

Extragonadal Germ Cell Cancer Diagnostic and Therapeutic Challenges

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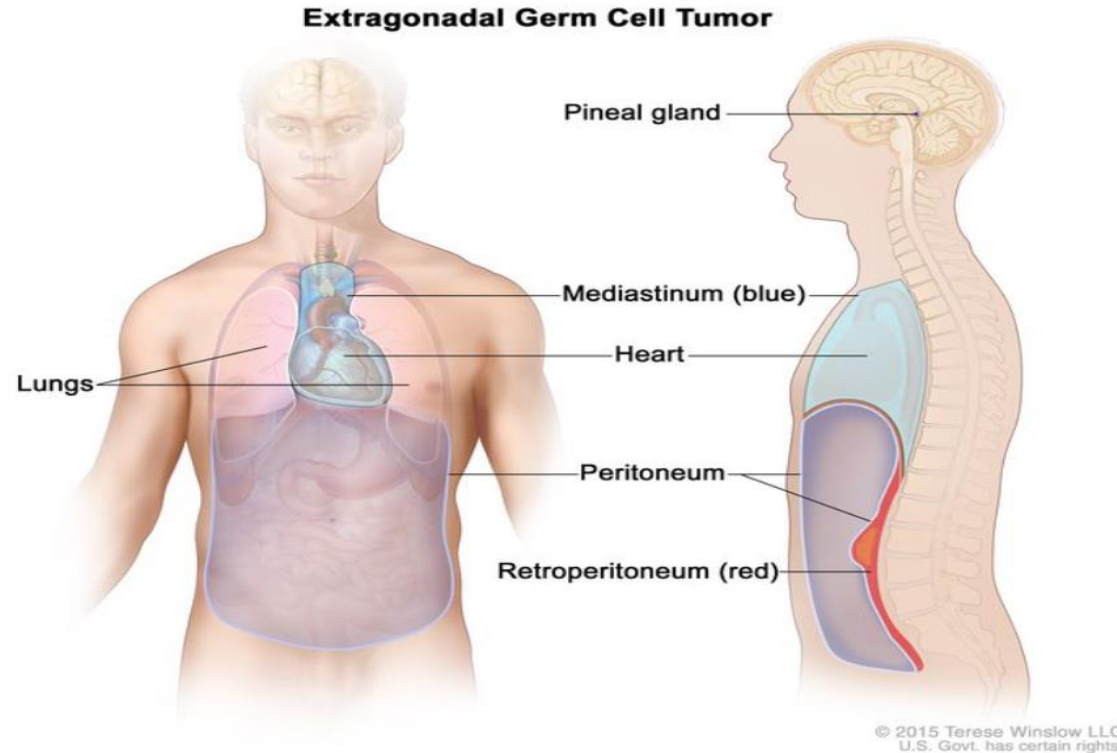
Disclosure

I have no conflicts of interest

Outline

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- ☐ Seminomatous Extragenadal Germ Cell Cancer Treatment
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Extragonadal Germ Cell Cancer Definition and Incidence



Extragonadal germ cell tumors form in parts of the body other than the gonads (testicles or ovaries). This includes the pineal gland in the brain, the mediastinum (area between the lungs), and retroperitoneum (the back wall of the abdomen).

Germ Cell tumors(GCT) typically arise in the male gonads. If GCT originates from the extragonadal region, it is called extragonadal germ cell tumors(EGCT)

EGCT are located in the midline areas of the body which is due to the embryonic migration of primordial germ cells from the epiblast to the genital ridge

The incidence of EGCT is low, and only 2–3% of all GCT are diagnosed as EGCT

Extragonadal Germ Cell Cancer Definition and Incidence

Location of EGCT

Common

Mediastinum

50–70%

Retroperitoneum

30–40%

Pineal and suprasellar regions

Sacrococcyx (infants and young children only)

Very rare

Prostate

Liver and gastrointestinal tract

Orbita

Majority of Extragonadal Germ Cell Cancer being located in the upper anterior mediastinum followed by the retroperitoneum

Extragenadal Germ Cell Cancer Prognosis

Prognosis	5-year OS	Seminoma	Non-seminoma
Good	90%	- Any primary location - No non-pulmonary visceral metastases - Any marker level	- Testis or primary extragonadal retroperitoneal tumor - No non-pulmonary visceral metastases - Low markers - AFP < 1,000 ng/ml, HCG < 5,000 IU/l, LDH < 1.5 x normal level
Intermediate	75%	- Any primary location - Presence of non-pulmonary visceral metastases (liver, CNS, bone, intestine) - Any marker level	- Testis or primary extragonadal retroperitoneal tumor - No presence of non-pulmonary visceral metastases - Intermediate markers - AFP 1,000-10,000 ng/ml - HCG 5,000-50,000 IU/l - LDH 1.5-10 x normal level
Poor	50%	Does not exist	Primary mediastinal GCT with or without testis - Presence of non-pulmonary visceral metastases (liver, CNS, bone intestine) - High markers - AFP > 10,000 ng/ml, HCG > 50,000 IU/l, LDH > 10 x normal level

IGCCCG, J Clin Oncol 1997

Primary EGCT are considered a special subgroup of GCT with a poorer prognosis due to larger volume and different biology

