Mature and Immature Teratoma: A Review of Pathological Characteristics and Treatment Options

David Wetherell1*, Mahesha Weerakoon1, David Williams2, Bhawanie Koonj Beharry1, Ania Sliwinski1, Darren Ow1, Kiran Manya1, Damien MBolton1 and Nathan Lawrentschuk1,3

1Department of Surgery, University of Melbourne, Urology Unit, Austin Hospital, Heidelberg, Victoria, Australia
2Department of Anatomical Pathology, Austin Hospital, Heidelberg, Victoria, Australia
3Ludwig Institute for Cancer Research, Austin Hospital, Heidelberg, Victoria, Australia

Abstract
Testicular teratoma is a sub-type of Non-Seminomatous Germ Cell Tumour (NSGCT) and often occurs in two distinct age groups. Adult testicular teratomas are often mixed and are malignant. Teratoma can be divided histologically into mature and immature. Pure mature teratoma of the testis is rare. Intratubular Germ Cell Neoplasia (ITGCN) is a common feature associated with teratoma. Teratoma is frequently chemoresistant and clinical management of these tumours includes radical inguinal orchidectomy followed by Retroperitoneal Lymph Node (RPLND) dissection if indicated. Long-term oncological outcomes for mature and immature testicular teratoma are equivocal.

Keywords: Testis; Testicular cancer; Teratoma; Mature teratoma; Immature teratoma

Introduction
Testicular teratoma is a sub-type of Non-Seminomatous Germ Cell Tumours (NSGCT) of the testis. Gonadal germ cell tumours (GCT) can be diagnostically challenging for pathologists and correct classification has a major implication on prognosis and therapeutic treatment [1].

Teratoma is a GCT that predominantly occurs in the gonads: the testis and ovaries. They contain well-differentiated or incompletely differentiated elements of at least two germ cell layers (endoderm, ectoderm and/or mesoderm). Mature teratomas are well differentiated relative to the germ cell layers. Immature teratomas are incompletely differentiated and are similar to foetal or embryonic tissue [2]. This article discusses and summaries the pertinent features of mature and immature teratomas of the testis and their significance.

Discussion
Teratomas are the second most common neoplasm in children following yolk sac tumour and occur with a relative frequency ranging from 13 to 19% [3,4]. Two distinctive groups of testicular teratomas occur according to age: pre and post-pubertal. Pure teratomas (non-mixed) are common in the paediatric sub-group, however these are rare in adults. A mixed variant neoplasm is more commonly seen in adults. Mature pre-pubertal teratomas are benign and represent approximately 30% of testicular germ cell tumours in children [5]. Post-pubertal (adult) testicular teratomas are malignant. Malignant testicular teratomas have a higher metastasis rate of 20% as opposed to their ovarian counterparts [6]. Pure teratoma in the testis is rare accounting for 4% of GCTs in the ovary [1]. As previously mentioned, teratomatous features are more commonly found in mixed GCTs than pure teratoma, and are apparent in approximately 50% of these tumours [1].

Clinical presentation and diagnosis
Clinical presentation of teratoma is similar to other neoplasms of the testis. Teratoma, both mature and immature, often present clinically as a painful testicular mass [7]. The presenting symptom of testicular pain can be attributed to haemorrhage and haematoama formation and thus the pressure applied to the testicle during tumour formation [8]. Teratomas are renowned for their rapid growth and highly vascultic nature compared to seminoma. These tumours are often discovered incidentally or indirectly during the assessment of testicular trauma as an initial presenting complaint. They can be present for some time prior to detection, as is the case with most testicular masses.

Examination findings for teratoma are usually consistent with those for a suspected testicular neoplasm. On examination atrophy of the affected or contralateral testis is common and a palpable firm mass within the testis is suggestive of malignancy. An associated hydrocele may be present. For teratomas, which cannot be distinguished clinically from other tumours, the patient workup should be the same as would be for the evaluation of any other suspicious testicular masses. Thoracic abdominal examination specifically for masses or tenderness, inguinal and supraclavicular lymphadenopathy, gynecomastia and chest auscultation for evidence of metastatic disease should be performed [9].

