

*This practice algorithm has been specifically developed for MD Anderson using a multidisciplinary approach and taking into consideration circumstances particular to MD Anderson, including the following: MD Anderson's specific patient population; MD Anderson's services and structure; and MD Anderson's clinical information. Moreover, this algorithm is not intended to replace the independent medical or professional judgment of physicians or other health care providers.*

## TABLE OF CONTENTS

Suspicious Testicular Cancer .....	Page 2
Nonseminomatous Germ Cell Tumor (NSGCT): workup and clinical stage .....	Page 3
Seminoma: workup and clinical stage .....	Page 4
Clinical Stage I Nonseminoma: post-orchietomy management.....	Page 5
Clinical Stage I Pure Seminoma: post-orchietomy management.....	Page 6
Stage IIA, IIB, IIC Nonseminoma: post-orchietomy management.....	Page 7
Stage IIIA, IIIB Nonseminoma: post-orchietomy management.....	Page 8
Stage IIIC (poor prognosis) Nonseminoma: initial management .....	Page 9
Seminoma: treatment and follow-up .....	Page 10
Management for Advanced Seminoma .....	Page 11
Nonseminoma: post-chemotherapy management .....	Page 12
Nonseminoma Surveillance .....	Page 13
Nonseminoma Post-chemotherapy Recurrence .....	Page 14
APPENDIX A: International Classifications for Germ Cell Cancer .....	Page 15
Suggested Readings .....	Page 16
Development Credits .....	Page 17

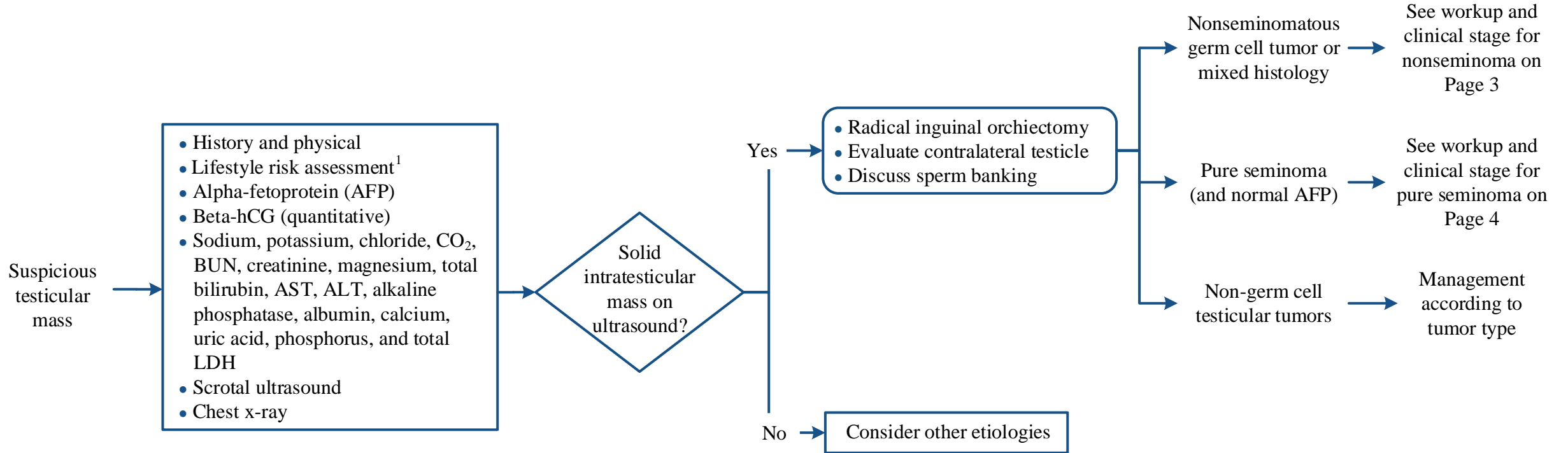
*This practice algorithm has been specifically developed for MD Anderson using a multidisciplinary approach and taking into consideration circumstances particular to MD Anderson, including the following: MD Anderson's specific patient population; MD Anderson's services and structure; and MD Anderson's clinical information. Moreover, this algorithm is not intended to replace the independent medical or professional judgment of physicians or other health care providers.*

**Note:** Consider Clinical Trials as treatment options for eligible patients.

## CLINICAL PRESENTATION

## INITIAL EVALUATION

## TUMOR HISTOLOGY



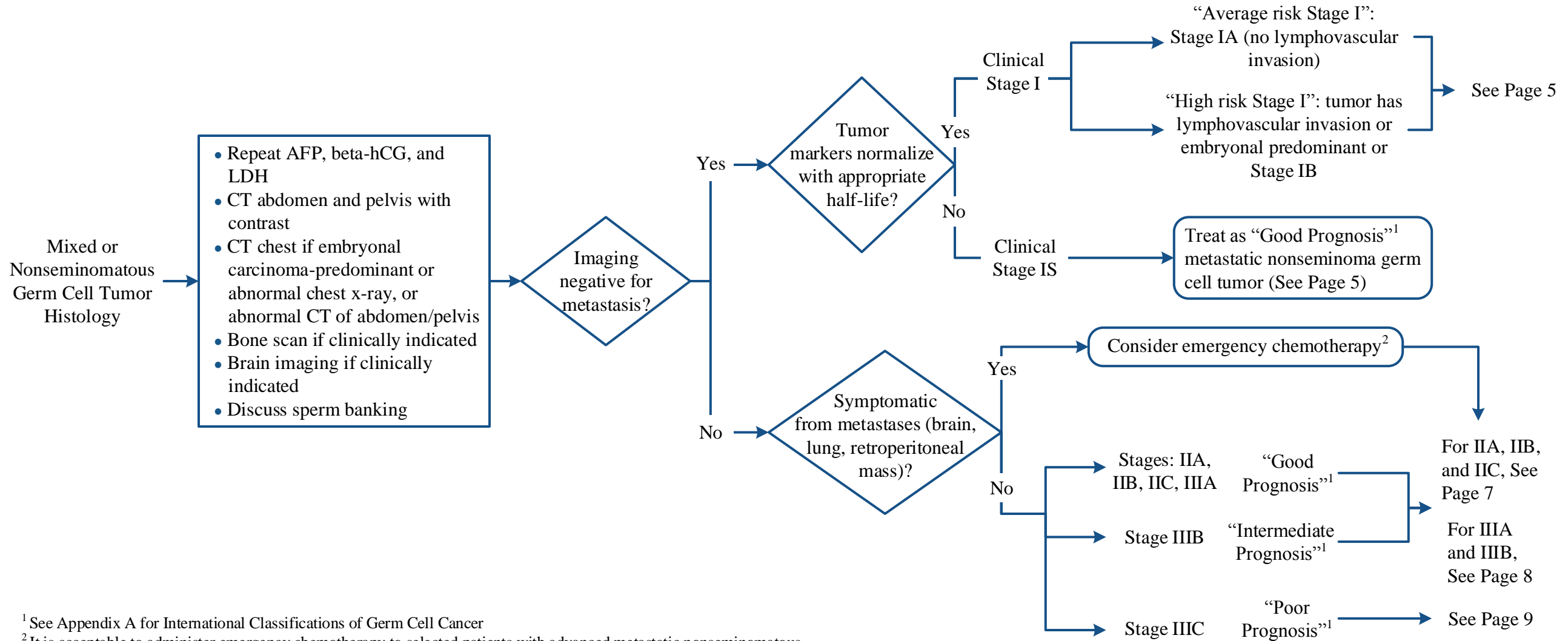
<sup>1</sup>See Physical Activity, Nutrition, and Tobacco Cessation algorithms; ongoing reassessment of lifestyle risks should be a part of routine clinical practice

