Bilateral Synchronous Classical Seminoma of Testes with Bilateral Cannon Ball Metastases: A Case Report with a Review of the Literature

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Bilateral Synchronous Classical Seminoma of Testes with Bilateral Cannon Ball Metastases: A Case Report with a Review of the Literature

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Abstract

Background: Synchronous bilateral germ cell tumours of the testis are rare. About 25% of testicular seminomas present with advanced clinical stage disease. Management of bilateral synchronous seminoma may quite often necessitate the performance of bilateral radical orchidectomy which could be associated with psychological trauma to the patient. A patient who undergoes bilateral radical orchidectomy would require testosterone replacement or life and if he is a young man who has not had a child he would require pre-operative sperm banking for future assisted conception to enable him have a child.

Aims: To report a case of bilateral synchronous classical seminoma with bilateral cannon ball lung metastases

To review the literature regarding germ-cell-tumours of testes including bilateral tumours of testes

Case Report: A 31-year-old man was seen in the clinic because he had noticed a lump in his left testis and this lump had been present for a year but he did not seek any medical opinion. He was found on examination to have a palpable hard lump in both testes suspicious of testicular cancer. He had raised serum levels of β-HCG and LDH. He was offered pre-operative sperm banking but he did not want it in view of the fact that he has already had children and he did not want any more children. He underwent bilateral radical orchidectomy without insertion of testicular prostheses because he did not want any prosthesis. Histology of the testicular specimens was consistent with bilateral classic seminoma. He had a chest X-ray which revealed bilateral cannon ball lung metastases. He was referred to the Regional Oncology centre where he is undergoing chemotherapy and radiotherapy. He was referred to and seen by an endocrinologist who has put him on long-term /permanent testosterone replacement therapy.

Conclusions and recommendations: While bilateral radical orchidectomy is the standard practice for patients with synchronous bilateral seminoma, some data support the use of testis sparing techniques to avoid the sequelae of this treatment which include: infertility, dependence on androgen replacement therapy, and the psychological effects of castration. It would be expected that as a result of education in this modern era all men who notice abnormal lumps in their testes would seek medical attention early but this case illustrates the fact that despite education some men would still present late for medical attention. Further education is required to encourage patients to report to their doctors whenever they notice any abnormally palpable lumps in their testes.

Pre-orchidectomy sperm banking should be discussed with patients as well as made available for those patients who have not completed having their children for future use in assisted conception.

Introduction

Synchronous bilateral tumours of the testes are rare. It can be traumatic to a man who presents to his medical practitioner with a painless lump in one testis to be told he has tumours in both testes and that he would require bilateral radical orchidectomy. We report a case of synchronous-bilateral -classical seminoma of testes with a review of the literature.

Case Report

A 31-year-old gentleman presented with a one year history of a painless lump in his left testicle. He did not report any notable change in the size of the lump. He denied any history of injury or previous surgery to the testicle. He had three children but not a wife or a partner at the time of presentation.

On examination, he was found to have an irregular lump on the left testicle and another one on the medial pole of the right testicle. His general and systematic examinations were otherwise normal. He had a number of investigations which were reported as follows:

- Full blood count – Normal
- Serum urea and electrolytes – Normal
- Liver Function test – normal
- Coagulation screen – normal
Serum β-HCG 66407 IU/L (normal range < 5 IU/L), 
Serum Lactic Dehydrogenase (LDH) 861 U/L - (normal range - 125 -243 U/L)
Alpha-feto Protein (AFP) - normal.

He also had ultrasound-scan of testes which was reported to have shown ultra-sonographic features of bilateral malignant testicular tumours. The ultrasound scan report was summarized as follows:

* The ultra-sound scan showed bilateral multiple low echogenicity focal lesions of different sizes, involving parenchyma of both testicles with strongly positive Doppler flow. The biggest lesion within the left testis which measured 2.3 cm x 1.7 cm and at least 3 more lesions which measured approximately 1 cm in size.
* On the right side the biggest lesion measured 1.8 cm and 2 more lesions of less than 1 cm size (see Illustrations 1 to 6 for some of the images).

