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# Management Consideration in Nonpulmonary Visceral Metastatic Seminoma of Testis

To develop a more appropriate therapeutic strategy for treatment of nonpulmonary visceral metastatic testicular seminoma based on the International Germ Cell Consensus Classification, we reviewed the medical records of patients with nonpulmonary visceral metastatic testicular seminoma who were treated over a 20-year period. Only 15 (2.2%) of the 686 cases of testicular seminoma were nonpulmonary visceral metastatic seminoma. The median age of patients was 38 years (range, 22-53 years). Ten (67%) of the patients had an initial diagnosis of supradiaphragmatic or visceral metastatic disease. In addition to nonpulmonary visceral metastasis, all patients had lymph node metastasis as well, the majority of which involved the retroperitoneal lymph nodes. The median and mean progression-free survival durations after chemotherapy for advanced disease were 19 months and 63.7 months, respectively. Six patients (40%) survived, five relapsed after radiation therapy and four died of chemorefractory disease not dependent on the specific regimen. Although the number of cases reviewed in this study was small, we conclude that the choice of chemotherapeutic regimen among the current treatments for nonpulmonary visceral metastatic seminoma of testis primary does not present a different outcome. Therefore, multimodality therapies using new strategies or new agents are well indicated.

Key Words: *Seminoma; Testis; Neoplasm metastasis; Therapeutics*

**Dong Soo Park, Debra M. Prow*, Robert J. Amato*, Christopher J. Logothetis***

Department of Urology, Pundang CHA Hospital, Pochon CHA University, Sungnam, Korea
Department of Genitourinary Medical Oncology*, The University of Texas M.D. Anderson Cancer Center, Houston, Texas, U.S.A.

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**Address for correspondence**
Dong Soo Park, M.D.
Department of Urology, Pundang CHA Hospital, Pochon CHA University, Pundang-gu, Sungnam, Kyunggi 463-712, Korea
Tel: +82.342-780-5350, Fax: +82.342-780-5323
E-mail: dsparkmd@netsgo.com

## INTRODUCTION

The finding that seminomas are chemosensitive (1), is clear evidence that chemotherapy is well indicated in the treatment of advanced seminoma, especially combination regimens that include cisplatin-based alkylating agents (2-6). However, the effectiveness of radiation therapy or surgery to control residual masses that persist following chemotherapy for advanced seminoma is the subject of much debate (7-10).

Seminomas are characterized by unique clinicopathological features, including an indolent clinical course i.e., a low potential for metastasis. When metastasis does occur, it is predominantly nodal with a predictable pattern of spread to the retroperitoneum; hematogenous spread is rare (11). Therefore, treatment for the metastasis is influenced by the clinical course of the disease, metastatic pattern, and radiosensitivity and chemosensitivity of the metastatic lesion.

In the past, primary testicular seminoma was classified according to nodal involvement (size and site) and extranodal visceral involvement (4). The major clinical dilemma in treating seminoma with nodal involvement was the selection of therapy for patients with retroperitoneal metastasis. The choice of treatment, whether single- or combined-modality, was typically based on the size of the metastatic mass. However, chemotherapy is considered the standard of care for first-line treatment of stage III disease (supradiaphragmatic or visceral involvement) (11). Based on current advances in chemotherapy, the International Germ Cell Cancer Collaborative Group has suggested that a prognostic-factor-based staging system be used to stage for metastatic germ cell cancers. According to this system, seminomas are divided into two groups: good prognosis and intermediate prognosis (12), regardless of the primary tumor origin. The only prognostic feature that differentiates the two groups is the absence or presence of nonpulmonary visceral metastasis; there is no poor prognosis group in seminoma according to the International Germ Cell Cancer Collaborative Group. Nonpulmonary visceral metastasis occurs in only about 10% of patients with seminoma; thus, seminoma gener-

ally has a good prognosis compared with nonseminomatous germ cell tumor. However, considering the potential with direct invasion to adjacent structures, there may be other clinical implications with regard to the origin of the disease (testis primary vs extragonadal primary).

In this study, we reviewed the medical records of 15 patients with nonpulmonary visceral metastatic testicular seminoma who were treated at M.D. Anderson Cancer Center over a 20-year period. We analyzed the effectiveness of chemotherapy as a treatment for this disease and the application of radiation therapy and surgery as consolidation for residual disease following chemotherapy.