This practice algorithm has been specifically developed for MD Anderson using a multidisciplinary approach and taking into consideration circumstances particular to MD Anderson, including the following: MD Anderson's specific patient population; MD Anderson's services and structure; and MD Anderson's clinical information. Moreover, this algorithm is not intended to replace the independent medical or professional judgment of physicians or other health care providers.

**Note:** Consider Clinical Trials as treatment options for eligible patients.

### HISTOLOGY

### FURTHER WORK-UP



<sup>1</sup> See Appendix A for International Classifications of Germ Cell Cancer

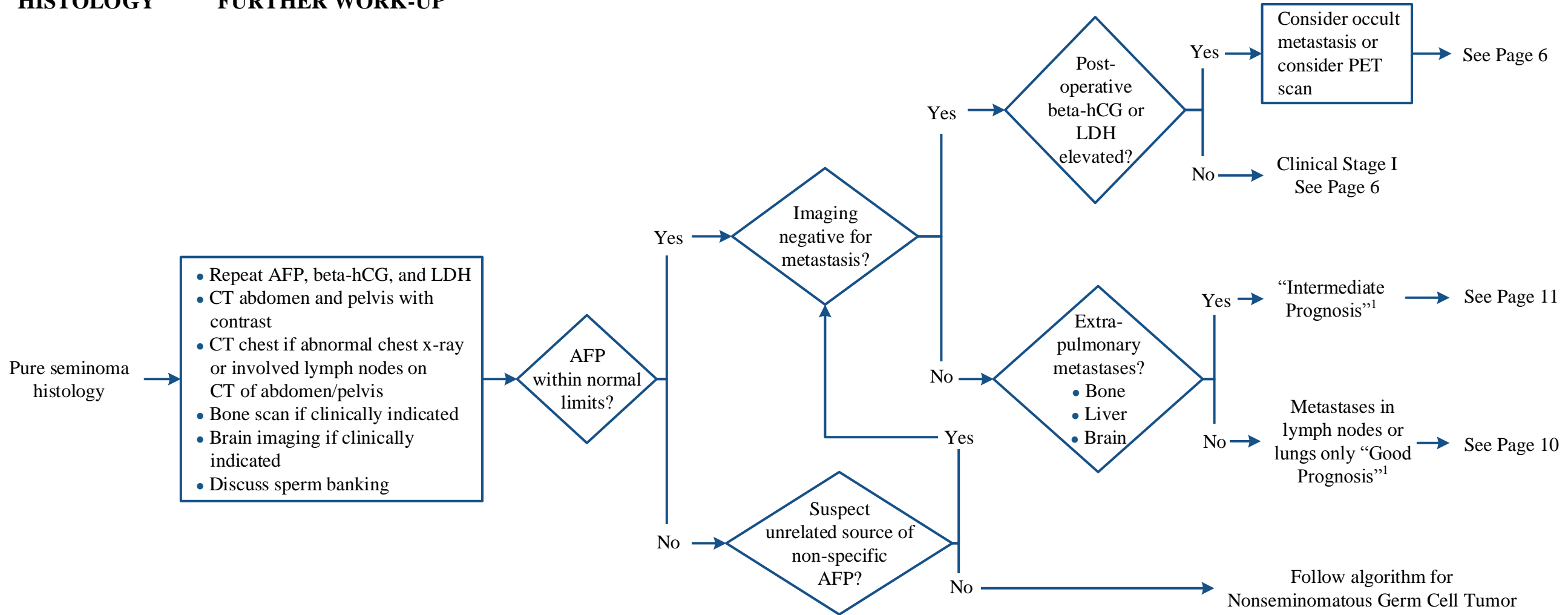
<sup>2</sup> It is acceptable to administer emergency chemotherapy to selected patients with advanced metastatic nonseminomatous germ cell tumor on the basis of clinical presentation before orchiectomy, and without a tissue diagnosis.

This practice algorithm has been specifically developed for MD Anderson using a multidisciplinary approach and taking into consideration circumstances particular to MD Anderson, including the following: MD Anderson's specific patient population; MD Anderson's services and structure; and MD Anderson's clinical information. Moreover, this algorithm is not intended to replace the independent medical or professional judgment of physicians or other health care providers.

**Note:** Consider Clinical Trials as treatment options for eligible patients.

### HISTOLOGY

### FURTHER WORK-UP



<sup>1</sup> See Appendix A for International Classifications of Germ Cell Cancer

This practice algorithm has been specifically developed for MD Anderson using a multidisciplinary approach and taking into consideration circumstances particular to MD Anderson, including the following: MD Anderson's specific patient population; MD Anderson's services and structure; and MD Anderson's clinical information. Moreover, this algorithm is not intended to replace the independent medical or professional judgment of physicians or other health care providers.

**Note:** Consider Clinical Trials as treatment options for eligible patients.

### TUMOR MARKERS

- Any pT/Tx
- N0
- M0
- S1-3

Stage IS:

- Beta-hCG or AFP elevated
- Metastatic workup negative

Consider sperm banking

### MANAGEMENT OPTIONS

- 3 cycles BEP<sup>2</sup> **or**
- 4 cycles etoposide and cisplatin

See Page 12 for post-chemotherapy management

- Any pT/Tx
- N0
- M0
- S0

High risk features<sup>1</sup>?

Yes

High Risk – probability of recurrence is approximately 50%

- Consider sperm banking

No

Average Risk – probability of recurrence is approximately 30%

- Consider sperm banking

Embryonal carcinoma predominant?