The diagnosis was explained to the patient and he was told that he would need to undergo bilateral radical orchidectomy. He was counseled regarding the need for sperm banking in case he had a desire to have more children in the future. But he stated that he had three children and he did not want to have any more children. He was also told about the possibility of insertion of bilateral testicular prosthesis in order to give him a good cosmetic appearance of the scrotum post-operatively but he stated that he did not want a testicular prosthesis and he had no worries about the cosmetic appearance of his scrotum. He reported then that he had been coughing up blood in his sputum.

He also had a chest X-ray which was reported as showing multiple cannon ball metastases in the lungs (see illustration 7).

He underwent bilateral radical orchidectomy and had an unremarkable post-operative recovery. Histological examination of the specimens, were reported as follows:

* Macroscopic examination revealed a tumor in the right testicular parenchyma with whitish cut surface and well defined edges. The tumor measured 20 mmx20 mmx18 mm. The tumor was confined within the testis and did not breach the tunica. There was another separate tumor nodule located 10mm proximally. This nodule was confined within the testis and it measured 14mm in diameter. The residual normal testicular parenchyma away from the tumor was 25mm in maximum dimension. The left testis showed no abnormal features externally. On sectioning the testis there was a whitish firm well defined tumor with yellowish area in the middle. The tumor measured 35 mmx20 mmx25mm and was confined within the testis and did not breach the tunica. The epididymis and cord showed no evidence of tumor infiltration. The residual non-neoplastic testicular parenchyma showed no abnormal features.

* Microscopic examination of the specimens confirmed that the tumour in the right testis was a classical seminoma (see illustration 8, 9 & 10). The tumor in the right testis was confined within the testis and did not breach the tunica albuginea. The tumor had infiltrated the rete testis but the epididymis and the cord were free of tumor. The testicular parenchyma adjacent to the tumor showed intratubular germ cell neoplasia (ITGCN). There was no evidence of lymphovascular invasion. The resection margin of the cord was free of tumor. The left testicular tumor was also reported to be a classical seminoma with areas of necrosis (see illustrations 11 and 12). Again, the testicular parenchyma adjacent to the tumor showed intratubular germ cell neoplasia (ITGCN). The tumor did not breach the tunica albuginea but the rete testis was infiltrated. The epididymis and cord were free of tumor. The resection margin was free of tumor but there was evidence of lymphovascular invasion (see illustrations 11 and 12).

Based upon the results of the histological microscopic examination and chest X-ray the patient was diagnosed as having bilateral classical seminoma and cannon ball pulmonary metastasis.

He developed hemoptysis and he was transferred to the Regional Oncology centre to be considered for chemotherapy. At the Regional Oncology centre he had Magnetic Resonance Imaging (MRI) scans of head, thorax, abdomen and pelvis which showed haemorrhagic brain metastases, multiple pulmonary metastases with pleural involvement, and retroperitoneal lymph node mass. He was noted to have lost a lot of weight. He required chest physiotherapy for breathing difficulties. He also had nutritional support (parenteral feeding).

He is undergoing cycles of combination systemic chemotherapy (Vinblastine/etoposide/cisplatin and high dose methotrexate) and his progress would be regularly monitored.

He was also referred to an endocrinologist for the long-term management and follow-up regarding his testosterone replacement therapy and he has been started on topical testrogel for life.

**Discussion**

Testicular tumors comprise 1% of all malignancies [1] and may be germ-cell or sex-cord tumors. The most common germ-cell tumour is seminoma. [1] The other germ-cell tumors include: choriocarcinoma, teratoma, embryonal carcinoma and yolk sac tumour (non seminomatous). [1] Germ-cell tumors may occur in the
testis, retroperitoneum, mediastinum and pineal gland. [1] Reinberg and associates [2] reported that only about 2 to 3 per cent of testicular tumors occur bilaterally. Synchronous and metachronous testicular tumours account for 1% to 5% of all testicular cancer [3], [4], [5].

