data regarding the response to BMS-247550 will be published shortly and will help define the further role of epothilones in this disease. There is a preclinical rationale that makes the mammalian target of rapamycin inhibitors attractive for the treatment of muscle-derived neoplasms. In addition, there are cell-line data suggesting activity in rhabdomyosarcoma. These agents are being tested in adult STS and will likely be tested in pediatric histologies when there are more safety data available in that population. SU11248 will continue to be tested in patients refractory to imatinib mesylate and may well prove to be another active agent for patients with gastrointestinal stromal tumors. As depicted by the analysis of gemcitabine efficacy, agents with activity in a subgroup of STS may be overlooked by the "come one come all" approach to clinical trials in STS. Identifying key targets in specific STS will be helpful in the testing of newer molecularly targeted agents. Biologic differences will support histology-specific trials to better understand the activity of an agent in a specific disease site or specifically target a biologic pathway with relevance to the malignant potential of the disease. For future clinical trials in STS to achieve the goal of histology-specific trials, cooperative group and multi-institutional trials will be required to obtain the appropriate patients with these rare histologies. It will also be increasingly important to be committed to obtaining tumor tissue in these patients to validate hypotheses regarding tumor biology and the effectiveness of therapeutic agents.

Introduction

Soft tissue sarcomas (STS) are an uncommon and challenging set of diseases. They are histologically and biologically heterogeneous. Primary therapy of these tumors involves surgical resection often in conjunction with radiation therapy. Chemotherapy has been primarily relegated to the metastatic disease setting. Standard therapy with doxorubicin, ifosfamide, and dacarbazine alone or in combination has reported response rates up to 35% [1]. Recent trials evaluating novel combination therapies incorporating gemcitabine have demonstrated impressive results. In addition, novel targeted therapies are being tested in metastatic disease. This article reviews data on the role of gemcitabine alone and in combination with other agents, in addition to new therapeutic agents under investigation in STS (*eg*, ecteinascidin-743 [ET-743], PS-341, epothilones, and CCI-779). Preliminary results of the multitargeted tyrosine kinase inhibitor SU11248 in patients with imatinib mesylate refractory gastrointestinal stromal tumors (GIST) are presented. Novel immunologic approaches for STS are also discussed.

Treatment

The role of gemcitabine in soft tissue sarcoma

Gemcitabine as a single agent in soft tissue sarcoma

- Gemcitabine hydrochloride is a pyrimidine nucleoside analogue that inhibits DNA replication and synthesis. It is a prodrug that requires intracellular phosphorylation to derive di- and triphosphate compounds. These inhibit ribonucleotide reductase and terminate DNA synthesis when the triphosphorylated compound is incorporated into DNA [2,3]. Phase II clinical trials have evaluated the efficacy of gemcitabine in STS in first- and second-line metastatic disease (Table 1). The low overall response rate for these trials, which treated a spectrum of STS, ranges from 3.3% to 18% [4•,5•]. If clinicians evaluate the response in distinct histologies, there are interesting trends to be noted (Table 2). As expected, leiomyosarcoma and liposarcomas were well represented in the patient populations of these studies. There appears to be activity in leiomyosarcomas, although not in gastrointestinal leiomyosarcomas, and there was no activity in liposarcomas. In a small population of angiosarcomas, malignant fibrous histiocytomas (MFHs), and spindle cell sarcomas, response rates greater than 10% were noted, although the number of patients treated with each histology was limited. It should be underscored that the trials with the highest reported response rates for gemcitabine were heavily weighted toward leiomyosarcoma in contrast to trials with the lowest response rates, and most of the responses noted were in uterine leiomyosarcoma [5•,6].