Yes

- Consider management options:
- Surveillance (in compliant patients, pT1-2) **or**
  - Adjuvant chemotherapy (1-2 cycles BEP<sup>2</sup>)

No

- Consider management options:
- Surveillance (in compliant patients, pT1-2)
  - Prophylactic RPLND
  - Adjuvant chemotherapy (1-2 cycles BEP<sup>2</sup>)

- Consider management options:
- Surveillance (in compliant patients)
  - Prophylactic RPLND

See appropriate surveillance schedule based on treatment

<sup>1</sup> High Risk Features (in the primary tumor):  
 a. Lymphovascular invasion  
 b. Invasion of tunica vaginalis  
 c. Invasion of spermatic cord or scrotum (pT3-4)  
 d. Embryonal carcinoma predominant

<sup>2</sup> Medical oncologist should discuss options with patient based on clinical data  
 BEP = bleomycin, etoposide, and cisplatin  
 RPLND = retroperitoneal lymph node dissection

This practice algorithm has been specifically developed for MD Anderson using a multidisciplinary approach and taking into consideration circumstances particular to MD Anderson, including the following: MD Anderson's specific patient population; MD Anderson's services and structure; and MD Anderson's clinical information. Moreover, this algorithm is not intended to replace the independent medical or professional judgment of physicians or other health care providers.

**Note:** Consider Clinical Trials as treatment options for eligible patients.

### TUMOR MARKERS

### MANAGEMENT OPTIONS

- Any pT/Tx
- N0
- M0
- S1-3

Stage IS:

- Beta-hCG or AFP elevated
- Metastatic workup negative

Consider sperm banking

- Any of the following?
- Horseshoe or pelvic kidney
  - Inflammatory bowel disease
  - Prior radiotherapy

Consider management options:  
 Surveillance **or** single-dose carboplatin AUC = 7 **or** AUC = 7 x 2 cycles for all others

See appropriate surveillance schedule based on treatment

- Any pT/Tx
- N0
- M0
- S0

Primary tumor greater than 4 cm or pT3-4 ?

Yes  
No

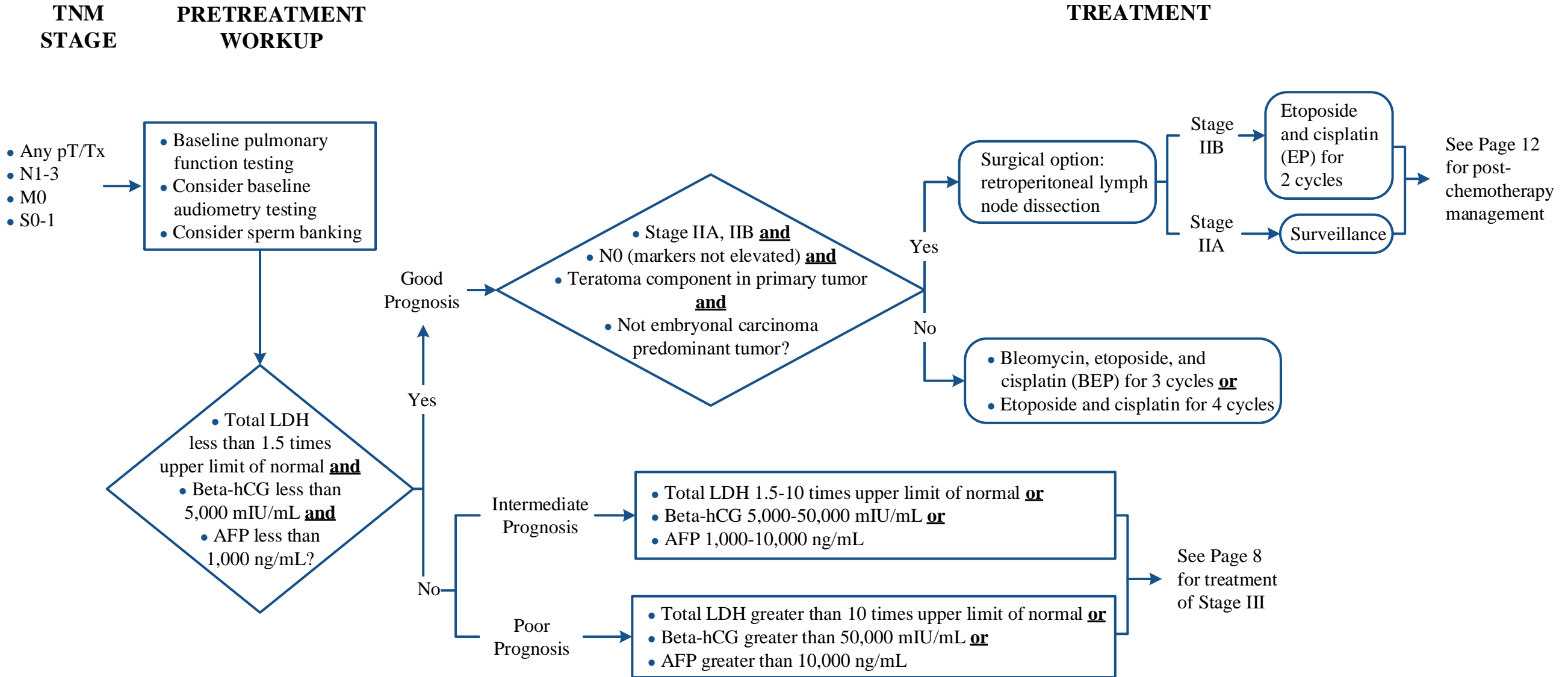
Consider sperm banking

Most patients with clinical stage IA pure seminoma can be offered three options:

- Surveillance in compliant patients who are committed to long term follow-up **or**
- Radiotherapy to para-aortic **with or without** ipsilateral iliac lymph nodes **or**
- Adjuvant carboplatin single dose, AUC =7 **or** AUC = 7 x 2 cycles

This practice algorithm has been specifically developed for MD Anderson using a multidisciplinary approach and taking into consideration circumstances particular to MD Anderson, including the following: MD Anderson's specific patient population; MD Anderson's services and structure; and MD Anderson's clinical information. Moreover, this algorithm is not intended to replace the independent medical or professional judgment of physicians or other health care providers.