Both mature and immature teratomas are generally associated with normal testicular tumour markers: Beta Human Chorionic Gonadotropin (B-hCG) and Alpha Feto-Protein (aFP). Occasionally some exhibit mildly elevated aFP levels. On sonographic evaluation, teratomas typically demonstrate the appearance of cystic areas with intervening septa and solid areas. The presence of calcifications in the tumour is another helpful sonographic finding associated with teratomas, however, diagnosis can only be confirmed by pathologic evaluation [4]. To evaluate for metastatic disease a staging CT thorax and abdomen is recommended in all cases of testicular cancer [7]. Up to 10% of patients present with subpleural nodes, which are not detectable by conventional chest radiograph [8]. There is no evidence for fluorodeoxyglucose-PET (FDG-PET) imaging in the staging of testicular cancer [9].

Genetics of testicular teratomas
Pre-pubertal teratomas are diploid, often lack chromosomal

*Corresponding author: Dr David Wetherell, Department of Surgery, University of Melbourne, Urology Unit, Austin Hospital, Room 8244, Level 8, Harold-Stokes Building, Austin Hospital, 145 Studley Road, Heidelberg, Victoria 3141, Australia, Tel: +61 3 9496 5458; Fax: +61 3 9496 3617; E-mail: dwetherell@doctors.org.uk

Received November 13, 2013; Accepted January 27, 2014; Published January 29, 2014

Citation: Wetherell D, Weerakoon M, Williams D, Beharry BK, Sliwinski A, et al. (2014) Mature and Immature Teratoma: A Review of Pathological Characteristics and Treatment Options. Med Surg Urol 3: 124. doi:10.4172/2168-9857.1000124

Copyright: © 2014 Wetherell D, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.
imbalances and do not exhibit isochromosome formation (i(12p)) [10,11]. In contrast, adult teratomas, most of which are mixed type, are hypotriploid and are associated with chromosomal abnormalities. A prominent genetic feature of testicular GCTs is the acquisition and over representation of 12p sequences. Gain of one or more of these genes on 12p is crucial in the development of testicular GCTs [12]. Other genetic changes found in a quarter of these tumours include: partial loss of chromosome 13 (particularly q31) and gain of chromosome 7 (particularly q11), chromosome 8 and the X chromosome [13].

Macroscopic and microscopic features

Mature post-pubertal teratomas have a macroscopic appearance of solid testicular tumours. Microscopically mature teratomas have a disordered arrangement and demonstrate cytological atypia [1]. Adjacent seminiferous tubules often display carcinoma in situ or intratubular germ cell neoplasia (ITGCN) in up to 90%, which is associated with malignant potential. Pre-pubertal teratomas, which are benign tumours, are seldom associated with ITGCN. There is frequently widespread testicular atrophy and absent spermatogenesis [14]. As teratomas are germ cell tumours they can host a variety of non-tumour native tissues. For instance, in mature ovarian teratomas choroid plexus, thyroid and pituitary tissue can be present, with the latter manifesting systemically as prolactinomas [15]. In mature testicular tumours however, this non-tumour native tissue is seen less frequently.

Pure adult testicular teratomas are rare and around a third are mixed GCTs. The occurrence of mixed teratoma GCTs can be attributed to the pathogenesis whereby malignant germ cells (ITGCN) differentiate into non-teratomatous cells prior to the formation of teratomatous elements [1]. This accounts for the association of ITGCN seen in pure teratomas, as well as metastases of non-teratomatous cell types.

