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Desmoplastic Small Round Cell Tumors: Prognostic Indicators and Results of Surgical Management

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Background: Desmoplastic small round cell tumors (DSRCT or DSCT) are rare aggressive cancers of adolescence and early adulthood. There are few reported series to guide clinical therapy. This study correlates survival with treatment variables, including aggressive surgical debulking.

Methods: Thirty-two patients with documented DSRCT received treatment at our institution. Demographic, clinical, and treatment variables were correlated with progression-free survival using log-rank statistics.

Results: Thirty patients were male (96%), and two were female (4%), with a median age at diagnosis of 22 years. The primary site of disease in 97% of cases was the abdomen or pelvis. Twenty-nine patients (91%) had extensive disease involving peritoneal surfaces, lymph nodes, or discontinuous organs. All 32 patients received systemic chemotherapy. Fifteen (47%) underwent tumor debulking greater than 90% at diagnosis or during therapy. A complete or very good response to therapy occurred in 13 patients, and depended on surgical removal of bulk disease in all. Thirteen patients remained progression-free, but three of these patients died from treatment toxicity. Improved survival was correlated with a complete or very good partial response to multimodality therapy, surgical debulking of more than 90% either before or after chemotherapy, and use of the P6 protocol.

Conclusions: DSRCT is an aggressive cancer that occurs predominantly in young males. Improved survival is correlated with intense chemotherapy and aggressive resection.

Key Words: Desmoplastic small round cell tumor—Chemotherapy—Resection—Surgery.

Desmoplastic small round cell tumors (DSRCT) are rare but well-characterized tumors that typically occur in adolescent and young males. Microscopically, nests of poorly differentiated small, round cells within a desmoplastic stroma are observed.[1] They have a multidirectional phenotype with epithelial, myogenic, and neural marker expression, but the exact histogenesis is unclear.[2] Recently, a consistent chromosomal translocation, t (11;22)(p13;q12), has been identified in DSRCT. This results in the fusion of the Ewing's sarcoma gene (EWS) with the Wilms tumor gene (WT1).[3–9] This unique DNA sequence, along with specific histologic and electron microscopic features, differentiates DSRCT from other cancers.

Patients usually present with extensive involvement of the serosal lining of the abdominal and pelvic peritoneal cavity. This presentation suggests an origin from serosa, but rare primary extraperitoneal sites also have been reported.[7,10–13] Rapid multifocal growth and metastasis to liver, lungs, and lymph nodes is common.[2,11,14] The reported median survival is 17 months, but long-term survival is uncommon, and there were no survivors in the initial clinicopathologic study.[2,15] Most of the published information on DSRCT consists of case reports.[11,13,15–24] A recent publication from our institution suggested that high-dose multiagent alkylator-based systemic chemotherapy (P6 protocol), aggressive surgical debulking, and radiation therapy improved response rates and progression-free survival.[25]

The present analysis includes all cases of DSRCT

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TABLE 1. *Frequency of clinical symptoms and signs at the time of diagnosis of desmoplastic small round cell tumors (n = 32)*

Presenting sign/symptom	No.	Patients affected (%)
Mass (including umbilical and testicular)	17	57
Pain	9	30
Abdominal distention	8	27
Constipation	6	20
Weight loss	5	17
Diarrhea	3	10
Dysphagia	3	10
Hematemesis	2	7
Jaundice	2	7
Hematuria	1	3

treated at our institution over a 25-year period and correlates progression-free survival with clinical variables, including aggressive surgical debulking.

PATIENTS AND METHODS

This study was a retrospective review, and patient information was obtained from hospital charts, a DSRCT registry, and office notes. During the period from January 1, 1972 to April 1, 1997, 35 consecutive patients with DSRCT who had received the bulk of their treatment at Memorial Sloan-Kettering Cancer Center were identified. All diagnoses were confirmed by histochemical, molecular genetic, and, sometimes, electron microscopic analyses. In three cases, complete treatment and follow-up information was unavailable; these patients were not included in the present report, leaving a total of 32 patients. We obtained patient demographics, clinical presentation, and diagnostic and treatment information on these 32 patients. The median length of follow-up was 1.9 years (range, 0.3 to 5.8 years). Most of the tumors were diffuse, with multiple separate nodules scattered over the peritoneal surfaces. Therefore, standard resection with negative microscopic margins almost never was feasible; rather, we performed surgical debulking, removing as much gross disease as possible. We did omentectomies if there was any evidence of omental involvement. This is similar in concept to the debulking procedures carried out for ovarian carcinomas. For purposes of analysis, we categorized patients as having undergone either a greater than 90% removal of all identifiable tumors or a lesser procedure, as determined by review of operative notes and postoperative imaging studies. Ten patients received radiation therapy, administered to areas from which large tumor masses had been resected, such as the pelvis or upper abdomen. Patients with large numbers of small (1 mm) metastases on the peritoneal surfaces received total abdominal radiation. Because radiation therapy usually was given as part of the P6 protocol, we did not evaluate its use as a separate variable.