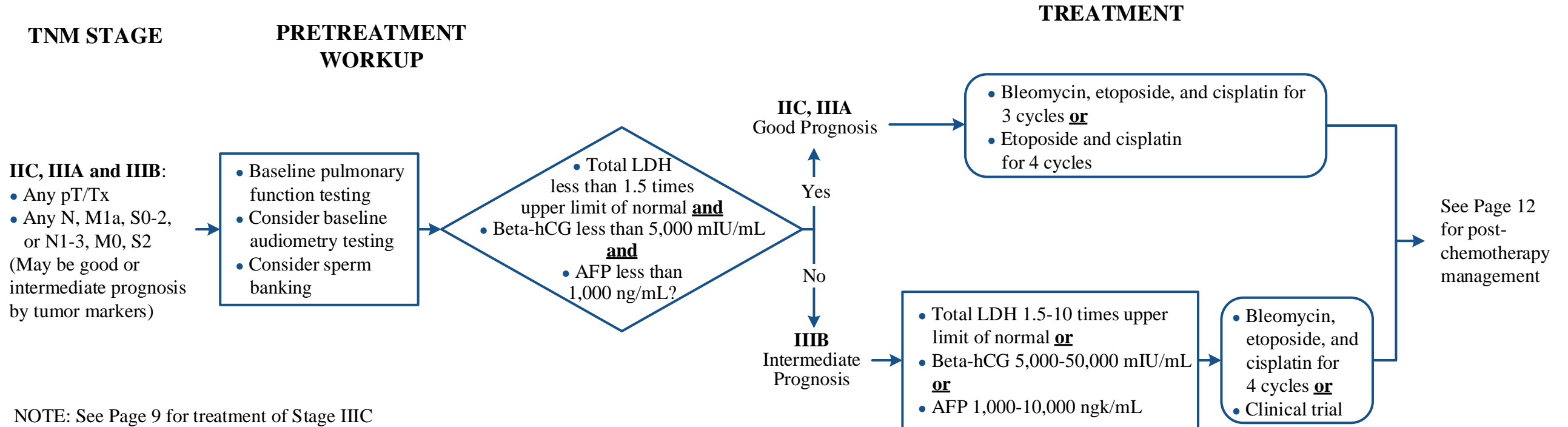
**Note:** Consider Clinical Trials as treatment options for eligible patients.





*This practice algorithm has been specifically developed for MD Anderson using a multidisciplinary approach and taking into consideration circumstances particular to MD Anderson, including the following: MD Anderson's specific patient population; MD Anderson's services and structure; and MD Anderson's clinical information. Moreover, this algorithm is not intended to replace the independent medical or professional judgment of physicians or other health care providers.*

**Note:** Consider Clinical Trials as treatment options for eligible patients.





This practice algorithm has been specifically developed for MD Anderson using a multidisciplinary approach and taking into consideration circumstances particular to MD Anderson, including the following: MD Anderson's specific patient population; MD Anderson's services and structure; and MD Anderson's clinical information. Moreover, this algorithm is not intended to replace the independent medical or professional judgment of physicians or other health care providers.

**Note:** Consider Clinical Trials as treatment options for eligible patients.

### TNM STAGE

#### IIIC, Poor Prognosis:

- Any pT/Tx, Any N, M1b<sup>1</sup>, Any S
- Total LDH greater than 10 times upper limit of normal or
- Beta-hCG greater than 50,000 mIU/mL or
- AFP greater than 10,000 ng/mL

To avoid delay in the start of chemotherapy, the diagnosis can be made on clinical grounds. Orchiectomy can be deferred.

Respiratory distress or symptomatic brain metastases?

Yes

Patient with respiratory distress

- Vincristine and cisplatin
- Etoposide and cisplatin (limit to 3 days in unstable patient)

Patient with symptomatic brain metastases

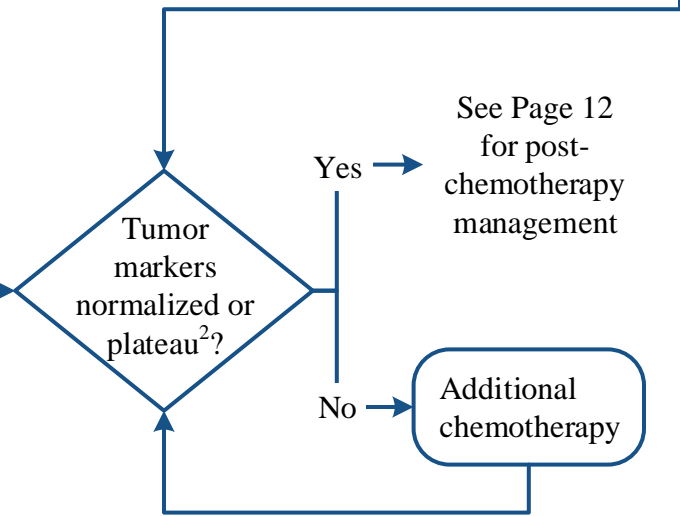
Primary chemotherapy with **or** without surgery if clinically indicated

No

- Baseline pulmonary function testing
- Consider baseline audiometry testing
- Consider sperm banking

- Clinical trial preferred **or**
- Bleomycin, etoposide, cisplatin for 4 cycles

After first cycle, continue for a minimum of 4 cycles:  
 First line  
 • Clinical trial (preferred) **or**  
 • Bleomycin, etoposide, and cisplatin **or**  
 • Etoposide, ifosfamide, and cisplatin **or**  
 Second line  
 • Paclitaxel, ifosfamide, and cisplatin (TIP) **or**  
 • High dose chemotherapy regimens **or**  
 • Stem Cell Transplant **or**  
 • Clinical trial (preferred)  
 (Monitor pulmonary function tests for patients receiving bleomycin)