## PATIENTS AND METHODS

From 1978 to 1997, we treated 2,107 patients for testicular germ cell tumors: 686 (32.6%) had seminoma and 1,421 (67.4%) had nonseminomatous germ cell tumors.

In our study, we used the International Germ Cell Consensus Classification system (12) to stage the seminomas. Fifteen (15/686; 2.2%) of the patients with seminomas had nonpulmonary visceral metastatic lesions derived from testicular primaries; these 15 patients comprise our patient population. Patient characteristics, including pretreatment status, metastatic lesions and treatment outcome are presented in Table 1. Among the patients with nonpulmonary visceral metastatic tumors, three patients (Pt. No. 5, 11, and 12) had a history of undescended testicle.

Of the 15 patients studied, 7 (46.7%) initially presented with nonpulmonary visceral metastatic testicular seminoma and eight (53.3%) presented with relapsed nonpulmonary visceral metastatic testicular seminoma.

Treatments included consisted of chemotherapy, radiation therapy and surgery depending on the stage and status of the disease (Table 2).

## RESULTS

The median age at the time of diagnosis was 38 years (range, 22-53 years). The predominant site of the primary tumor was the right testis (12/15 cases: 80%); the other three (20%) primaries occurred in the left testis. Initial staging based on a previous report from M.D.

**Table 1.** Presentation and outcome of patients with nonpulmonary visceral metastatic testicular seminoma

| Pt. No. | Pretreatment | | | | | | Metastatic lesions | | | | | | PFS time after CT (M) | FU (M) | Alive | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Age | TL | Stage | STM status | Metastatic sites | UO | No. | Lung | NPV | Retro | Med | SC | | | | |
| 1 | 39 | R | III | ↑LDH>X2, HCG | Lung, Liver, retro, Med | + | 5 | + | Liver, bone | + | + | − | 19 | 22 | No | Refractory |
| 2 | 53 | R | I | Normal | None | − | 3 | − | Liver, bowel | + | − | − | 10 | 26 | No | Refractory |
| 3 | 48 | L | IIA | ↑HCG | Retro | − | 2 | − | Liver | + | − | − | 71 | 93 | No | Sudden death |
| 4 | 29 | R | III | ↑LDH>X2, ↑HCG | Retro, Med | − | 4 | − | Liver, bowel | + | + | − | 4 | 65 | No | CBD obstruction, IVC collapse |
| 5 | 52 | R | III | ↑HCG | Retro, bowel | + | 2 | − | Bowel | + | − | − | 187 | 188 | Yes | CR |
| 6 | 36 | R | III | ↑LDH>X2, ↑HCG | Med | − | 3 | − | Bone | − | + | + | 0 | 39 | No | Refractory |
| 7 | 34 | L | III | ↑LDH>X2, ↑HCG | Bone, Retro, med, SC | − | 4 | − | Bone | + | + | + | 0 | 5 | No | SVC SD, sudden death |
| 8 | 41 | L | IIA | ↑HCG | Retro | − | 2 | − | Bone | + | − | − | 91 | 107 | Yes | CR |
| 9 | 38 | R | III | ↑LDH>X2, ↑HCG | Lung, liver, pancreas, Retro | − | 6 | + | Liver, pancreas, bone, muscle | + | − | − | 0 | 58 | Lost | Sarcomatous muscular mets |
| 10 | 22 | R | I | Normal | None | − | 2 | − | Liver | − | − | + | 24 | 31 | Yes | CR |
| 11 | 26 | R | III | ↑HCG | Bladder, bowel | + | 3 | − | Bladder, bowel | + | − | − | 187 | 193 | Yes | CR |
| 12 | 45 | R | III | ↑LDH>X2, ↑HCG | Bowel | − | 2 | − | Bowel | + | − | − | 18 | 18 | Yes | CR |
| 13 | 37 | R | III | No data | Lung, thyroid, retro | − | 3 | + | Thyroid | + | − | − | 23 | 31 | No | Died of pneumonia |
| 14 | 44 | R | III | ↑LDH<X2 | Lung, Retro | − | 3 | + | Liver | + | − | − | 0 | 15 | No | Refractory |
| 15 | 26 | R | I | Normal | None | − | 2 | − | Liver | + | − | − | 221 | 227 | Yes | CR, Secondary tumor |