Combination therapy with gemcitabine in soft tissue sarcoma

- The activity of gemcitabine in leiomyosarcoma has been further supported by the phase II trial reported by Hensley *et al.* [7•], which combined gemcitabine with docetaxel in patients with uterine or nonuterine leiomyosarcoma. Thirty-four patients were enrolled (85% of patients had uterine primaries). The combination was selected because of the novel mechanisms of action of these agents compared to standard sarcoma therapeutics. Patients received gemcitabine 900 mg/m^2 on days 1 and 8 and docetaxel 100 mg/m^2 on day 8. Patients with prior pelvic radiation were treated with a 25% dose reduction of both agents. All of the patients received granulocyte colony-stimulating factor on days 9 to 15. In addition, to prolong the exposure of intracellular phosphorylated gemcitabine metabolites, the rate of infusion of the gemcitabine was increased from 30 minutes to 90 minutes. Thirty-four patients with metastatic disease were treated (14 patients had prior radiation therapy and 16 had progressed after doxorubicin-based chemotherapy). The response rate in this

Table 1. Synopsis of single-agent gemcitabine trials in soft tissue sarcoma

Study	Dose	Patients, *n*	Prior RX	RR, %
Merimsky *et al.* [61]	1 g/m^2	51	Doxorubicin/ifosfamide	5.5
Patel *et al.* [5•]	1 g/m^2	56	Doxorubicin/ifosfamide	18
Okuno *et al.* [62]	1.25 g/m^2	25	None	4
Okuno *et al.* [63]	1.25 g/m^2	25	One prior	3
Spath-Schwalbe *et al.* [6]	200–250 mg/m^2	18	One prior: doxorubicin and ifosfamide	11
Svancarova *et al.* [4•]	1.25 g/m^2	32	One prior	3.23

RR—response rate; RX—therapy.

Table 2. Response by histology to single-agent gemcitabine

Histology	Patients, *n*	Responses, *n*	RR, %
Angiosarcoma	6	2	33
ASPS	1	0	0
Chondrosarcoma	5	0	0
Ewing's sarcoma	1	0	0
Fibrosarcoma	2	0	0
Giant cell	1	0	0
Hemangiosarcoma	1	0	0
GI leiomyosarcoma	25	0	0
Leiomyosarcoma	54	9	14.8
Liposarcoma	14	0	0
MFH	16	2	12.5
MPNST	2	0	0
Osteosarcoma	9	0	0
Spindle cell	5	1	20
Synovial	8	0	0
Other	26	1	3.8

ASPS—alveolar soft part sarcoma; GI—gastrointestinal; MFH—malignant fibrous histiocytomas; MPNST—malignant peripheral nerve sheath tumors; RR—response rate.

single-institution study was 53%, with a median time to progression of 5.6 months. Three of 15 responses were complete responses. Leu *et al.* [8•] presented their experience with gemcitabine and docetaxel at the 2003 American Society of Clinical Oncology annual meeting. There single-institution retrospective analysis involved patients treated with gemcitabine 675 mg/m^2 on days 1 and 8 and docetaxel 100 mg/m^2 on day 8, with granulocyte colony-stimulating factor support and a prolonged gemcitabine infusion schedule. This combination demonstrated activity in a variety of histologies, including leiomyosarcoma. Complete responses or partial responses (PRs) were noted in leiomyosarcoma (seven of 12 patients), angiosarcoma (three of four patients), osteogenic sarcoma (two of four patients), Ewing's/primitive neuroectodermal tumor (one of two patients), malignant peripheral nerve sheath tumors (one of two patients), and MFH (one of three patients) for an overall response rate of 43%.

• A recent phase I trial evaluated the combination of gemcitabine with dacarbazine [9]. In this trial, gemcitabine was delivered at doses ranging from 800 to 2160 mg/m^2, with a constant rate of infusion of 10 mg/min. The dacarbazine was administered at 500 mg/m^2 to all of the patients. Twenty-one patients were treated with the dose-limiting toxicity being elevated

transaminases at the highest dose level. Five PRs were observed, although two were observed in patients treated above the maximum tolerated dose. In addition, gemcitabine has been evaluated with doxorubicin in this patient population [10]. The recommended dose for phase II studies is doxorubicin 60 mg/m^2 and gemcitabine 800 mg/m^2 by prolonged infusion. Twelve patients were treated in the phase I study, with two responses in nine evaluable patients, which included one PR in a patient with uterine leiomyosarcoma and one PR in a patient with MFH.