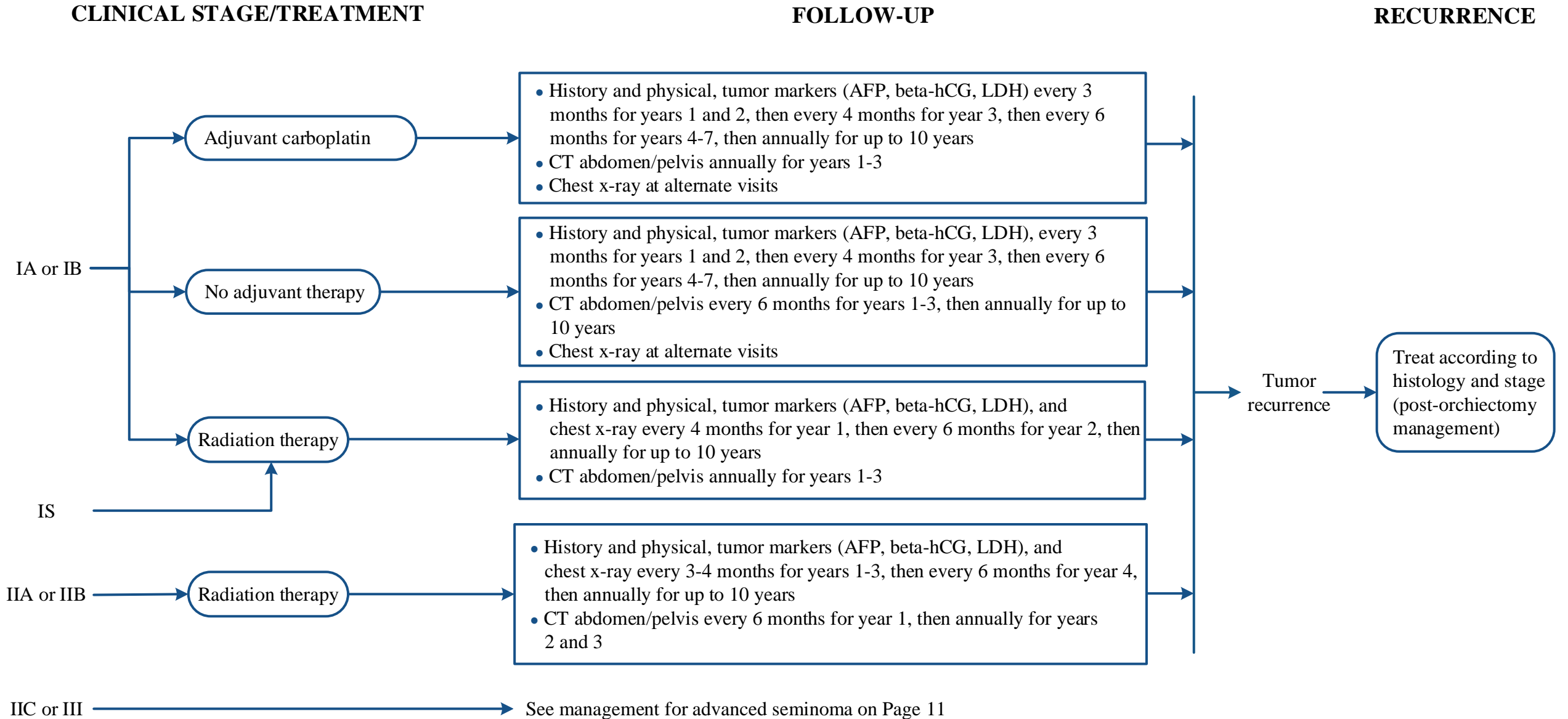


<sup>1</sup> M1b - Distant metastases other than to non-regional lymph nodes and lungs

<sup>2</sup> Plateau: The observed rate of decline in tumor markers should be compared to the expected serum half-lives of 5-7 days (AFP) and 2-3 days (beta-hCG). It is common to see a slower rate of decline after the second cycle of chemotherapy. A continued rate of decline that is much less than the expected half life and does not normalize should be interpreted as a plateau. The decision to stop chemotherapy should be based on clinical judgement, taking into consideration the clinical status of the patient, which of the markers are elevated, extent of elevation, and after ruling out potential sources of spurious elevation.

*This practice algorithm has been specifically developed for MD Anderson using a multidisciplinary approach and taking into consideration circumstances particular to MD Anderson, including the following: MD Anderson's specific patient population; MD Anderson's services and structure; and MD Anderson's clinical information. Moreover, this algorithm is not intended to replace the independent medical or professional judgment of physicians or other health care providers.*

**Note:** Consider Clinical Trials as treatment options for eligible patients.



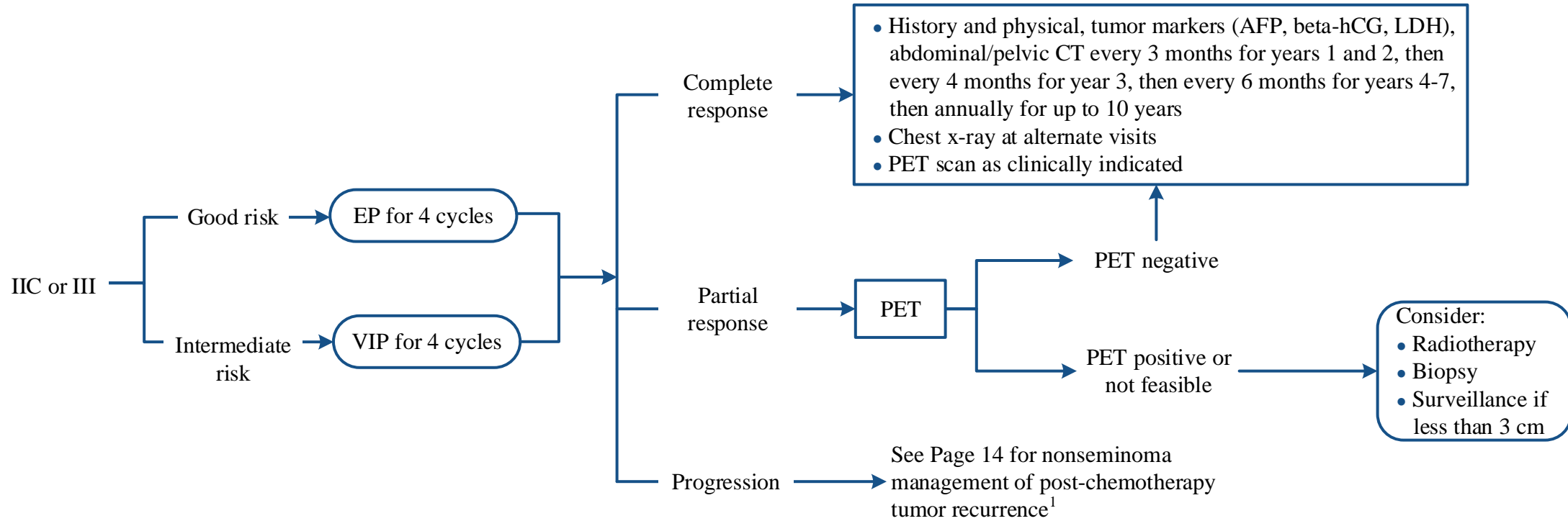
*This practice algorithm has been specifically developed for MD Anderson using a multidisciplinary approach and taking into consideration circumstances particular to MD Anderson, including the following: MD Anderson's specific patient population; MD Anderson's services and structure; and MD Anderson's clinical information. Moreover, this algorithm is not intended to replace the independent medical or professional judgment of physicians or other health care providers.*