The diagnosis of immaturity for a teratoma requires tissue resembling embryonic origin, in particular the appearance of neuroepithelium [1]. However, the presence of this tissue or ‘immaturity’ of a post-pubertal testicular teratoma is not significant. Some pathologists believe that the teratomas should not be classified as mature or immature due to they having the same genetic changes and biological potential, in both pre and post-pubertal populations [15]. As mentioned previously, the pathogenesis of testicular teratoma is that malignant transformation occurs prior to teratomatous differentiation. Hence the further immature differentiation of teratomatous tissue is irrelevant, as the malignant process has occurred earlier [1].

Primitive Neuro ectodermal Tumour (PNET) is diagnosed in the presence of an overgrowth of immature neural elements in teratomas [1]. Extra testicular PNETs from GCTs as a result of metastatic spread are frequently resistant to chemotherapy and are associated with a high rate of mortality [16]. Despite testicular teratomas having malignant behaviour in the absence of excess neural tissue (i.e. PNET), the presence of this tissue does have a negative prognostic value [1].

Associated tumours: dermoid and epidermoid cysts

Testicular dermoid cysts are rare lesions and whether these should be classed as a variant of mature teratoma is still under discussion [17]. Epidermoid cysts represent 1% of all testicular tumours but whether they are true neoplasms still remains a topic of debate [18]. Testicular dermoid cysts are synonymous with the features of ovarian dermoid cysts. Their macroscopic appearance is of a cystic tumour often containing grossly identifiable hair [19]. In contrast to mature post-pubertal teratomas, these lesions often occur in a testis with normal spermatogenesis and lack of atrophy. They lack adjacent ITGCN and cytological atypia, which are microscopic features of mature post-pubertal teratomas [18]. Lipogranuloatous reaction in the testicular parenchyma and pilosebaceous cyst arrangement is diagnostically characteristic of testicular dermoid cysts [1]. Epidermoid cysts are similarly not associated with ITGCN and lack atypia and mitotic activity [14] (Figures 1-3).

Treatment and Outcomes

Low- stage (Stage I)

Only 2 to 6% of NSCGT consist of pure teratoma in adults. As previously discussed, mature pre-pubertal teratoma has a benign clinical course, however in adults metastases for both mature and immature teratoma have been reported in 13 to 60% of cases at initial presentation [4,19,20]. The standard treatment for all testicular tumours (GCTs) in adults is radical inguinal orchidectomy. Retroperitoneal metastasis has been identified in approximately 20 to 30% of patients with clinical stage I pure testicular teratoma treated by primary Retroperitoneal Lymph Node Dissection (RPLND) [6,20]. However, RPLND is still controversial in patients with clinical stage I pure teratoma. The adjuvant treatment options remain RPLND or surveillance, however as previously stated around a quarter of these patients will have retroperitoneal metastasis and increased to 75% for patients with clinical stage IIA disease. The teratomatous component of GCTs is particularly resistant to chemotherapy, which is often an

Figure 1: Mature teratoma (H&E, 40x) showing squamous epithelium (left upper) and enteric glandular epithelium (bottom right).