• How do you account for the differences observed in the response rates in the combination trials compared to single-agent gemcitabine? The combination studies have been conducted at single institutions. In addition, the trial involving gemcitabine with docetaxel enrolled only patients with leiomyosarcoma, particularly uterine leiomyosarcoma, sensitive histologies based on single-agent gemcitabine trials. Another hypothesis is that the prolonged infusion of gemcitabine may enhance the cytotoxic effects of the compound. Of the five single-agent trials, all infused gemcitabine over 30 minutes, with the exception of the trial conducted by Spath-Schwalbe *et al.* [6]. In the study by Spath-Schwalbe *et al.* [6], a relatively low dose of gemcitabine (200–250 mg/m^2) was infused over 3 hours weekly for 3 weeks and repeated every 4 weeks. Although this study used a relatively low dose of gemcitabine, the response rate in this study was one of the highest, and these responses were seen in patients with uterine leiomyosarcoma. Alternatively, the combination of gemcitabine and docetaxel may be synergistic and there are preclinical data to suggest that the sequence of administration is important [8•]. To further assess the impact on the addition of docetaxel to prolonged infusion gemcitabine, the North American Sarcoma Study Group is conducting a randomized phase III trial comparing gemcitabine alone with gemcitabine with docetaxel. The results of this large multicenter trial will be of interest because there are limited data suggesting activity of taxanes in leiomyosarcomas and other STS histologies [11•,12,13•,14].

Novel agents in the therapy of soft tissue sarcoma

Ecteinascidin-743

• Ecteinascidin-743 is a novel chemotherapeutic agent identified from a screen of marine organisms (Table 3). This agent, derived from a Caribbean tunicate *Ecteinascidia turbinata,* is a tetrahydroisoquinolone alkaloid that binds the minor groove of DNA and blocks cell cycle progression and the organization and assembly of the microtubular cytoskeleton [15,16]. Preclinical data have shown in vitro activity of ET-743 in multiple STS cell lines, leading to cell cycle arrest without the induction of P-glycoprotein or Bcl-2 family proteins [17•]. Further preclinical work has suggested a decreased rate of cell cycle progression and a decrease in the induction of alkaline phosphatase in osteogenic sarcoma cell lines, induction of apoptosis in Ewing's sarcoma cell lines, and possible synergy with other active agents, such as doxorubicin and cisplatin [18].

• Phase I trials have evaluated a variety of schedules. Lengthening infusion times has allowed for an increase in dose delivery with decreased hematologic toxicity [19]. A phase I trial using a 24-hour infusion schedule revealed activity in liposarcoma and osteosarcoma [20]. The recommended dose from this phase I trial was 1500 mg/m^2. The expanded experience from the phase I trial and compassionate-use program in STS has also been reported [21•]. In 25 patients with STS, there were two PRs observed, with an additional two PRs in three patients with osteosarcoma who were treated. Median duration of response was 10.5 months, with a median duration of disease stabilization

Table 3. Novel agents with their targets and phase of testing

Agent	Target	Phase of testing
ET-743	Minor groove of DNA	Phase II
PS-341	Proteosome inhibitor	Phase II
Epothilones	Microtubule stabilizer	Phase II
CCI-779	mTOR inhibitor	Phase II
RAD 001	mTOR inhibitor	Phase I
SU11248	Multityrosine kinase inhibitor	Phase I

ET-743—ecteinascidin-743; mTOR—mammalian target of rapamycin.

of 5.2 months. In both trials, patients were refractory to anthracyclines, which is a standard first-line therapy for STS in the adjuvant and metastatic disease setting. A phase I trial using a schedule of five times daily has been reported [22]. The maximum tolerated dose for this schedule was 325 mg/m^2. There were five patients with STS enrolled in this study and a single patient with uterine leiomyosarcoma had a greater than 25% decrease in tumor volume. A phase I trial studied a 72-hour continuous infusion repeated every 21 days. This study enrolled four patients with leiomyosarcoma and two patients with GIST, none of whom responded. The recommended phase II dose in this study was 1050 mg/m^2. In all of the schedules examined, including a 24-hour infusion, the most common toxicities were neutropenia, thrombocytopenia, and liver function abnormalities.