Pt, patient; TL, testis lesion; STM, serum tumor marker; UO, ureteral obstruction; NPV, nonpulmonary visceral; Retro, retroperitoneal; Med, mediastinal; SC, supraclavicular; PFS, progression free survival; CT, chemotherapy; FU, followup; M, months; R, right; L, left; ↑, increased; +, presence; −,absence; LDH, Lactic dehydrogenase; HCG, human chorionic gonadotropin; CBD, common bile duct; IVC, inferior vena cava; SVC SD, superior vena cava syndrome; CR, complete remission

**Table 2.** Chemotherapeutic regimens and other treatment methods applied to patients with nonpulmonary visceral metastatic testicular seminoma

| Pt. No. | Chemotherapeutic regimen | Radiation therapy | Surgery |
|---|---|---|---|
| 1 | PVB/CA, EP, VIP | Retroperitoneum | - |
| 2 | CTX+CDDP, EP | Retroperitoneum, mediastinum | - |
| 3 | CTX+CDDP, EP | Retroperitoneum, pelvis | Salvage retroperitoneal lymph node dissection |
| 4 | VAB-6 | Retroperitoneum | Gastrojejunostomy |
| 5 | CISCA/VB | - | Right colectomy, pelvic mass excision |
| 6 | BEP, VIP, Taxol+CTX+CDDP, CISCA+Taxol | Neck, mediastinum, bone | - |
| 7 | CTX+carboplatin | - | - |
| 8 | CTX+CDDP | Retroperitoneum, bone | - |
| 9 | BEP, ifosfamide+EP | Bone | Muscle mass excision |
| 10 | CISCA/VB | Retroperitoneum | - |
| 11 | CTX+CDDP | - | Pelvic mass excision |
| 12 | CTX+carboplatin | - | Pelvic mass excision, small bowel resection |
| 13 | CTX+VCR+MTX+5FU | Retroperitoneum | Right lobectomy of lung, thyroidectomy |
| 14 | PVB, EP, ACD+FuDR+EP, ACD+CTX+ACC+MTX | Retroperitoneum | - |
| 15 | CTX+CDDP | Retroperitoneum & iliac | - |

Pt, patient; PVB, cisplatin, vinblastine, bleomycin; EP, etoposide, cisplatin; VIP, etoposide, ifosfamide, cisplatin; CTX, cyclophosphamide; CDDP, cisplatin; VAB-6, cisplatin, vinblastine, bleomycin, cyclophosphamide, and dactinomycin; CISCA/VB, cisplatin, cyclophosphamide; BEP, bleomycin, etoposide, cisplatin; VCR, vincristine; MTX, methotrexate; 5FU, 5 flurouracil; ACD, dactinomycin; FuDR, Floxuridine; ACC, Actinomycin C

Anderson Cancer Center (11) were three (20%) cases of stage I disease (tumor confined to the testis), two (13.3 %) cases of stage IIA disease (subdiaphragmatic tumor $\leq$5 cm), no stage IIB disease (subdiaphragmatic tumor >5 cm, $\leq$10 cm), no stage IIC disease (subdiaphragmatic tumor >10 cm) and ten (66.7%) cases of stage III disease (supradiaphragmatic tumor or visceral involvement). Therefore, these ten patients (66.7%) of nonpulmonary visceral metastasis of testicular seminoma were diagnosed with supradiaphragmatic or visceral involvement at initial presentation. With application of the International Germ Cell Classification (12), these seven patients had nonpulmonary visceral metastatic lesions at initial presentation. Eight patients had nonpulmonary visceral metastasis after the initial diagnosis; five of these patients had radiation therapy as initial treatment and three had chemotherapy plus radiation therapy. The sites of the nonpulmonary visceral metastases were the liver, bowel, bone, pancreas, bladder, thyroid, and muscle. The number of metastatic lesions per patient ranged from two-six (mean, three lesions per patient) (Table 2).

There were five cases of direct nonpulmonary visceral involvement and 11 cases of hematogenous metastasis among our 15 cases (one patient was belong to both categories). Three of the patients (Pt. No. 5, 11, and 12) had a history of undescended testicle. In another patient (Pt. No. 4), metastasis of the upper retroperitoneal lymph nodal mass directly invaded adjacent structures. In another patient (Pt. No. 7) metastatic thoracic lymphatic metastasis spread to a vital organ. This patient had bony metastasis at the same time. In six of the 11 cases of hematogenous metastasis (Pt. No. 1, 6, 7, 9, 13, and 14), nonpulmonary visceral metastases occurred from the time of diagnosis; and in the other five patients (Pt. No. 2, 3, 8, 10, and 15), nonpulmonary visceral metastasis developed later.