Figure 2: Mixed mature (right) and immature (left) teratoma (H&E 40x), including nodules of immature cartilage (centre, bottom and left).
immature teratoma, should be assessed and stratified on a clinical
disease [20]. All advanced (stage III) NSGCTs, including mature and
combination with surgical excision of residual mass (e.g. teratoma)
chemotherapy is required to kill the chemosensitive components in
mature and immature teratoma, are often mixed cell type therefore
recommended for the treatment of NSGCTs. These tumours, including
discussion needs to be taken between patient and clinician with regards
rate [6]. The side effects of either treatment are different, thus extensive
outcomes post RPLND and chemotherapy are equivocal with 98% cure
with adjuvant PEB (2 cycles) in the case of metastatic disease. The
Patients refusing to undergo primary chemotherapy may have RPLND
the chemotherapy of choice as per the IGCCCG guidelines [7,23,24].
[7]. If tumour markers are also raised, then chemotherapy is the
initial indication; with PEB (cisplatin, etoposide, bleomycin) being
[7]. There is a general consensus that patients with advanced
stage NSGCT can be managed with chemotherapy except for stage II
NSGCT disease without elevated tumour markers; this subgroup can
be alternatively treated with RPLND or surveillance. If surveillance
is chosen, patients should be scheduled for review six weeks post-
diagnosis specifically looking for disease progression. Growth of the
lesion without a respective raise in tumour markers suggests teratoma
or other malignant transformation and RPLND is highly recommended
[7]. If tumour markers are also raised, then chemotherapy is the
initial indication; with PEB (cisplatin, etoposide, bleomycin) being
the chemotherapy of choice as per the IGCCCG guidelines [7,23,24].
Patients refusing to undergo primary chemotherapy may have RPLND
with adjuvant PEB (2 cycles) in the case of metastatic disease. The
outcomes post RPLND and chemotherapy are equivocal with 98% cure
rate [6]. The side effects of either treatment are different, thus extensive
discussion needs to be taken between patient and clinician with regards
to treatment options.

Seminomas are radiosensitive hence Radiotherapy (RT) is an
effective treatment for stage I and IIA-B disease. However, RT is not
recommended for the treatment of NSGCTs. These tumours, including
mature and immature teratoma, are often mixed cell type therefore
chemotherapy is required to kill the chemosensitive components in
combination with surgical excision of residual mass (e.g. teratoma)
[25].

Advanced stage (Stage IIC and III)

Around 37% of patients with pure teratoma present with advanced
disease [20]. All advanced (stage III) NSGCTs, including mature and
immature teratoma, should be assessed and stratified on a clinical
basis into either favourable-risk or intermediate/poor risk group.
Recommended treatment for the favourable risk group is at least
three cycles of adjuvant chemotherapy (PEB). These patients should
all undergo restaging following primary chemotherapy and if there
is complete remission resection is not indicated [26]. The extent of
resection of residual masses (e.g. RPLND or wedge lung resection)
should also take into account individual patient and quality of life
factors [7]. The histological diagnosis should not influence the
treatment course in stage III disease and in general all advanced stage
NSGCTs, including pure teratoma, should be treated according to the
same pathway as described above [7,20].

The Impact of teratoma in Mixed NSGCTs

Teratoma in adults frequently presents as a mixed type tumour,
with yolk sac or embryonal sac tumour in 50% of cases [6]. The
impact of teratomatous elements in orchidectomy specimens has been
investigated to detail. Currently, evidence shows a correlation between
teratoma within the orchidectomy specimen with an increased
likelihood of teratoma in the post chemotherapy RPLND specimen
with a current rate of 20% of teratomatous elements found in primary
RPLND and 40% of teratomatous elements in patients undergoing
RPLND post chemotherapy [19-21]. On the contrary, the absence of
teratoma in the retroperitoneum is not suggested if teratoma is not
present in the orchidectomy specimens [6,21].

Mature teratoma is found in approximately 35 to 40% of primary
chemotherapy RPLND (PC-RPLND) specimens for advanced NSGCT
[27]. One study by Steyerberg et al. analysed 556 RPLND specimens
post-chemotherapy for NSGCTs and found mature teratoma in 42%
and that a teratoma negative primary tumour was a strong predictor
of necrosis in the PC-RPLND specimen [28]. Currently there is no
imaging modality that accurately distinguish between necrosis, viable
cancer or teratoma in patients treated with chemotherapy for NSGCTs
[29].