• Phase II studies have evaluated patients with metastatic disease who are chemotherapy naïve and previously treated. For chemotherapy-naïve patients, objective response rates were noted in 14% of patients, with an additional 14% of patients with stable disease [23]. Two phase II trials of ET-743 enrolled patients who were previously treated with single-agent doxorubicin or ifosfamide or a combination therapy [23,24]. In the French study, patients generally had more extensive pretreatment [24]. In these two studies, objective responses were noted in 8% and 6% of patients, respectively, with an additional 35% and 50% of patients, respectively, achieving stable disease for longer than 2 months. Although response rates have been low in these early trials, patients have had significant progression-free survival rates. The 12-month progression-free survival rate for chemotherapy-naïve patients was 18% and 11%, respectively, in pretreated patients, with 12-month overall survival of 49% and 55%, respectively [23]. These results may be because of a change in growth kinetics from tumors in patients receiving ET-743 [25]. A recently completed phase II study found no clinical activity in patients with GIST, with only two of 20 patients having stable disease for 4 and 10 months [26•]. Based on the activity seen in phase I and II trials, an ongoing phase II randomized trial is comparing the 24-hour infusion schedule to a 3-hour weekly infusion 3 of every 4 weeks in patients with metastatic leiomyosarcoma and liposarcoma who have progressed after doxorubicin and ifosfamide chemotherapy.

• Pharmacokinetic studies have suggested some notable findings. Patients with elevated alkaline phosphatase levels but not elevated serum hepatic enzymes have had statistically higher area under the curve (AUC) [27]. Additionally, patients with retroperitoneal primary tumors had significantly higher AUC compared to patients with tumors arising at other primary sites. In contrast, these studies revealed significantly lower AUC in patients with GISTs and in patients with no evidence of response to ET-743 [26•,27]. The relevance of the differences in AUC in terms of response is intriguing, but it is unclear if dose escalation would be feasible and lead to

increased responses. Severe toxicities were more frequent in patients with abnormal liver function tests at baseline or patients with liver metastases. The addition of dexamethasone has mitigated some of the hepatic toxicity and is associated with a decrease in the drug AUC.

- In addition, preclinical data have shown that the sequencing of combination therapy is important in STS cell lines. Using fibrosarcoma and liposarcoma cell lines, ET-743 before doxorubicin was found to be more effective compared to concurrent exposure. However, the converse was true using paclitaxel with ET-743 [28]. Ongoing phase I clinical trials are testing the combination of ET-743 as a 3-hour infusion with doxorubicin hydrochloride liposome and docetaxel. Testing of doxorubicin hydrochloride liposome and ET-743 in metastatic sarcoma is under development.

PS-341

- PS-341, recently approved for the treatment of multiple myeloma, is undergoing phase II testing in STS. This agent is a proteosome inhibitor. In the normal cell, proteins are targeted for degradation when they are ubiquinated. An important controller of cell cycle regulators and antiapoptotic factors is nuclear factor-kappaB (NF-kB). Under stress and cell growth conditions, the normal inhibitor of NF-kB (IkB) is ubiquinated and degraded. This allows the transcription of genes regulating cell cycle, antiapoptosis, cytokines, and cell adhesion molecules. The inhibition of the proteosome prevents the loss of IkB inhibition of NF-kB [29].

- A phase II trial in previously untreated patients with recurrent or metastatic sarcoma evaluates response in STS and in the pediatric histologies of osteogenic sarcoma, rhabdomyosarcoma, and Ewing's sarcoma [30]. Patients receive 1.5 mg/m^2 intravenously twice weekly for 2 weeks with a 1-week rest period. Seventeen patients are evaluable for response, with four patients with STS and one pediatric histology patient achieving stable disease. No objective responses have been shown; however, the study has not met its accrual goals. This agent has in vitro evidence of synergy with radiation and some chemotherapeutic agents that may warrant further evaluation in this patient population [31–33].