Synchronous bilateral primary germ cell tumors of the testis are exceedingly rare. The most common synchronous testicular tumors are seminomas, followed by embryonal carcinomas, teratocarcinomas, and choriocarcinomas. [6] In a series of 385 patients Hoestra and associates [6] found nine with bilateral primary germ cell tumors of the testis (2.3%), including one with synchronous involvement of both testes. It has been stated that synchronous bilateral testicular tumors account for about 10% of bilateral tumors [7] Holzbeilerlein and associates [4] also stated that among bilateral testicular tumors, only 5 to 24% occur synchronously and the remaining 7% to 83% are metachronous.

Adham and associates [7] stated that different histology in synchronous bilateral testicular germ cell tumors is extremely rare. Coli and associates [8] stated that most synchronous tumors have an identical histologic diagnosis. Coli and associates’ literature review of 42 reported cases of synchronous bilateral testicular germ cell tumors with different histologic characteristics demonstrated that only six patients presented with concurrent seminomatous and mixed germ cell tumors. In support of this finding, Adham and associates [7] stated that nearly 43 cases of synchronous bilateral germ-cell tumors of the testis have been reported in the literature of which only eight cases were mixed germ-cell tumor with contra-lateral seminoma. In 2009, Suressh and associates [9] reported the ninth case of synchronous bilateral germ-cell tumors with different histology like seminoma with contralateral mixed germ-cell tumour according to their review of the literature.

Seminoma is a malignant germ-cell tumor which is composed of relatively uniform cells with the resemblance of primitive germ cells and with clear cytoplasm, well defined borders, and nuclei with one or more prominent nucleoli. [10]

It has been stated by a number of authors that seminoma is the most common pure germ-cell tumor of the testis which accounts for 35% to 50% of all germ-cell tumors. [10], [11], [12], [13]. The pathogenesis of germ-cell tumors of testis has been linked to primordial germ cells (PGC’s). [14], [15].

The receptor tyrosine Kinase (c-KIT) is necessary for migration and survival of PGC’s and is expressed in intratubular neoplasia germ-cells and seminomas [14], [15]. The mutation frequency of c-KIT exon 17 has been found to be significantly higher in bilateral synchronous seminomas. Biermann and associates [14] stated that this may be responsible for the pathological progression of such tumours.

Patients with seminoma of testis typically present with a self-detected testicular mass which is at times associated with an ill-defined aching sensation in the lower abdomen, inguinal region, or scrotum. [7] The average age of men who present with seminoma is 40.5 years [11]. Ueno and associates [16] stated that an estimated 5% to 25% of men with seminoma of testis have elevated levels of serum β-HCG which is produced by syncytiophoblastic giant cells. Classon and associates [13] stated that the elevated levels of serum β-HCG, is typically not high enough to cause clinical symptoms of gynecomastia.

Howlett and associates [12] stated that:
• Imaging findings of seminomas reflect the uniform cellular configuration of these tumours.
• Ultrasound-scan typically demonstrates a rounded, well-circumscribed, hypo-echoic, and homogenous mass which does not contain significant cystic or calcific foci.
• The tumour which is usually confined to the tunica albuginea is less aggressive than other neoplasms of the testis.

Mixed germ-cell tumors are malignant neoplasms which contain more than one germ-cell tumor component, excluding seminoma with syncytiophoblastic cells. [11] Krag Jacobsen and associates [17] in a study of 1,053 cases found that mixed germ-cell tumors constituted 69% of all non-seminomatous germ-cell tumors and 32% of all testicular germ-cell tumors. Woodward and associates [11] stated that embryonal carcinoma is the most common component and is often combined with teratoma, seminoma, or yolk sac tumor. Patients with these tumors tend to present with testicular enlargement, which is at times associated with pain. The average age of men who present with mixed germ-cell tumours is 30 years, and the tumors rarely occur in patients before they reach puberty. Elevation of serum marker levels is common and is reflective of the individual component of the tumor.