Retroperitoneal teratoma in NSCGT treated with primary
chemotherapy (<1 cm)

Serologic and radiographic complete response to first line
chemotherapy (defined as a residual transverse axial lesion on CT
less than 1 cm) is achieved in 26 to 64% of patients with advanced
NSGCT [27]. These patients are considered to be in a low-risk group,
however, some centers still recommend RPLND following primary
chemotherapy from a rationale that radiographic estimation of the size
of residual nodal tissue following primary chemotherapy is unreliable.
This remains a controversial topic and in particular the lack of imaging
criteria and consensus on nodal size criteria [27]. A study by Oldenburg
et al. of 87 RPLND patients post-chemotherapy showed that 30% with
lymph nodes <1 cm had viable tumour present (20% teratoma and 10%
malignant tumour) [30]. The European Germ Cell Consensus
group and recent literature recommends that patients who achieve
remission, defined as residual retroperitoneal lesion <1 cm, can be
safely observed [31-34].

Retroperitoneal teratoma in NSCGT treated with primary
chemotherapy (>1 cm)

Retroperitoneal lymph-node dissection should be performed
for radiographic masses >1cm post-chemotherapy for NSGCTs [27].
Loehrer et al. reported on 51 patients who had surgical resections of
teratoma after cisplatin-based chemotherapy. In this study twenty
patients (39%) experienced relapse with either histologically proven
teratoma (10 patients) or viable GCT (10 patients) [35]. Sonneveled
et al. reported on 51 patients with retroperitoneal teratoma after chemotherapy for NSGCT [36]. In their series, nine patients experienced a relapse, with growing mature teratoma in 56%, teratoma with malignant transformation in 33%, and viable GCT in 11%. Another contemporary cohort of 210 patients by Carver et al. with only pure teratomatous elements at post chemotherapy RPLND revealed mature teratoma in 178 patients (85%), immature teratoma in 15 patients (7%) and teratoma with malignant transformation in 17 patients (8%) [21]. Of the 193 patients with mature or immature teratoma, 24 patients (12%) experienced relapse after post chemotherapy RPLND and two patients experienced relapse with teratoma with malignant transformation. For men relapsing with only teratomatous histology, the most common sites of relapse were retro-cruetal and pulmonary in seven and four patients respectively. Other recurrence sites include liver, pelvis, neck and para-aortic [21]. Patients with teratoma with malignant transformation are known to have a poorer prognosis and attempted resection of the primary site of recurrence remains the treatment of choice due to the poor sensitivity of these tumours to chemotherapy [21].

Oncological outcomes

As previously discussed, the oncological outcomes for teratoma pre and post chemotherapy RPLND are determined by the IGCCCG staging and grading of severity. Significant predictors for increased risk of disease recurrence include higher pre and post chemotherapy nodal size, intermediate or poor IGCCG risk classification and evidence of malignant transformation [21]. Of particular note, histological findings of immature teratoma, when compared to mature teratoma did not increase the risk of disease recurrence [37]. However, mature teratoma in the PC-RPLND specimen is commonly associated with late relapse [36,38]. Overall, the oncological outcomes for immature and mature teratoma remain equivocal as per IGCCCG staging and degree of severity.

Conclusion

In adults mixed GCTs with teratomatous elements are more common than pure teratoma. Mature and immature teratomas in the post-pubertal setting and often exhibit malignant behavior. Distinction between mature and immature teratoma is made histologically, with the latter closely resembling foetal or embryonic tissue. The biological behaviour of immature teratoma is identical to that of mature teratoma. RPLND for patients with clinical stage I pure teratoma is still controversial. Treatment of metastatic testicular teratomas is complex but is often primary chemotherapy followed by RPLND or surveillance and is guided clinically. However, teratomas are resistant and therefore often respond poorly to chemotherapy. Long-term oncological outcomes are equivocal for both mature and immature teratoma.