Pretreatment serum tumor marker values revealed a markedly increased serum lactic dehydrogenase (LDH) level (more than twice the upper-normal limit) in six (40%) patients; serum human chorionic gonadotropin (hCG) levels also were increased in all six patients. Elevated hCG levels alone occurred in 4/15 (26.7%) patients.

Ureteral obstruction caused by retroperitoneal tumor mass occurred in three patients. These patients were managed with an indwelling ureteral stent. Two patients with retroperitoneal lymph node metastasis at right suprarenal hilar level had developed obstructive jaundice.

In this patient population, 13 of the 15 patients (86.7 %) also had retroperitoneal lymph nodal metastasis: four (26.7%) had mediastinal nodal disease and three (20%) had supraclavicular lymph nodal disease. Two patients

(13.3%) without retroperitoneal nodal disease had mediastinal or supraclavicular lymph nodal metastasis.

The median progression-free survival duration following chemotherapy was 19 months (mean, 63.7 months; range, 0-22 months). Median follow-up duration was 39 months (mean, 74.5 months; range, 5-227 months). Six (40%) patients are cured, and all of them were responsive to initial chemotherapy. One patient was lost to follow-up; presumably, this patient had progressive disease or died of disease. In four patients the tumors were refractory to chemotherapy (Tables 1 and 2).

Chemotherapy regimens consisted of cyclophosphamide plus cisplatin or cyclophosphamide plus carboplatin; however, other regimens were used for patients who were initially treated at other institutions (Table 2).

Five (33.3%) of the 15 patients had progressive disease after radiation therapy to the retroperitoneum, the mediastinum, or both; three of these patients (Pt. No. 2, 10, and 15) received this treatment prophylactically and two (Pt. No. 3 and 8) received it therapeutically. These five patients had stage I and IIA disease at the time of initial diagnosis. All five patients received chemotherapy for the metastatic lesion, two patients also received radiation therapy and one patient also underwent surgery. Three patients with cryptorchidism did not receive radiation therapy after pelvic mass excision. One patient (Pt. No. 7) died suddenly before radiation therapy could be performed. Surgery was performed in seven of the 15 patients, including three patients (Pt. No. 5, 11, and 12) with undescended testicular seminoma, one patient (Pt. No. 4) who underwent palliative surgery for duodenal obstruction, two patients who underwent metastatectomy involving the lung/thyroid, and skeletal muscle, and one patient underwent salvage retroperitoneal lymph node dissection (RPLND) (Table 2).

## DISCUSSION

Seminoma with distant visceral involvement, usually has a nodal pattern of metastatic spread and is unusual among advanced cases and even more rare with testis primary. Visceral involvement is categorized either as that occurring by hematogenous spread or by direct tumor invasion. In our study, the patients had nonpulmonary visceral metastasis of testicular seminoma and lymph nodal metastasis of the retroperitoneum or other sites. This finding demonstrates that all cases of nonpulmonary visceral metastasis of testicular seminoma also have lymph node metastasis.

Seminoma is commonly characterized by its advanced local complications. With the development of testicular seminoma in the undescended testicle, there is a tendency for direct invasion of adjacent structure, such as bladder, prostate, bowel and great vasculatures of the pelvis, which makes surgical resection difficult. Three patients with undescended testicle were among the patients with nonpulmonary visceral metastasis, who had direct metastatic invasion to the bowel and bladder, which required partial bowel and bladder resection. Even more ominous, however, is the presence of right upper retroperitoneal lymph node metastasis, which can induce obstruction of the bile duct or pancreas; these problems can be fatal and can hinder adequate chemotherapy. Also, these lesions cannot be resected or controlled well with radiation therapy.

The International Germ Cell Cancer Collaborative Group was formed in 1991 to analyze the records of 660 seminoma patients (12). They determined a lack of impact on prognosis of extragonadal primary site, and the adverse prognosis associated with the presence of nonpulmonary visceral metastasis. The presence of nonpulmonary visceral metastatic disease (to sites such as liver, bone, brain, bowel and adrenal glands) was the only factor used to determine the poor prognostic group for seminoma. Among our patients, sites of nonpulmonary visceral metastasis included the liver, bowel, pancreas, bladder, thyroid, and muscle; some patients had multiple sites of disease.