Ulbricht and associates [10] stated that:
• Elevation of α-fetoprotein occurs in 60% of patients, and β-HCG levels are elevated in about 55% of patients.
• The components of the tumor are associated with areas of necrosis, haemorrhage, and cystic degeneration.

In mixed germ-cell tumors the imaging findings are
reflective of their different histologic components.

Ueno and associates [16] stated that:

* Ultrasound-scan typically demonstrates a unilateral, mixed solid and cystic mass.
* The heterogeneous ultra-sonographic appearance is caused by hemorrhage, necrosis, histopathologic heterogeneity, or a combination thereof.
* Calcifications occur in 40% of cases.

For cases of testicular tumours in which the results of physical clinical examination and ultrasound scan are inconclusive magnetic resonance imaging (MRI-scan) has been proposed as a useful diagnostic tool. [18] Cramer and associates [19] stated that even though ultrasound scan is highly sensitive in the detection of testicular masses, it is non-specific for the diagnosis of tumor and detection of a tumor is difficult when the entire testicular parenchyma is replaced by neoplasm, especially when the contra-lateral testis has been removed.

Cramer and associates [19] also stated that:

* Ultrasound-scan does not have sufficient resolution for reliable visualization of the testicular septations and tunica albuginea.
* Magnetic Resonance Imaging provides higher resolution and sensitivity for differentiation of testicular tissue, capabilities which facilitate improved depiction of small tumours that may not be detectable with ultrasound scan.
* Magnetic Resonance Imaging is also useful for differentiating histologic types of testicular tumours.

Thumher and associates [20] stated that:

* Seminoma typically has a nodular appearance and a homogenous-low-signal intensity on T2-weighted images.
* Mixed germ-cell tumours on the contrary, are inhomogeneous in signal intensity, depending upon the histologic components and presence of hemorrhage.
* Magnetic Resonance Imaging is therefore considered to be a useful adjunct for evaluating testicular tumours for which the clinical and ultrasound-scan findings are discrepant, and for further characterization of the tumoral extent.

Some authors have recently stated that the prevalence of bilateral testicular cancer is increasing and postulates which have been put forward to explain this increased prevalence mention the overall improvement in survival and earlier manifestation of testicular cancer in patients [4], [7]. Holzbeierlein and associates [4] reported a study of 58 patients who presented with bilateral testicular tumors at Memorial Sloan Kettering Cancer Center in which the patients with bilateral testicular germ-cell tumours had clinical outcomes similar to those of patients with unilateral tumors when tumor stage was matched.

Coli and associates [8] have postulated that in view of the fact that there are no lymphatic or vascular connections between the testes, synchronous tumors develop independently as two separate primary tumours.

The standard treatment for synchronous bilateral seminoma is bilateral radical orchidectomy for local control and for histological confirmation of the diagnosis [21], rendering the patient infertile and dependent on exogenous androgens, which causes several psychological problems. Nevertheless, there are other possibilities of treatment, such as partial orchidectomy which is feasible in selected cases of small volume testicular tumours in solitary testis / bilateral tumours in men without pre-operative androgen deficiency and who could be the object of close clinical and imaging follow-up. This approach could avoid impairment of additional quality of life, without any prejudice on oncological results.

Because bilateral orchidectomy is associated with severe endocrinologic and psychologic distress chemotherapy and testis-preserving surgery are being considered for patients with early stages of the disease. [8] Heidenreich and associates [22] reported a series of 73 patients with bilateral testicular germ-cell tumors who were treated with testis-preserving surgery and radiotherapy in which 99% of the patients had no evidence of disease after a median follow-up of 7 years. The patients in this series had tumors that were smaller than 15 mm.