Survival was calculated using the Kaplan-Meier method,[26] and groups were compared with the log-rank test.[27,28] The end point of statistical analysis was overall disease-specific progression-free survival. The variables analyzed were as follows: primary tumor site (abdomen vs. pelvis vs. extraperitoneal); the presence of extra-abdominal disease at diagnosis; resection greater than 90% either before or after chemotherapy; use of the P6 protocol; and type of response to therapy. We evaluated the response to therapy based on imaging studies done at or near the end of all treatment including surgery, chemotherapy, and radiotherapy. In six cases, second-look laparotomy or laparoscopy was used to confirm the findings obtained from imaging studies. We grouped treat-

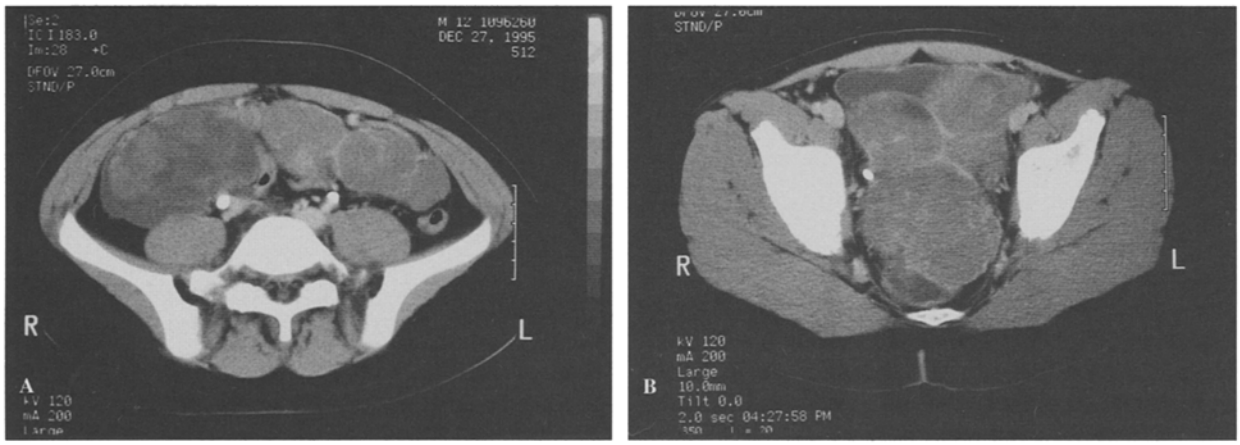

FIG. 1. Computed tomographic scan of a patient with desmoplastic small round cell tumor presenting with an abdominal mass. Representative abdominal (**A**) and pelvic (**B**) cuts are shown.