References

1. Ulbright TM (2005) Germ cell tumors of the gonads: a selective review emphasizing problems in differential diagnosis, newly appreciated, and controversial issues. Mod Pathol 18 Suppl 2: S61-79.
2. McDougal WS, Wein AJ, Kavoussi LR, Novick AC, Partin AW, et al. (2012) Campbell-Walsh Urology. (10thedn). Elsevier Saunders, USA.
3. Bromman SA (1979) Testicular tumors in prepubertal children. Urology 13: 581-588.
4. Simmonds PD, Lee AH, Theaker JM, Tung K, Smart CJ, et al. (1996) Primary pure teratoma of the testis. J Urol 155: 939-942.
5. Grady RW, Ross JH, Kay R (1997) Epidemiological features of testicular teratoma in a prepubertal population. J Urol 158: 1191-1192.
6. Carver BS, Al-Ahmadi H, Sheinfeld J (2007) Adult and pediatric testicular teratoma. Urol Clin North Am 34: 245-251.
7. Albers P, Albrecht W, Albaga F, Bokemeyer C, Cohan-Cedermark G, et al. (2011) EAU guidelines on testicular cancer: 2011 update. Eur Urol 60: 304-319.
8. See WA, Hoxie L (1993) Chest staging in testis cancer patients: imaging modality selection based upon risk assessment as determined by abdominal computerized tomography scan results. J Urol 150: 874-878.
9. de Wit M, Brenner W, Hartmann M, Kolitzer J, Hellwig D, et al. (2008) [18F]-FDG-PET in clinical stage I non-seminomatous germ cell tumours: results of the German multicentre trial. Ann Oncol 19: 1619-1623.
10. Silver SA, Wiley JM, Perlman EJ (1994) DNA ploidy analysis of pediatric germ cell tumors. Mod Pathol 7: 951-956.
11. Mostert M, Rosenberg C, Stoop H, Schuyer M, Timmer A, et al. (2000) Comparative genomic and in situ hybridization of germ cell tumors of the infantile testis. Lab Invest 80: 1055-1064.
12. Mostert MC, Verkerk AJ, van de Pol M, Heighway J, Maryn L, et al. (1998) Identification of the critical region of 12p over-representation in testicular germ cell tumors of adolescents and adults. Oncogene 16: 2617-2627.
13. Mostert MM, van de Pol M, Olde Weghuis D, Suijkerbuijk RF, Geurts van Kessel A, et al. (1998) Comparative genomic hybridization of germ cell tumors of the adult testis: confirmation of karyotypic findings and identification of a 12p- amplon. Cancer Genet Cytogenet 89: 146-152.
14. Manivel JC, Reinberg Y, Niehans GA, Fraley EE (1989) Intraabdominal germ cell neoplasia in testicular teratomas and epidermoid cysts. Correlation with prognosis and possible biologic significance. Cancer 64: 715-720.
15. Sesterhenn IA, Davis CJ Jr (2004) Pathology of germ cell tumors of the testis. Cancer Control 11: 374-387.
16. Michael H, Hull MT, Ulbright TM, Foster RS, Miller KD (1997) Primitive neuroectodermal tumors arising in testicular germ cell neoplasms. Am J Surg Pathol 21: 896-904.
17. Ulbright TM, Sriringle J (2001) Dermoid cyst of the testis: a study of five postpubertal cases, including one pilomatrixoma-like variant, with evidence supporting its separate classification from mature testicular teratoma. Am J Surg Pathol 25: 788-793.
18. Price EB Jr (1969) Epidermoid cysts of the testis: a clinical and pathologic analysis of 69 cases from the testicular tumor registry. J Urol 102: 706-713.
19. Rabban F, Farivar-Mohseni H, Leon A, Motzer RJ, Bosl GJ, et al. (2003) Clinical outcome after retroperitoneal lymphadenectomy of patients with pure testicular teratoma. Urology 62: 1092-1096.
20. Leibovitch I, Foster RS, Ulbright TM, Donohue JP (1995) Adult primary pure teratoma of the testis. The Indiana experience. Cancer 75: 2244-2250.
21. Carver BS, Shayegan B, Serlo A, Motzer RJ, Bosl GJ, et al. (2007) Long-term clinical outcome after postchemotherapy retroperitoneal lymph node dissection in men with residual teratoma. J Clin Oncol 25: 1033-1037.
22. Mead GM, Stening SP (1997) The International Germ Cell Consensus Classification: a new prognostic factor-based staging classification for metastatic germ cell tumours. Clin Oncol (R Coll Radiol) 9: 207-209.
23. Peckham MJ, Hendry WF (1985) Clinical stage II non-seminomatous germ cell testicular tumours. Results of management by primary chemotherapy. Br J Urol 57: 763-768.
24. Horwich A, Norman A, Fisher C, Hendry WF, Nicholls J, et al. (1994) Primary chemotherapy for stage II nonseminomatous germ cell tumors of the testis. J Urol 151: 72-77.
25. Shin YS, Kim HJ (2013) Current management of testicular cancer. Korean J Urol 54: 2-10.
26. Droz JP, Rivoire M (2001) Advanced testis cancer. Curr Treat Options Oncol 2: 421-429.
27. Daneshmand S, Albers P, Fossa SD, Heidenreich A, Kolmannsberger C, et al. (2012) Contemporary management of postchemotherapy testis cancer. Eur Urol 62: 867-876.
28. Seyerberg EW, Keizer HJ, Fossa SD, Steijler DT, Toner GC, et al. (1995) Prediction of residual retroperitoneal mass histology after chemotherapy for metastatic nonseminomatous germ cell tumor: Multivariate analysis of individual patient data from six study groups. J Clin Oncol 13: 1177-1187.
29. Daneshmand S, Djiladat H, Nichols C (2011) Management of residual mass in nonseminomatous germ cell tumors following chemotherapy. Ther Adv Urol 3: 163-171.
30. Oldenburg J, Alfsen GC, Lien HH, Aass N, Waehre H, et al. (2003) Postchemotherapy retroperitoneal surgery remains necessary in patients with nonseminomatous testicular cancer and minimal residual tumor masses. J Clin Oncol 21: 3310-3317.