Cases with invasion into an adjacent pelvic cavity structures, particularly extraperitoneal, with seminoma originating in an undescended testicle, would be expected to have a good prognosis. However, tumor development around a vital organ would be considered to be a poor prognosis if the mass invades the vital organ directly, regardless of its origin (primary or metastatic). Besides the direct invasion of the adjacent structure of seminoma, there was hematogenous nonpulmonary visceral metastasis. Therefore, metastatic seminoma lesions would be classified as: 1) those with direct invasion to adjacent structures and 2) those with hematogenous spread into distant organs. The state that is diagnosed as visceral metastatic disease would be considered as follows. First, the time point to be diagnosed as status of direct invasion of the pelvic cavity or lower abdominal structures in patients with an undescended testicle (Pt. No. 5, 11, and 12) appears later than direct extension of the metastatic lymph node into the upper abdominal cavity (one case among ours: Pt. No. 4) or thoracic cavity (one case: Pt. No. 7, this case had concomitant bony metastasis) that invades the adjacent vital organs in patients with normally descended testicular origin. This aspect might be different from extragonadal primary seminoma, although site of origin did not affect the prognostic classification of International Germ Cell Tumor Consensus. Second, nonpulmonary visceral metastasis could develop at initial

presentation or later, as in cases of distant hematogenous metastases to organs. In our study, six patients (Pt. No. 1, 6, 7, 9, 13, and 14) had nonpulmonary visceral metastases at initial presentation; the other five patients (Pt. No. 2, 3, 8, 10, and 15) developed nonpulmonary visceral metastases later.

Regardless of the primary origin, the treatment for nonpulmonary visceral metastatic seminoma should be chemotherapy-based. Even prior to cisplatin, the difference in chemotherapeutic response rates between seminoma and nonseminomatous germ cell tumors was apparent. Treatment for advanced seminoma is different than that for patients with nonseminomatous germ cell tumor. The combination chemotherapy regimen of vinblastine and bleomycin (VB) was effective in a significant proportion of patients with nonseminomatous tumors, but ineffective in patients with seminoma (13). Additionally, bleomycin-induced pulmonary toxicity has been reported more frequently in patients with seminoma patients than in those with nonseminomatous tumor, which is presumably attributed to age (patients with seminoma are generally older) (6, 9). In initial reports using cisplatin as a single agent for treatment of germ cell tumor, it was shown that patients with seminoma had a long-term disease free survival rate that was not seen in nonseminoma patients (14).

Cisplatin-containing chemotherapy is felt to be superior to non-cisplatin-based therapy by some investigators (2). In the past, M.D. Anderson Cancer Center treated advanced seminoma with cisplatin and cyclophosphamide and concluded that the combination was effective (4). However, toxicity is related to repeated doses of cisplatin, such as nephrotoxicity and neurotoxicity. The opportunity to evaluate the cisplatin-analogue carboplatin in seminoma was promising (9). However, the disease-progression-free rate of patients being treated with single-agent carboplatin was lower than patients treated with platinum-based combination chemotherapy. The addition of radiation therapy to chemotherapy did not affect the risk for progression (15). Ifosfamide in combination with carboplatin was also found to be active in germ cell tumor. This combination also caused no deaths (9, 16).

Although seminoma is more radiation-sensitive than nonseminomatous germ cell tumor, chemotherapy is the foundation of management in advanced seminoma (2-6). In our patients, there was no definitive difference in survival among the various regimens that had been applied.

In our review, 67% of patients with nonpulmonary visceral metastatic seminoma of testicular origin had been diagnosed with supradiaphragmatic or visceral involvement requiring chemotherapy. None of the patients had stage IIB disease or stage IIC disease, which are also treated with chemotherapy. However, three patients with stage I disease and two patients with stage IIA (total of five patients, 33%) were treated with radiation therapy rather than chemotherapy, subsequently developed nonpulmonary visceral metastasis (the outcome of these patients showed a 60% survival rate). These results suggest chemotherapy may be important in patients with stage IIB and higher disease. Multimodality therapy may be needed for patients with stage III disease.