TABLE 2. *Patient data**

Age (y)/sex	Primary site/upper abdomen involvement	Extent of disease	>90% debulking/ complete response	P6	Status/follow-up (y)
13/M	Abdomen/yes	Liver, peritoneal carcinomatosis, pelvic mass	Yes/no	Yes	PF/0.8
14/M	Abdomen/yes	Liver, retroperitoneal nodes, ascites	Yes/no	Yes	PF/2.4
14/M	Abdomen/no	Paraaortic lymph nodes	Yes/yes	Yes	PF/5.2
14/F	Pelvis/no	Bilateral pelvic, retroperitoneal and mediastinal lymph nodes	Yes/yes	Yes	PF/0.9
16/M	Pelvis/no	Omental and pelvic mass, peritoneal implants	Yes/yes	Yes	PF/5.8
17/M	Abdomen/yes	Peritoneal implants, liver	Yes/yes	Yes	PF, TD/1.1†
17/F	Thoracic/yes	Mediastinal lymph nodes	Yes/yes	Yes	PF, TD/2.0‡
22/M	Pelvis/no	Small nodules in pelvis	Yes/yes	Yes	PF/3.7
22/M	Pelvis/no	Pelvis, retroperitoneal nodes, ascites, pleural plaques	Yes/yes	Yes	PF/2.1
24/M	Pelvis/no	Peritoneal nodules, ascites	Yes/yes	Yes	PF/3.1
24/M	Abdomen/no	Pelvis, lung metastases	Yes/yes	Yes	PF/1.5
29/M	Pelvis/no	Lung metastases, retroperitoneal lymph nodes	Yes/no	Yes	PF, TD/2.3†
7/M	Abdomen/yes	Paraaortic and pelvic lymph nodes	No/no	Yes	DOD/1.6
10/M	Abdomen/yes		No/no	Yes	DOD/2.7
13/M	Pelvis/no	Peritoneal nodules, pelvis	Yes/yes	Yes	DOD/2.3
14/M	Abdomen/yes	Multiple hepatic metastases, CBD obstruction	No/no	Yes	DOD/2.8
14/M	Pelvis/yes	Lung metastases, pelvis, spleen, retroperitoneal lymph nodes	No/no	Yes	DOD/2.6
21/M	Abdomen/yes	Hepatic metastases, CBD obstruction, pelvis	No/no	No	DOD/0.3
21/M	Abdomen/yes	Diffuse hepatic metastases	No/no	No	DOD/1.7
22/M	Abdomen/yes	Omentum, hepatic metastases	No/no	No	DOD/1.5
22/M	Abdomen/yes	Mesentery, spleen, tail of pancreas	Yes/yes	Yes	PD, AWD/3.2
25/M	Pelvis/yes	Retroperitoneal lymph nodes	No/no	No	PD, AWD/2.7
25/M	Pelvis/yes	Hepatic metastases	No/no	No	DOD/0.3
28/M	Abdomen/yes	Omental mass, diffuse peritoneal involvement, ascites	No/no	No	DOD/1.9
28/M	Abdomen/yes	Hepatic metastases, peritoneal carcinomatosis	No/no	No	PD, AWD/0.6
28/M	Pelvis/no	Groin and mediastinal lymph nodes	No/no	No	DOD/2.0
31/M	Abdomen/no	Multiple peritoneal nodules	No/no	No	DOD/0.5
34/M	Abdomen/no	Pelvic and inguinal lymph nodes	No/no	No	DOD/3.6
34/M	Abdomen/yes	Serosa of colon, peritoneal nodules	No/no	No	DOD/0.8
40/M	Abdomen/yes	Retroperitoneal lymph nodes, pelvis	No/no	No	DOD/1.0
41/M	Abdomen/yes	Liver metastases	No/no	No	PD, AWD/1.4
28/M	Abdomen/yes	Splenic mass	Yes/yes	No	PD, AWD/1.0

* Patients who had undergone resection of greater than 90% of the *total* tumor burden as judged by the surgeon were listed as a greater than 90% resection. Usually this entailed resection of a large primary mass in the pelvis or abdomen and multiple secondary masses within the peritoneal cavity.

† Died from secondary myeloblastic leukemia. No evidence of DSRCT by imaging studies.

‡ Died from infection secondary to low white blood cell count. No evidence of DSRCT at autopsy.

CBD, common bile duct; NED, no evidence of disease; DOD, died of disease; AWD, alive with disease; PF, progression-free; TD, toxic death; PD, progressive disease.

ment responses into complete and very good partial response versus response less than 90%. A very good partial response was defined as a 90% reduction in tumor bulk at the end of multidisciplinary therapy.

RESULTS

Demographics and Presentation

There were 30 males (94%), and two females (6%). Twenty-nine patients were Caucasian, and three were African-American. The median age at diagnosis was 22 years (range, 7 to 41 years). Although most of the tumors were diffuse at diagnosis, the predominant site was abdominal in 20 patients (63%), pelvic in 11 patients (34%), and pleural in one patient (3%). Clinical presentations are listed in Table 1. All but two patients had extensive retroperitoneal and serosal disease with multiple peritoneal implants (Fig. 1). Twenty patients had bulky upper abdominal disease, including metastases to the liver, spleen, or pancreas, or bulky serosal deposits