31. Ehrlich Y, Brames MJ, Beck SD, Foster RS, Einhorn LH (2010) Long-term follow-up of cisplatin combination chemotherapy in patients with disseminated nonseminomatous germ cell tumors: is a postchemotherapy retroperitoneal lymph node dissection needed after complete remission? J Clinical Oncol 28: 531-536.

32. Krege S, Beyer J, Souchon R, Albers P, Albrecht W, et al. (2008) European consensus conference on diagnosis and treatment of germ cell cancer: a report of the second meeting of the European Germ Cell Cancer Consensus group (EGCCCG): part I. Eur Urol 53: 478-496.

33. Kollmannsberger C, Daneshmand S, So A, Chi KN, Murray N, et al. (2010) Management of disseminated nonseminomatous germ cell tumors with risk-based chemotherapy followed by response-guided postchemotherapy surgery. J Clin Oncol 28: 537-542.

34. Zuniga A, Kakiashvili D, Jewett MA (2009) Surveillance in stage I nonseminomatous germ cell tumours of the testes. BJU Int 104: 1351-1356.

35. Loehrer PJ Sr, Hui S, Clark S, Seal M, Einhorn LH, et al. (1986) Teratoma following cisplatin-based combination chemotherapy for nonseminomatous germ cell tumors: a clinicopathological correlation. J Urol 135: 1183-1189.

36. Sonneveld DJ, Sleijfer DT, Koops HS, Keemers-Gels ME, Molenaar WM, et al. (1998) Mature teratoma identified after postchemotherapy surgery in patients with disseminated nonseminomatous testicular germ cell tumors: a plea for an aggressive surgical approach. Cancer 82: 1343-1351.

37. Comiter CV, Kibel AS, Richie JP, Nucci MR, Renshaw AA (1998) Prognostic features of teratomas with malignant transformation: a clinicopathological study of 21 cases. J Urol 159: 859-863.

38. Ehrlich Y, Daniel J (2007) Late relapse of testis cancer. Urol Clin North Am 34: 253-258.