Epothilones

- Epothilones are a novel type of tubulin polymerizing agent, preventing normal mitosis. They have similar sites of binding as the taxanes, although in vitro have superior cytotoxicity and activity in multidrug-resistant cell lines and taxane-resistant cell lines [34–37]. Taxanes have been reported to have marginal activity in STS [12,13•,14,38], thus an agent with activity in multidrug-resistant and taxanes-resistant cell lines is of interest in this disease setting. Phase I testing has demonstrated tolerability of BMS-247550 and EPO906, although too few patients with sarcoma were treated to have a sense of its activity in this disease setting [39,40]. A phase II trial of BMS-247550 in STS has been conducted using 50 mg/m^2 intravenous 3-hour infusion every 21 days. The initial report on toxicity of the agent revealed the most common toxicity was neutropenia and leukopenia, with one death secondary to sepsis [41]. Efficacy data are not available at this time.

Role of mammalian target of rapamycin inhibitors

- The mammalian target of rapamycin (mTOR) is a member of the phosphati-dylinositol kinase-related kinase family, in which a lipid kinase homology domain functions as a serine/threonine kinase to regulate protein translation, cell cycle progression, and cellular proliferation [42,43]. Growth factor receptors mediate signals that affect protein translation through mTOR and its upstream partners protein kinase, phosphoinositide-3 kinase, and phospholipase C gamma. Akt, which interacts with mTOR, has been shown to be an important regulator of muscle hypertrophy [44,45]. The role of mTOR in malignancy has not been characterized, although it is an intriguing target in STS because of its role in muscle hypertrophy. Platelet-derived growth factor receptor (PDGFR), an upstream regulator of Akt, has also been shown to be present in STS, although it is unclear if its expression plays a role in the malignant phenotype of these tumors [46].

- CCI-779 is a derivative of rapamycin, an immunosuppressive agent. Both agents lead to G1 arrest in tumor cells in vitro through inhibition of mTOR. Inhibition of mTOR leads to inactivation of protein synthesis through inactivation of *p70* S6 kinase and dephosphorylation of 4E-BP1, which allows for binding of eIF4Ee and inhibition of protein translation. PTEN, a tumor suppressor gene, is a phospholipid phosphatase and it negatively regulates Akt. Therefore, when it is deleted or mutated, there is an upregulation of Akt and signaling through mTOR. Loss of the tumor suppressor PTEN, leads to upregulation of phosphoinositide-3 kinase and Akt and enhanced sensitivity to the mTOR inhibitor CCI-779 in some tumor types [47–49]. Preclinical data have shown that exposure of murine embryo fibroblasts and rhabdomyosarcoma cell lines to rapamycin leads to apoptosis that is not observed if wild type *p53* is present [50,51]. Mutations in *p53* are common in STS [52]. Phase I trials of the agent have evaluated 30-minute infusions weekly and daily 5 days every other week [53]. The toxicities noted were dermatologic, myelosuppression, hepatic, and asymptomatic hypocalcemia. Minor responses were noted in previously treated patients with STS. The drug is also available in an oral formulation. A phase II trial in STS sarcoma is under development (Personal communication, S. Okuno, Mayo Clinic, Rochester, MN). Other mTOR inhibitors are in clinical development, including RAD 001.

SU11248

- SU11248 is a multitargeted tyrosine kinase inhibitor that is being tested in patients with GISTs who are refractory to or intolerant of imatinib mesylate. This drug was developed to have enhanced solubility and decreased protein binding compared to vascular endothelial growth factor receptor inhibitor SU5416 and the PDGFRb inhibitor SU6668 [54•]. This agent has been shown to have in vitro activity against KIT, PDGFR, vascular endothelial growth factor receptor, and FTL3, thus potentially having antitumor and antiangiogenic effects [55]. It inhibits fetal liver kinase-1, although not as potently as other receptor tyrosine kinases.