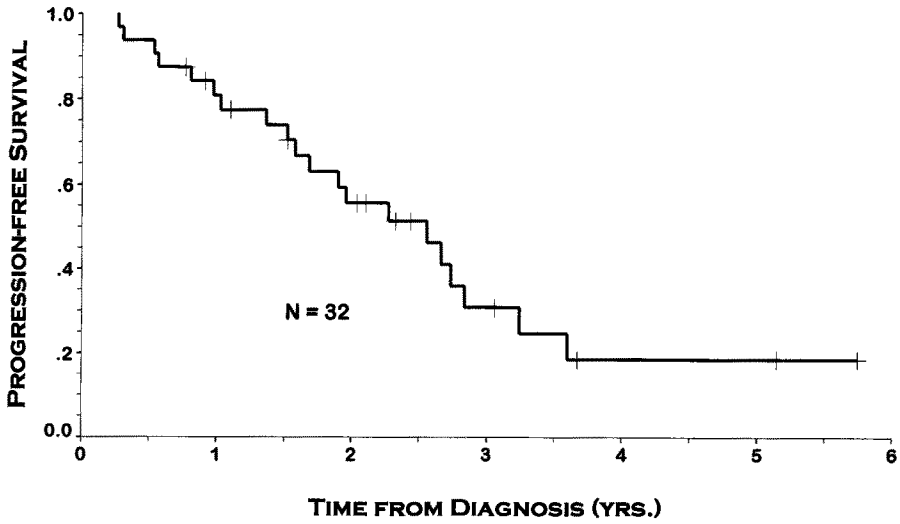

FIG. 2. Overall progression-free survival.

under the diaphragm. Seven patients had distant metastases at diagnosis, and five more developed distant metastases later. Three patients had pulmonary metastases, two patients had pleural or chest wall deposits, and the remainder had distant lymph node involvement. Two patients developed bony metastases after initial treatment. One patient developed bone marrow involvement, but we did not observe central nervous system metastases. In most patients, characteristic histopathologic findings were sufficient to confirm the diagnosis. Table 2 lists the 32 patients included in this series with the primary tumor site and sites of regional or distant extension at diagnosis. Extent of surgical debulking, response to multimodality therapy, and follow-up also are included.

Treatment

Seventeen patients underwent operative biopsy or attempted resection, but a complete or near-complete debulking was not performed or could not be done, usually because of the extent of tumor and involvement of major structures. The other 15 patients did undergo at least a 90% debulking of tumor in the abdomen and, in one case, the chest. Only three DSRCTs were completely resectable before chemotherapy; 12 other patients underwent a greater than 90% tumor removal after initial chemotherapy. Resection of bulk disease was essential to induction of a complete response or very good partial response in all patients.

All 32 patients received systemic multiagent chemotherapy, and the P6 protocol was used in 18 patients (56%). This protocol consisted of four courses of high-dose cyclophosphamide, doxorubicin, and vincristine, interspersed with ifosfamide, etoposide, and mesna in three cycles.[25] In addition, four patients underwent myeloablative chemotherapy with stem cell rescue as a component of the P6 regimen. Ten patients received radiation therapy to high-risk tumor sites, including one patient who received intraoperative radiation treatment and four patients who received total abdominal irradiation.

TABLE 3. *Correlation of clinical parameters and overall survival*[a]

Parameter	Group with better survival	Significance
Predominant primary site (abdomen vs. pelvis)	None	NS
Extra-abdominal disease	None	NS
Response to multimodality therapy	Complete response or very good partial response	$P < .0004$
Resection	>90% resection	$P < .0001$
Chemotherapy protocol	P6	$P < .0001$

[a] Groups were compared using the log-rank test. The end point was progression-free survival.
NS, not significant.

Complications of Surgery

Major treatment-related complications after operative therapy included two cases of *Clostridium difficile* enterocolitis, one case of postoperative small bowel obstruction, and one case of urinary retention and hematuria. One patient developed appendicitis while undergoing systemic therapy, and one patient presented with a colovesical fistula after abdominal irradiation. This patient has required both fecal and urinary tract diversion. One patient died from a tumor-related Budd-Chiari syndrome and upper gastrointestinal hemorrhage while undergoing systemic treatment.

Survival

Twelve patients were progression-free after institution of therapy. Nine of these remain alive and have no evidence of disease or stable sites of minimal disease. Three patients who responded well to therapy died from toxic complications. Two developed secondary acute myeloblastic leukemia, which was their cause of death. Neither had evidence of disease by imaging studies, and, in addition, one had a negative laparoscopy before death. A third developed fungal sepsis that proved fatal, but a postmortem examination showed no evidence of desmoplastic small round cell tumor.

Twenty patients developed progressive disease, and 16 of them have died from the disease. The overall progression-free survival for the total group of 32 patients is depicted in Figure 2. The median progression-free survival was 2.6 years (95% CI; 1.6–3.5 years), and the progression-free survival at 5 years after diagnosis was 18%.