There is a lot of heterogeneity in the reported series regarding the management of synchronous bilateral germ cell tumors and only broad generalizations can be made from these. Agrawal and associates [23] have made the following recommendations for the treatment of bilateral synchronous seminomas of testis:

* With regard to the available options for stage 1 patients with seminoma of surveillance, prophylactic para-aortic lymph node irradiation, or one to two cycles of adjuvant chemotherapy, bilateral seminomas have a higher tumour burden and, therefore, these patients should not be kept on surveillance, rather they should be treated with prophylactic para-aortic lymph node irradiation or one to two cycles of adjuvant chemotherapy.
* Patients in Stage II or higher should be treated with chemotherapy.
* For selected patients whose tumors are less than 25 mm confined to the testis and with normal pre-operative testosterone, testis sparing surgery (TSS) to avoid life-long androgen replacement and preservation of fertility should be offered to patients.
Well defined masses equal or larger than 3 cm are poorly defined masses equal or greater than 3 cm. Residual masses smaller than 3 cm as well as for poorly or well defined. Surveillance is indicated for advanced seminoma may be assessed by imaging.

* Residual retroperitoneal masses after chemotherapy transplantation.

Patients who experience salvage chemotherapy vincristine with complete response rate of 83%. Chemotherapy is the choice treatment for advanced stage II disease. Radiotherapy was performed for clinical sub-stage IIA and IIB and chemotherapy for Stage IIC disease. All the patients were followed-up closely. The average age of the patients was 39.3 years (range 28 – 47). The mean follow-up was 88.6 months (range 28 – 232). Clinical stage IIA-IIB was detected in 12 patients (86%) and IIC in 2 (14%). They reported that relapse did not occur in any patient and at the last follow-up all patients were alive and disease-free. Based upon their literature review they made the following concluding statements.

* Radiation therapy is the standard of care in managing seminoma small bulk retroperitoneal disease including sub-stages IIA and IIB. Over-all toxicity of radiotherapy is mild and treatment is well tolerated. After radiotherapy 20% of patients may undergo relapses.

* Chemotherapy is the choice treatment for advanced seminoma presenting with clinical stage IIC – IIB disease; recently it has been advocated for stage IIB when presenting with multiple lymph nodes. Carboplatin and cisplatin are the most effective agents with complete response rates of 89-91%.

* Patients developing progressive disease after first-line chemotherapy undergo combined salvage chemotherapy with cisplatin, ifosfamide, and vincristine with complete response rate of 83%.

* Patients who experience salvage chemotherapy failure are treated with high dose chemotherapy associated with autologous bone marrow transplantation.

* Residual retroperitoneal masses after chemotherapy for advanced seminoma may be assessed by imaging as poorly or well defined. Surveillance is indicated for residual masses smaller than 3 cm as well as for poorly defined masses equal or greater than 3 cm. Well defined masses equal or larger than 3 cm are treated with surgery or radiotherapy.

* Ongoing clinical trials for testicular germ-cell metastatic disease are focused on reducing toxicity without compromising efficacy as well as exploring new salvage strategies and improving survival rates. For many years, the standard treatment for stage 1 testicular seminoma has been radical orchidectomy, followed by adjuvant radiotherapy to the para-aortic and ipsi-lateral pelvic regions. [25], [26], [27]. This approach to the management of stage 1 seminoma of testis has led to a recurrence rate of less than 5%, with salvage chemotherapy being very effective in the management of the few patients that did relapse [25], [26], [27], [28]. Nevertheless, long-term follow-up data of follow-up beyond 10 to 15 years have indicated that treatment-related morbidity and mortality (especially from a second malignancy) have been significant concerns following radiotherapy [28], [29], [30]. A number of approaches have been investigated to minimise the toxicity associated with routine use of radiotherapy. One of these treatment approaches has been to minimise toxicity by reducing radiotherapy field sizes and doses [[31], [32]; and another approach has been to avoid radiotherapy altogether [28]. This change in treatment strategy has, in turn, resulted in the adoption of surveillance after radical orchidectomy as viable option of management because of the general availability of computed tomography (CT) imaging for follow-up evaluations [33]. Another treatment option is the use of single-agent chemotherapy (most commonly 1 to 2 cycles of carboplatin) which has been recognized as a potential option instead of radiotherapy [34], [35], [36]. These various approaches to the management of stage 1 seminoma of testis are focused not only on maintaining high rates of cure, but they have also been aimed at minimising both short-term and long-term toxicity [28], [33], [37].