- Patients who have failed imatinib mesylate have been shown to have new mutations in KIT or the development of alternate signaling through PDGFR [56]. Therefore, the inhibition of multiple pathways affecting the malignant driving force of GISTs and angiogenesis may result in clinical efficacy. Demetri *et al.* [57•] are conducting a phase I trial of SU11248, testing daily dosing for 2 to 4 weeks with 1 to 2 weeks rest. Forty-two patients with refractory disease have been treated, two of whom never had a response to

imatinib mesylate. An additional three patients who were intolerant to imatinib mesylate have also been treated. Positron emission tomography scanning has been used as an early indicator of clinical efficacy, with 72% of patients evaluated demonstrating a decrease in tumor 18F-fluorodeoxy-glucose-avidity. Responses have been slow to evolve, with only two patients having confirmed responses. However, an additional 10 patients have had stable disease for longer than 6 months. Severe side effects have been primarily gastrointestinal, including diarrhea, nausea, vomiting, and abdominal pain. Other grade 3 to 4 toxicities noted are fatigue, asymptomatic increase in lipase, and headache. The recommended dose for further studies in this patient population is 50 mg for 14 days, followed by 7 days of rest.

Novel immunologic strategies

- Approaches to target the destruction of cancer cells by stimulating an immune response are being evaluated in a variety of disease types. In STS, there has been less activity because of fewer identified tumor-related antigens. NY-ESO-1, a germ cell protein, not found in normal somatic proteins has been demonstrated in some STS and may elicit an antibody and T-cell response in nonimmunized patients [58]. There is an ongoing phase I trial evaluating a peptide vaccine against this antigen and another antigen called LAGE. Tumor types with unique translocations have novel proteins produced by the translocation. These proteins by definition are considered tumor-associated antigens and are potential targets for vaccines. A phase I trial testing this approach in patients with advanced Ewing's sarcoma and rhabdomyosarcoma isolated circulating dendritic cells and pulsed with peptides from the breakpoints of the EWS/FL1-1 and PAX3/FKHR proteins. Patients received pulsed cells with a continuous infusion of rhIL-2 at 9×10^2 [59]. A minority of patients demonstrated immunologic response with no clinical benefit. This approach may be more beneficial in patients with less extensive disease without prior chemotherapy. This strategy could also be used in myxoid liposarcoma, clear-cell sarcomas, and synovial cell sarcoma because of their translocations. Another approach in vaccine development that has been tested in the phase I setting is the introduction of granulocyte macrophage colony-stimulating factor into sarcoma cells from the tumor of a patient [60]. This study revealed that only a minority of patients produced clinically relevant levels of production of granulocyte macrophage colony-stimulating factor, thus alternate strategies will be required.

Expert opinion

- The management of patients with recurrent STS is challenging because of the broad spectrum of histologies. Gemcitabine may have activity in leiomyosarcomas, particularly leiomyosarcomas originating in the uterus. It is unclear if the addition of other agents in combination with gemcitabine improves the response rate or, more importantly, the survival of patients with STS. ET-743 is an intriguing agent for patients with previously treated STS. It has not demonstrated large numbers of objective responses, but it does seem to lead to prolonged disease stabilization. The possibility of improved responses with combination therapy is being evaluated and may have a role in STS. The activity of the epothilones, mTOR inhibitors, and PS-341 requires further testing and follow-up to know if they will have activity in this disease setting.

- As depicted by the analysis of gemcitabine efficacy, agents with activity in a subgroup of these diseases may be overlooked by the "come one come all" approach to phase II trials in STS. Identifying key targets in specific STS will be helpful in the testing of newer molecularly targeted agents. Biologic differences will support histology-specific trials to better understand the activity of an agent in a specific disease site or specifically target a biologic pathway with relevance to the malignant potential of the disease. The SU11248 phase I trial targeting patients with imatinib mesylate refractory GIST is clearly an example of this type of trial, facilitated by a defined target and patient population. This trial is of great significance because imatinib mesylate has been an important therapy for the palliation of metastatic GIST. It has not been, nor was it anticipated to be, a cure. The activity seen in the phase I study reported will likely lead to further trials and will provide another therapeutic agent for patients who do not respond to or progress with imatinib mesylate. For future clinical trials in STS to achieve the goal of histology-specific trials, cooperative group and multi-institutional trials will be required to obtain the appropriate patients with these rare histologies.

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