Factors correlated with improved survival included a complete or very good partial response to therapy; the P6 protocol; and a greater than 90% tumor resection (Table 3; Figs. 3 through 5). Predominant anatomic site and extra-abdominal extension of disease did not correlate with progression-free survival.

DISCUSSION

Clinicopathologic studies have documented the aggressive nature and poor prognosis of DSRCT but have focused on clinical presentation and diagnostic criteria rather than specific treatment and prognostic variables.[2,11,14,25,29–31] The overall progression-free survival of 18% at 5 years that we observed confirms the very poor prognosis reported by others. This mortality is not surprising, given the diffuse nature of these tumors at presentation. We have observed primary masses that measured 20 or 30 cm in diameter, and at exploration have found hundreds of satellite lesions covering the peritoneal surfaces. Hepatic involvement and regional or distant nodal metastases are relatively common. This cancer has a propensity to infiltrate the peritoneal surfaces that is similar to that of ovarian carcinomas. It is noteworthy that the great bulk of disease is localized to the abdominal cavity and pelvis. Thus, surgical debulking is feasible despite extensive regional dissemination.

Previous reports suggest that aggressive multiagent chemotherapy can induce a complete response of limited duration but that less dose-intensive regimens have been ineffective against this tumor.[11,29] Kushner reported improved progression-free survival after aggressive chemotherapy with a high-dose multiagent regimen and aggressive resection followed by total abdominal radiation.[25] We found in the present study that the dose-intense P6 protocol was associated with an improved outcome compared to other regimens. Our data also indicated that a complete or very good partial therapeutic response was associated with better progression-free survival. Induction of this type of response depended on surgical resection to remove bulk sites of disease in all cases. We conclude that aggressive surgical debulking is necessary for improved progression-free survival.

Because only three patients were completely resected before receiving chemotherapy, a comparison of outcome for pre- and post-chemotherapy resection was not possible. We found nothing to suggest an advantage for resection before or after systemic treatment.

We performed these procedures through a long midline incision after mechanical bowel preparation. DSRCT usually is located on the serosal surfaces and

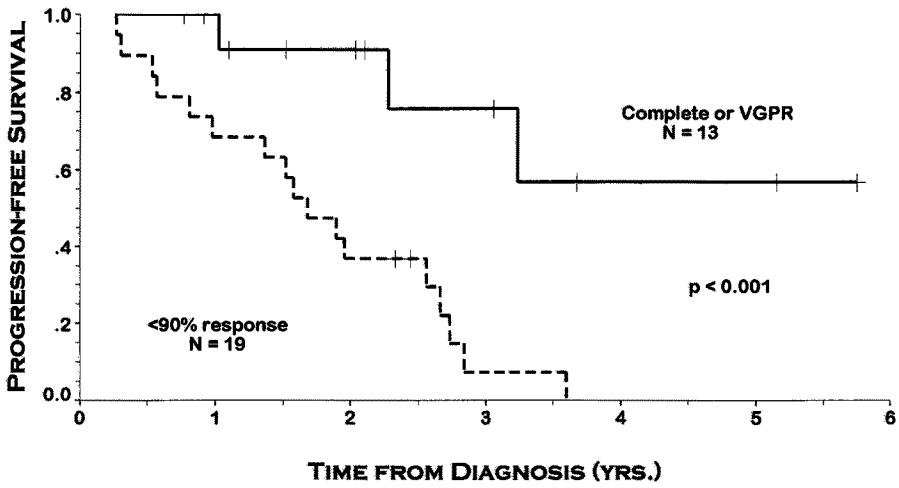

FIG. 3. Progression-free survival in patients who had a complete or very good partial response to therapy based on clinical, radiologic, and, in some cases, histologic criteria, compared to survival in patients who had a partial or no response.