Williams and Schwartz [38] stated that:

* BEP (Bleomycin, Etoposide, and Platinol) is the most common chemotherapy regimen administered for Germ Cell tumours.

* It is usually administered in 4 cycles.

* Additional agents involved in primary high-risk, and salvage protocols may include ifosfamide and vinblastine.

* Antineoplastic agents that are used in the treatment of testicular seminoma inhibit deregulated cells; these antineoplastic agents include Bleomycin (Benoxane), Etoposide (VP-16), Cisplatin (Platinol, Platinol-AQ), Ifosfamide (Ifex) and Vinblastine (Alkaban-AQ, Velban).

Bleomycin (Benoxane) is composed of cytotoxic
glycopeptides antibiotics, which appear to inhibit DNA synthesis with evidence of RNA and protein synthesis inhibition to a lesser degree. It is used in the management of several neoplasms as a palliative measure. [38]

Etoposide (VP-16) arrests cells in the G2 portion of the cell cycle and induces DNA strand breaks by interacting with DNA topoisomerase II and forming free radicals. [38]

Cisplatin (Platinol, Platinol-AQ) is an inorganic metal complex which is believed to act analogously in alkylating agents and it is thought to inhibit DNA synthesis and thus cell proliferation by causing DNA crosslinks and denaturation of double helix. [38]

Ifosfamide (Ifex) inhibits DNA and protein synthesis and thus cell proliferation by causing DNA cross-linking and denaturation of double helix. [38]

Vinblastin (Alkaban-AQ, Velban) inhibits microtubule formation, which in turn, disrupts the formation of mitotic spindle; thus causing cell proliferation arrest at metaphase. [38]

A number of staging systems that have been used for seminoma of testis include:

* American Joint Committee on Cancer and the International Union against Cancer: Testicular cancer staging system [39] which is illustrated in tables 1, 2 and 3.

* Other staging systems have been discussed by Prow [40].

Conclusions and Recommendations

Synchronous bilateral seminomas of testes are rare. While bilateral radical orchidectomy is the standard practice for patients with synchronous bilateral seminoma, some data support the use of testis sparing techniques to avoid the sequelae of this treatment which include: infertility, dependence on androgen replacement therapy, and the psychological effects of castration.

It would be expected that as a result of education in this modern era all men who notice abnormal lumps in their testes would seek medical attention early but this case illustrates the fact that despite education some men would still present late for medical attention.

Further education is required to encourage patients to report early to their doctors whenever they notice any abnormally palpable lumps in their testes.

Pre-orchidectomy sperm banking should be discussed with patients as well as made available for those patients who have not completed having their children for future use in assisted conception.

References


12. Howlett D C, Marchbank N D. Sallomi D F.
Illustrations

Illustration 1

Ultrasound-scan showing lesions in right testis with two lesions (a small one and a larger lesion)
Illustration 2

Another view of ultrasound-scan showing 3 lesions in right testis
Illustration 3

Another view of Ultrasound-scan showing at least 2 lesions in right testis
Illustration 4

Another view of ultra-sound scan showing lesions in right testis and Doppler flow
Illustration 5

Ultra-sound scan showing low echo-genic lesions in left testis
Illustration 6

Another view of ultra-sound scan showing low echo-genic lesions in left testis and Doppler flow
Illustration 7

Chest X-ray showing bilateral cannon ball metastases in the lungs
Illustration 8

Hematoxylin and Eosin staining of right testicular tumour- X4 Magnification. Section of right testis showing classical seminoma with normal testicular parenchyma at the edge
Illustration 9

Hematoxylin and Eosin staining of right testicular tumour- X 10 Magnification. Classical seminoma in right testis; The tumour cells are showing clear cytoplasm, prominent nucleoli and well-defined cell borders. There is infiltrate of inflammatory cells.
Illustration 10

Haematoxylin and Eosin staining X 20 Magnification. Classical Seminoma in Right Testis
Illustration 11