**Note:** Consider Clinical Trials as treatment options for eligible patients.

### CLINICAL STAGE/TREATMENT

### RESPONSE TO TREATMENT

### FOLLOW-UP



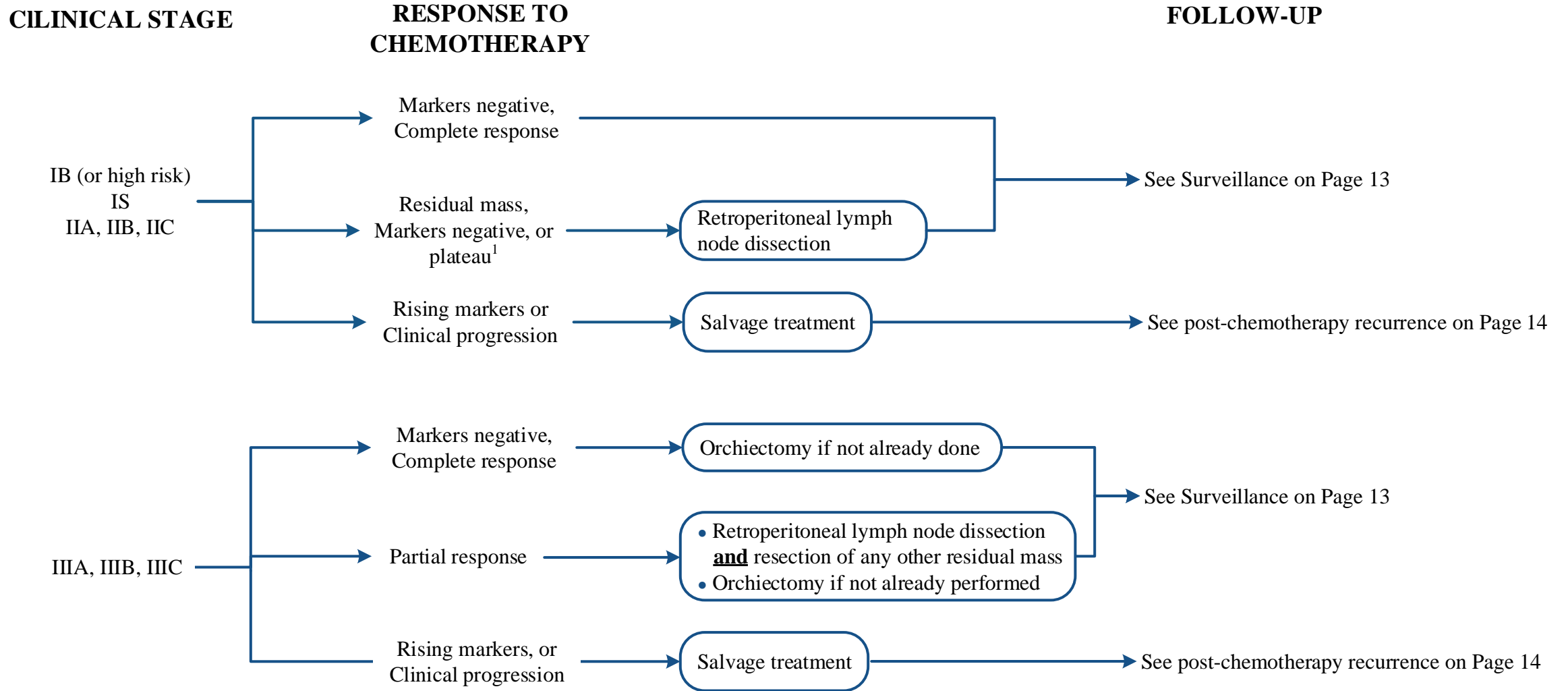
EP = etoposide and cisplatin

VIP = etoposide, ifosfamide, and cisplatin

<sup>1</sup>Seminoma that is refractory to chemotherapy is rare and should be managed as nonseminoma

*This practice algorithm has been specifically developed for MD Anderson using a multidisciplinary approach and taking into consideration circumstances particular to MD Anderson, including the following: MD Anderson's specific patient population; MD Anderson's services and structure; and MD Anderson's clinical information. Moreover, this algorithm is not intended to replace the independent medical or professional judgment of physicians or other health care providers.*

**Note:** Consider Clinical Trials as treatment options for eligible patients.



<sup>1</sup> Plateau: The observed rate of decline in tumor markers should be compared to the expected serum half-lives of 5-7 days (AFP) and 2-3 days (beta-hCG). It is common to see a slower rate of decline after the second cycle of chemotherapy. A continued rate of decline that is much less than the expected half life and does not normalize should be interpreted as a plateau. The decision to stop chemotherapy should be based on clinical judgement, taking into consideration the clinical status of the patient, which of the markers are elevated, extent of elevation, and after ruling out potential sources of spurious elevation.

*This practice algorithm has been specifically developed for MD Anderson using a multidisciplinary approach and taking into consideration circumstances particular to MD Anderson, including the following: MD Anderson's specific patient population; MD Anderson's services and structure; and MD Anderson's clinical information. Moreover, this algorithm is not intended to replace the independent medical or professional judgment of physicians or other health care providers.*

**Table 1: IA, IB NONSEMINOMA SURVEILLANCE**

Year	Visits, Markers, and Chest X-ray	Abdominal/Pelvic CT
1	Every 1-2 months	Every 4 months
2	Every 2-3 months	Every 6 months
3	Every 3 months	Every 6 months
4	Every 4 months	Every 8 months
5	Every 6 months	Annually
6 and above	Annually	Annually