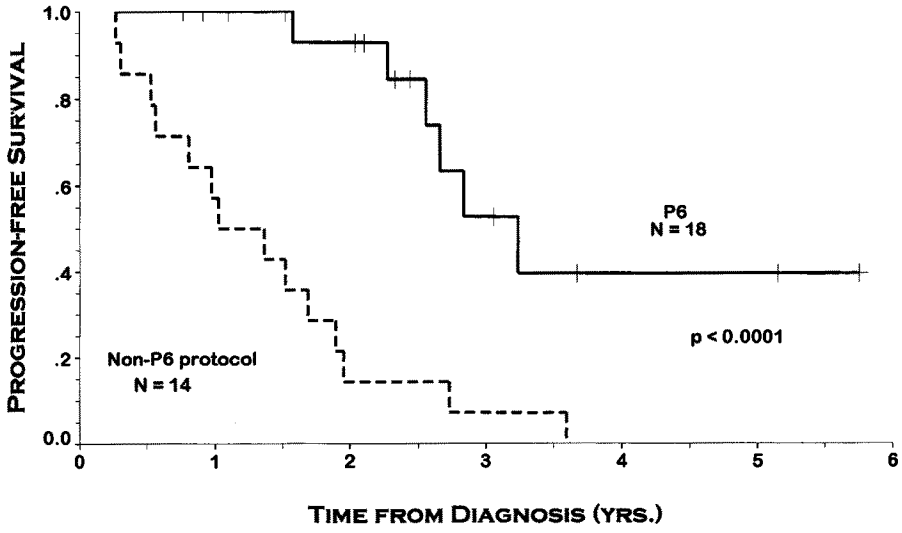

FIG. 4. Progression-free survival in patients treated with the P6 protocol versus that in patients receiving other regimens.

often does not invade deeply, allowing removal without major organ resections in many patients. We were able to remove bulky areas of disease with subserosal dissection. In the pelvis, tumor masses often are located in the rectovesical area, and dissection off the anterior rectal wall is required. Prerectal tumors may require low anterior resection, and splenic involvement usually requires splenectomy. Hepatobiliary disease can be extensive, precluding complete resection, but localized hepatic tumors may be amenable to wedge or anatomic resection. We resected nodules under the surface of the diaphragm, and diaphragmatic resection with reconstruction was sometimes required. We performed omentectomies if there was evidence of omental involvement.

The two patients with the longest disease-free survival in our series received total abdominal irradiation in addition to complete resection, but we did not evaluate the overall effect of external beam radiation on survival.

In our practice, if imaging studies indicate that the tumor or tumors are resectable, we perform resection before chemotherapy. However, patients usually have regionally advanced disease at diagnosis, making resection difficult or impossible. In this situation, a biopsy, often performed laparoscopically, is done to verify the diagnosis and a central venous catheter for subsequent chemotherapy is placed. After three to five cycles of induction chemotherapy we perform aggressive surgical debulking. We remove multiple serosal nodules as well as the major tumor deposits that often are found in the rectovesical area or in the upper abdomen. Initially, the number of small (<1 mm) residual peritoneal implants may be dismaying. However, we observed long-term

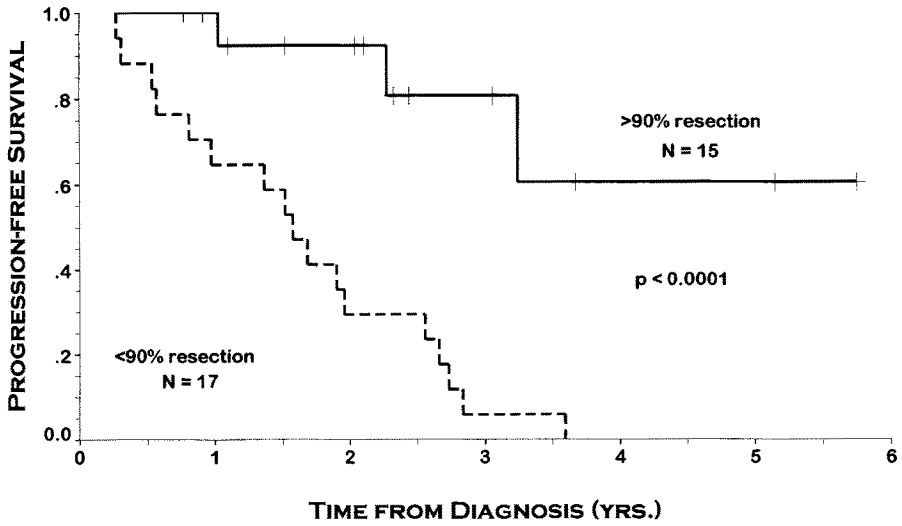

FIG. 5. A comparison of progression-free survival for patients undergoing a greater than 90% resection of tumor versus those in whom only a partial resection or biopsy was performed.

survival in two patients in this series after debulking followed by further chemotherapy and total abdominal radiotherapy. These operations are similar in concept to debulking procedures performed for ovarian carcinoma. Chemotherapy in itself did not result in a complete response in this series of patients.

In conclusion, overall prognosis in DSRCT remains poor. Our data support a role for aggressive tumor debulking combined with multiagent high-dose chemotherapy and radiation.

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