Haematoxylin and Eosin staining X 10 Magnification. Classical Seminoma in the left testis showing lymphovascular invasion
Illustration 12

Haematoxylin and Eosin Staining X 20 magnification. Classical Seminoma with lymphovascular invasion in left testis
Illustration 13

Table 1

**Primary Tumor (T)**

- pTx Primary tumor cannot be assessed
- pTis Intra-tubular germ cell neoplasia
- pT1 Tumor limited to the testis and epididymis
  - No vascular / lymphatic invasion
  - May invade the tunica albuginea
  - No invasion of tunica vaginalis
- pT2 Tumor limited to the testis and epididymis
  - Vascular / lymphatic invasion or tumor extending through the tunical albuginea with involvement of the tunica vaginalis
  - Invades beyond the tunica albuginea or into the epididymis
- pT3 Tumor invades the spermatic cord with or without vascular / lymphatic invasion
- pT4 Tumor invades the scrotum scrotum with or without vascular / lymphatic invasion
Illustration 14

Table 2a

Regional lymph Nodes (N): Clinical

Nx Nodes not assessed
N0 No regional lymph node metastasis
N1 Lymph node mass or multiple masses ≤ 2 cm in greatest dimension
N2 Lymph node mass or multiple lymph node masses > 2 cm but ≤ 5 cm in greatest dimension
N3 Lymph node mass > 5 cm in greatest dimension
Illustration 15

Table 2b

**Regional Lymph Nodes (N): Pathologic**

PN0 No evidence of tumor in lymph nodes

pN1 lymph node mass ≤ 2 cm in greater dimension ≤ 5 nodes

pN2 Lymph node mass > 2 cm but < 5 cm in greatest dimension > 5 nodes positive;

Evidence of Sextranodi-al extension of tumor

pN3 Lymph node mass > 5 cm in greatest dimension
## Illustration 16

Table 3

<table>
<thead>
<tr>
<th>Distant Metastases (M)</th>
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<tbody>
<tr>
<td>M0 No evidence of distant metastases</td>
</tr>
<tr>
<td>M1a Non regional nodal or pulmonary metastases</td>
</tr>
<tr>
<td>M2b Non-pulmonary visceral metastases</td>
</tr>
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Table 4

**Serum Tumor Markers (S)**

<table>
<thead>
<tr>
<th>S</th>
<th>LDH</th>
<th>+HCG (mIU/mL)</th>
<th>AFP (ng/mL)</th>
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<tbody>
<tr>
<td>Sx</td>
<td>Not assessed</td>
<td>Not assessed</td>
<td>Not assessed</td>
</tr>
<tr>
<td>S0 ≤ N</td>
<td>and Normal</td>
<td>and Normal</td>
<td></td>
</tr>
<tr>
<td>S1 &lt;1.5 x N</td>
<td>and &lt;5,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>S2 1.5 – 10 x N</td>
<td>or 5,000-50,000</td>
<td>or 1,000-10,000</td>
<td></td>
</tr>
<tr>
<td>S3 &gt; 10 x N</td>
<td>or &gt;50,000</td>
<td></td>
<td></td>
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</tbody>
</table>

N = upper limit of normal for LDH assay
+ HCG = human chorionic gonadotropin
**Illustration 18**

**Table 5**

<table>
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<th>Stage Grouping</th>
<th>T</th>
<th>N</th>
<th>M</th>
<th>S</th>
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<td>pTis</td>
<td>N0</td>
<td>M0</td>
<td>S0</td>
</tr>
<tr>
<td>Stage I</td>
<td>T1-T4</td>
<td>N0</td>
<td>M0</td>
<td>Sx</td>
</tr>
<tr>
<td>Stage IA</td>
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<td>M0</td>
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<td>T2-4</td>
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<td>Any T</td>
<td>N2</td>
<td>M0</td>
<td>S0-S1</td>
</tr>
<tr>
<td>Stage IIC</td>
<td>Any T</td>
<td>N3</td>
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<td>S0-S1</td>
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<td>Any N</td>
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