Treatment strategies are based on the fact that seminoma is sensitive to both chemotherapy and radiation therapy, difficult to resect and shown as a unique clinical entity in an older patient population. Our patients received four courses of induction chemotherapy and two courses chemotherapy after obtaining complete remission or normalization of serum tumor markers and best radiographic response. Complete remission is defined as the disappearance of all clinical and biochemical evidence of disease. Patients that have obtained a complete remission or have residual mass less than 3 cm in size on postchemotherapy radiographic study are observed. Responses to chemotherapy requiring consolidation is the persistently stable discrete residual mass of 3 cm or greater in diameter with disappearance of all clinical and biochemical evidence of disease (9). Patients with persistent residual mass of 3 cm or more receive the consolidation with 30 Gy of radiation therapy (9).

Postchemotherapeutic residual mass may have two clinical features (17). First, the tumor mass surround the great vessels and obliterate radiographic planes. Second the mass may be distinct and clearly delineated. With an indiscrete mass, the residual mass may be mingled with great vessels and other retroperitoneal structures, resembling retroperitoneal fibrosis. Thus, this is an ill-defined mass that is unresectable and surgery is therefore not indicated. Nondiscrete masses have a high incidence of negative pathologic findings. Therefore, we do not give consolidation therapy to this subset of patients. In others if the residual mass is more than 3 cm in size and well-delineated with distinct margins, radiation therapy is given as consolidation.

Surgery was performed in seven (46.7%) patients in our study group, including three patients with undescended testicular seminomas. Among these patients, three (20%) had surgery for removal of residual mass, including one salvage RPLND after chemotherapy. One palliative surgery was done.

On the contrary, radiation therapy was done in the majority of cases (6/7: 85.7%; one patient who did not received radiation therapy died suddenly before initiation of radiation therapy) excluding the three patients with undescended testicular seminoma and the five patients who relapsed after prophylactic or therapeutic radiation therapy. Only one of the five patients, relapsed at non-

pulmonary visceral site after receiving radiation therapy as the initial treatment, developed chemotherapy-refractory disease.

These findings suggest that the seminoma is responsive to chemotherapy in patients with progressive disease after radiation therapy for stage IIA or lower stage disease. However, long-term survival was low in this patient population. Factors that may play a role in this outcome include chemotherapy toxicity (older aged patient) and capacity for recovery of bone marrow in patients treated with prior radiation therapy. Therefore, surgery may be beneficial in a subset of patients; relatively older patients who have already received enough doses of chemotherapy. If the clinical features suggest the presence of non-seminomatous germ cell tumor component, such as poor response to chemotherapy and rising serum AFP level are shown, a surgical intervention may be needed.

LDH has been confirmed as an important prognostic factor for germ cell tumors (12). In our population, 7/15 (46.7%) patients had increased LDH at diagnosis and in six patients (6/15: 40%) the LDH levels were greater than two times of the upper normal limit of LDH.

The presence of lung metastases and raised hCG were reported as being less important prognostic factors than elevated LDH by the International Germ Cell Collaborative Group (12). In our patients, 67% (10/15) had increased hCG and four of the 15 patients (26.7%) had lung metastasis. These results reflect the pattern of testicular seminoma spread by the lymphatic system, especially considering that all patients reviewed had lymph nodal metastasis as well.

Although, the number of patients reviewed here is small, in light of our findings and those in the literature, chemotherapy is the most important modality for patients with nonpulmonary visceral metastatic testicular seminoma. The role of further therapy in patients with a postchemotherapeutic residual mass is being defined (for example, it has been reported (15) that radiation therapy after chemotherapy has no progression-free survival benefit). In reviewing the literature, the factors affecting treatments for residual mass are size less than 3 cm or greater, discrete or nondiscrete and site (organ or lymph node). The present options in the management of the residual mass are observation, irradiation or surgery. If the residual mass measures 3 cm or greater in a resectable portion of an organ, not surrounding the great vessel of retroperitoneum, surgery may be an option. If the appearance of the mass is a well-defined shape, it could be biopsied or definitive irradiation could be performed. On the other hand, if the appearance of the mass is non-discrete, observation may be appropriate. Residual masses less than 3 cm in size, regardless of the site, which are either at organ or at lymph node, could be observed using follow-up every three months for the first two years and then anually without biopsy or further therapy.

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