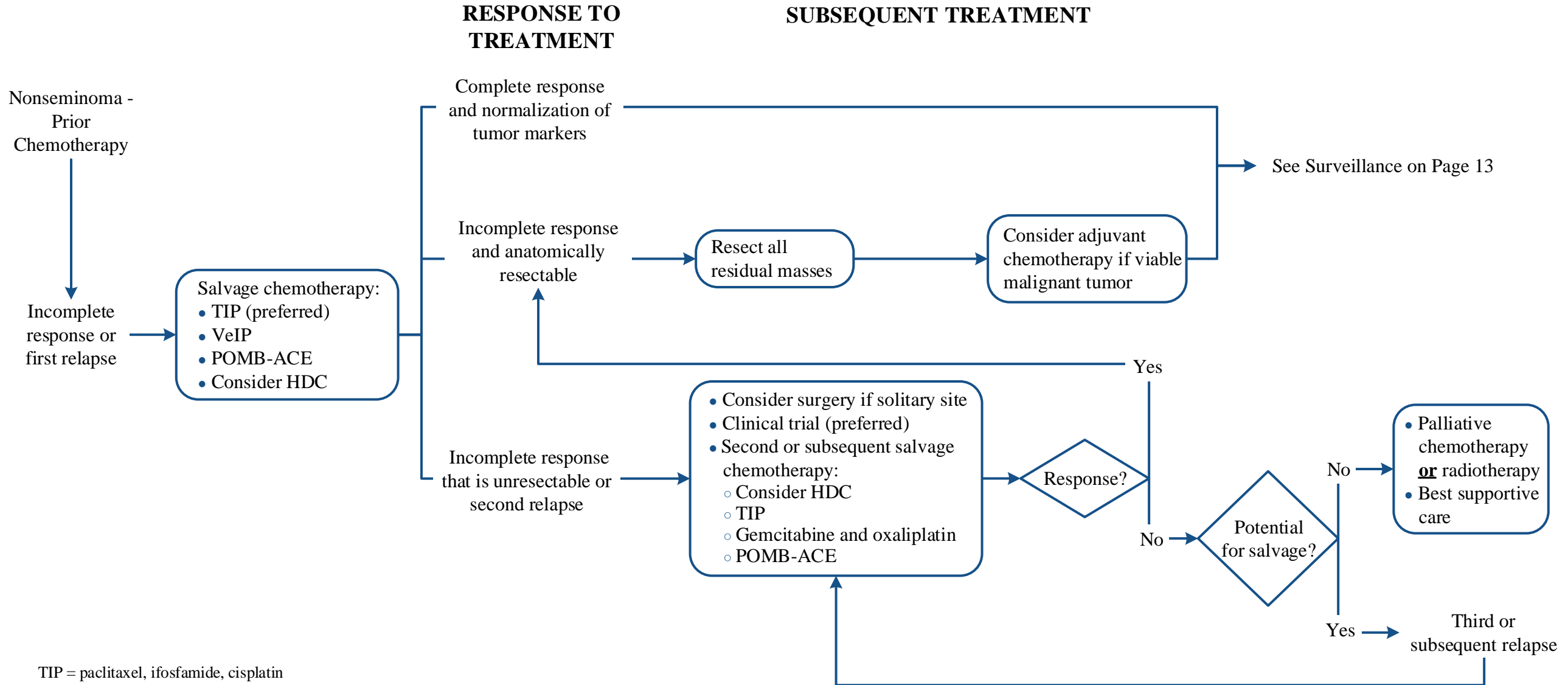
**Table 2: NONSEMINOMA FOLLOW-UP after Complete Response to Chemotherapy and/or Retroperitoneal Lymph Node Dissection (RPLND)**

Year	Visits, Markers, and Chest X-ray	Abdominal/Pelvic CT <sup>1</sup>
1	Every 2-3 months	Every 6 months
2	Every 2-3 months	Every 6-12 months
3	Every 4 months	Annually
4	Every 6 months	Annually
5	Every 6-12 months	Annually
6 and above	Annually	Every 12-24 months

<sup>1</sup> CT scans for patients treated with chemotherapy. Baseline CT scan for patients status post RPLND

This practice algorithm has been specifically developed for MD Anderson using a multidisciplinary approach and taking into consideration circumstances particular to MD Anderson, including the following: MD Anderson's specific patient population; MD Anderson's services and structure; and MD Anderson's clinical information. Moreover, this algorithm is not intended to replace the independent medical or professional judgment of physicians or other health care providers.

**Note:** Consider Clinical Trials as treatment options for eligible patients.



TIP = paclitaxel, ifosfamide, cisplatin

VeIP = vinblastine, ifosfamide, cisplatin, mesna

POMB-ACE = cisplatin, vincristine, methotrexate and bleomycin alternating with actinomycin-D, cyclophosphamide, and etoposide

HDC = high-dose chemotherapy and autologous stem cell transplant

*This practice algorithm has been specifically developed for MD Anderson using a multidisciplinary approach and taking into consideration circumstances particular to MD Anderson, including the following: MD Anderson's specific patient population; MD Anderson's services and structure; and MD Anderson's clinical information. Moreover, this algorithm is not intended to replace the independent medical or professional judgment of physicians or other health care providers.*

## APPENDIX A: International Classifications for Germ Cell Cancers<sup>1</sup>

		NONSEMINOMA	SEMINOMA
GOOD PROGNOSIS	<b>FEATURES</b>	Testes/retroperitoneal primary <b>and</b> No non-pulmonary visceral metastases <b>and</b>	Any primary site <b>and</b> No non-pulmonary visceral metastases <b>and</b>
	<b>All Good Markers:</b>		
	• <b>AFP</b>	less than 1,000 ng/mL <b>and</b>	Normal
	• <b>Beta-hCG</b>	less than 5,000 iu/L (1,000 ng/mL) <b>and</b>	Any value
	• <b>LDH</b>	less than 1.5 times upper limit of normal	Any value
INTERMEDIATE PROGNOSIS	<b>FEATURES</b>	Testes/retroperitoneal primary <b>and</b> No non-pulmonary visceral metastases <b>and</b>	Any primary site <b>and</b> Non-pulmonary visceral metastases <b>and</b>
	<b>Markers any of:</b>		
	• <b>AFP</b>	greater than or equal to 1,000 and less than or equal to 10,000 ng/mL <b>or</b>	Normal
	• <b>Beta-hCG</b>	greater than or equal to 5,000 iu/L and less than 50,000 iu/L <b>or</b>	Any value
	• <b>LDH</b>	greater than or equal to 1.5 times normal and less than 10 times normal	Any value
POOR PROGNOSIS	<b>FEATURES</b>	Mediastinal primary <b>or</b> Non-pulmonary metastases	No patients classified as poor prognosis
	<b>Markers any of:</b>		
	• <b>AFP</b>	greater than 10,000 ng/mL <b>or</b>	
	• <b>Beta-hCG</b>	greater than or equal to 50,000 iu/L (10,000 ng/mL) <b>or</b>	
	• <b>LDH</b>	greater than 10 times normal	

<sup>1</sup> From the International Germ Cell Consensus Classification from the International Germ Cell Cancer Collaborative Group



This practice algorithm has been specifically developed for MD Anderson using a multidisciplinary approach and taking into consideration circumstances particular to MD Anderson, including the following: MD Anderson's specific patient population; MD Anderson's services and structure; and MD Anderson's clinical information. Moreover, this algorithm is not intended to replace the independent medical or professional judgment of physicians or other health care providers.

## SUGGESTED READINGS

- AJCC Cancer Staging Handbook*. (2010). (7 ed.). Chicago, IL: American Joint Committee on Cancer.
- Albers, P., Siener, R., Krege, S., Schmelz, H. U., Dieckmann, K. P., Heidenreich, A., ... & Köhrmann, K. U. (2008). Randomized phase III trial comparing retroperitoneal lymph node dissection with one course of bleomycin and etoposide plus cisplatin chemotherapy in the adjuvant treatment of clinical stage I nonseminomatous testicular germ cell tumors: AUO trial AH 01/94 by the German Testicular Cancer Study Group. *Journal of Clinical Oncology*, 26(18), 2966-2972.
- Beyer, J., Kramar, A., Mandanas, R., Linkesch, W., Greinix, A., Droz, J. P., ... & Nichols, C. R. (1996). High-dose chemotherapy as salvage treatment in germ cell tumors: a multivariate analysis of prognostic variables. *Journal of Clinical Oncology*, 14(10), 2638-2645.
- Bokemeyer, C., Kollmannsberger, C., Meisner, C., Harstrick, A., Beyer, J., Metzner, B., ... & Nichols, C. (1999). First-line high-dose chemotherapy compared with standard-dose PEB/VIP chemotherapy in patients with advanced germ cell tumors: a multivariate and matched-pair analysis. *Journal of clinical oncology*, 17(11), 3450-3456.
- Einhorn, L. H., Williams, S. D., Chamness, A., Brames, M. J., Perkins, S. M., & Abonour, R. (2007). High-dose chemotherapy and stem-cell rescue for metastatic germ-cell tumors. *New England Journal of Medicine*, 357(4), 340-348.
- Fizazi, K., Delva, R., Caty, A., Chevreau, C., Kerbrat, P., Rolland, F., ... & Malhaire, J. P. (2014). A risk-adapted study of cisplatin and etoposide, with or without ifosfamide, in patients with metastatic seminoma: results of the GETUG S99 multicenter prospective study. *European urology*, 65(2), 381-386.
- Fizazi, K., Prow, D. M., Do, K. A., Wang, X., Finn, L., Kim, J., ... & Pagliaro, L. C. (2002). Alternating dose-dense chemotherapy in patients with high volume disseminated non-seminomatous germ cell tumours. *British journal of cancer*, 86(10), 1555-1560.
- Wilkinson, P. M., & Read, G. (1997). International Germ Cell Consensus Classification: a prognostic factor-based staging system for metastatic germ cell cancers. International Germ Cell Cancer Collaborative Group. *Journal of Clinical Oncology*.
- Kondagunta, G. V., Bacik, J., Donadio, A., Bajorin, D., Marion, S., Sheinfeld, J., ... & Motzer, R. J. (2005). Combination of paclitaxel, ifosfamide, and cisplatin is an effective second-line therapy for patients with relapsed testicular germ cell tumors. *Journal of Clinical Oncology*, 23(27), 6549-6555.
- Margolin, K., Doroshow, J. H., Ahn, C., Hamasaki, V., Leong, L., Morgan, R., ... & Tetef, M. (1996). Treatment of germ cell cancer with two cycles of high-dose ifosfamide, carboplatin, and etoposide with autologous stem-cell support. *Journal of clinical oncology*, 14(10), 2631-2637.
- Motzer, R. J., Nichols, C. J., Margolin, K. A., Bacik, J., Richardson, P. G., Vogelzang, N. J., ... & Bosl, G. J. (2007). Phase III randomized trial of conventional-dose chemotherapy with or without high-dose chemotherapy and autologous hematopoietic stem-cell rescue as first-line treatment for patients with poor-prognosis metastatic germ cell tumors. *Journal of Clinical Oncology*, 25(3), 247-256.
- Motzer, R. J., Sheinfeld, J., Mazumdar, M., Bains, M., Mariani, T., Bacik, J., ... & Bosl, G. J. (2000). Paclitaxel, ifosfamide, and cisplatin second-line therapy for patients with relapsed testicular germ cell cancer. *Journal of clinical oncology*, 18(12), 2413-2418.
- Motzer, R. J., Mazumdar, M., Bosl, G. J., Bajorin, D. F., Amsterdam, A., & Vlamis, V. (1996). High-dose carboplatin, etoposide, and cyclophosphamide for patients with refractory germ cell tumors: treatment results and prognostic factors for survival and toxicity. *Journal of clinical oncology*, 14(4), 1098-1105.
- National Comprehensive Network. Testicular Cancer (Version 2.2017- December 8, 2016) [https://www.nccn.org/professionals/physician\\_gls/pdf/testicular.pdf](https://www.nccn.org/professionals/physician_gls/pdf/testicular.pdf) Accessed September 5, 2017
- Nieto, Y., Aldaz, A., Rifón, J., Pérez-Calvo, J., Zafra, A., Zufia, L., ... & Centeno, C. (2007). Phase I and pharmacokinetic study of gemcitabine administered at fixed-dose rate, combined with docetaxel/melphalan/carboplatin, with autologous hematopoietic progenitor-cell support, in patients with advanced refractory tumors. *Biology of Blood and Marrow Transplantation*, 13(11), 1324-1337.
- Oliver, R. T. D., Mason, M. D., Mead, G. M., von der Maase, H., Rustin, G. J. S., Joffe, J. K., ... & Kirk, S. J. (2005). Radiotherapy versus single-dose carboplatin in adjuvant treatment of stage I seminoma: a randomised trial. *The lancet*, 366(9482), 293-300.
- Tandstad, T., Dahl, O., Cohn-Cedermark, G., Cavallin-Stahl, E., Stierner, U., Solberg, A., ... & Klepp, O. (2009). Risk-adapted treatment in clinical stage I nonseminomatous germ cell testicular cancer: the SWENOTECA management program. *Journal of Clinical Oncology*, 27(13), 2122-2128.

*This practice algorithm has been specifically developed for MD Anderson using a multidisciplinary approach and taking into consideration circumstances particular to MD Anderson, including the following: MD Anderson's specific patient population; MD Anderson's services and structure; and MD Anderson's clinical information. Moreover, this algorithm is not intended to replace the independent medical or professional judgment of physicians or other health care providers.*

---

## DEVELOPMENT CREDITS

This practice algorithm is based on majority expert opinion of the Genitourinary Center Faculty at the University of Texas MD Anderson Cancer Center. It was developed using a multidisciplinary approach that included input from the following:

Ana Aparicio, MD  
John Araujo, MD  
Seungtaek Choi, MD  
Paul Corn, MD  
Olga Fleckenstein<sup>♦</sup>  
Eric Jonasch, MD  
Jeri Kim, MD  
Karen Hoffman, MD  
Deborah Kuban, MD<sup>‡</sup>  
Andrew Lee, MD  
Christopher Logothetis, MD  
Yago Nieto, MD  
Louis Pisters, MD<sup>‡</sup>  
Padmanee Sharma, MD  
Arlene O. Siefker-Radtke, MD  
Nizar M. Tannir, MD  
Shi-Ming Tu, MD<sup>‡</sup>  
Gloria Trowbridge, MSN, RN<sup>♦</sup>  
John Ward, MD  
Amado Zurita-Saavedra, MD

<sup>‡</sup> Core Development Team Lead

<sup>♦</sup> Clinical Effectiveness Development Team