Extragenadal Germ Cell Cancer Prognosis

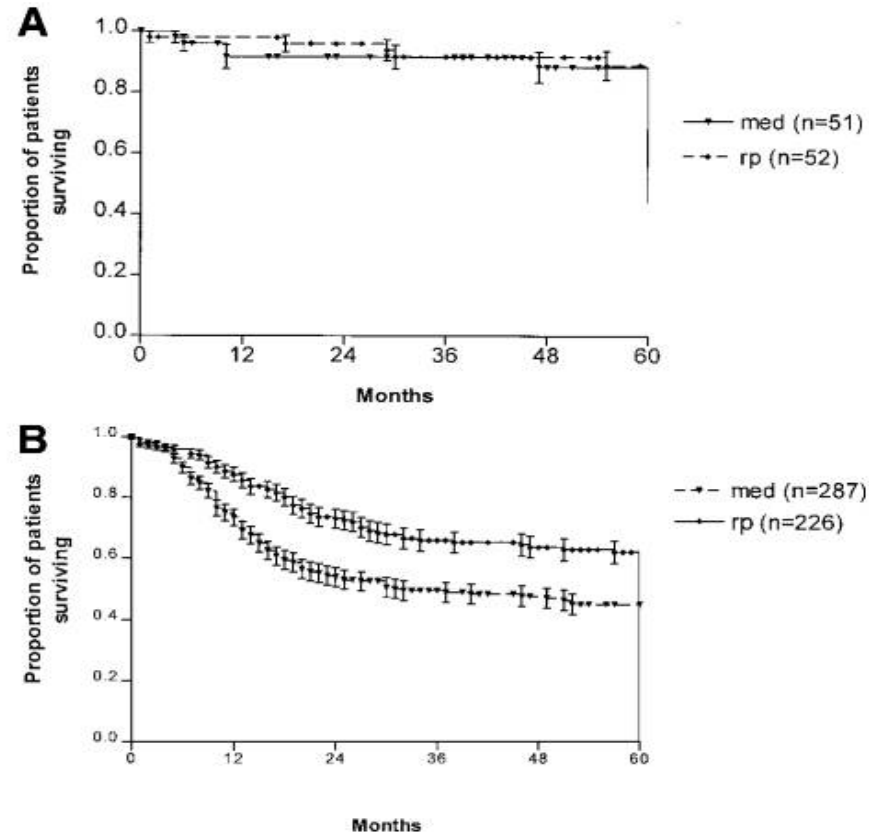


Fig 1. Calculated overall survival rates of (A) 104 seminomatous EGCT patients and (B) 524 nonseminomatous EGCT patients according to the primary tumor location. Log-rank: A, $P = .89$; B, $P = .006$. rp, retroperitoneal extragonadal nonseminoma; med, mediastinal nonseminoma.

341 patients (54%) had primary mediastinal EGCT, and 45% had retroperitoneal EGCT.

84% had a nonseminomatous germ cell tumor (GCT), and 16% had a seminomatous histology

5-year Overall survival rate for patients with a seminomatous EGCT is 88%, with no difference between patients with mediastinal or retroperitoneal tumor location

5-year OS were 45% in patients with mediastinal nonseminomas EGCT and 62% for retroperitoneal nonseminoma EGCT

Outcomes of mediastinal nonseminomas EGCT is clearly inferior compared with patients with nonseminomatous retroperitoneal primary tumors and mediastinal seminomatous histology EGCT

Clinical symptoms and diagnosis

Patients with mediastinal EGCT initially presentation

- ☐ Dyspnea (25%),
- ☐ Chest pain (23%)
- ☐ Cough (17%)
- ☐ Fever (13%),
- ☐ Weight loss (11%)
- ☐ Vena cava occlusion syndrome and fatigue/weakness (6%)

Patients with primary retroperitoneal EGCT initially presentation

- ☐ Abdominal pain(29%)
- ☐ Back pain (14%)
- ☐ Weight loss (9%)
- ☐ Fever (8%)
- ☐ Vena caval or other thrombosis (9%),
- ☐ Palpable abdominal tumor (6%)

In generally, the clinical presentation of EGCC varies widely dependent of anatomic locations

Clinical symptoms and diagnosis

- ❑ Depending on the localization, diagnosis can be performed by fine-needle aspiration cytology, percutaneous biopsy or specimen resection during mediastinoscopy/laparoscopy¹
- ❑ The evaluation of serum tumor markers (AFP, beta-hCG, LDH) is required for the correct diagnosis and classification of EGCT according to the International Germ Cell Cancer Collaborative Group (IGCCCG)¹
- ❑ Serum tumor markers might be elevated in about 40% to 60% of cases¹
- ❑ The role of the new biomarker miR371, which has been shown to be diagnostic and predictive for GCT, has not been evaluated in EGCT¹
- ❑ FISH analysis or PCR-based techniques can be applied to identify abnormalities of the 12p chromosome, ¹
- ❑ The incidence of Klinefelter's syndrome is highly increased in EGCT and karyographic examination should be performed in all patients²

Extragenital Germ Cell Cancer Testicular biopsy and removal testis

In the largest international EGCT series

- ❑ 11% of the patients with sonographic non-suspicious testis and underwent a testicular biopsy
- ❑ 3% of the cases, a Sertoli cell-only syndrome was diagnosed
- ❑ 31% had atrophic or fibrotic testicular tissue
- ❑ 9% germ cell neoplasia in situ (GCNIS) lesions

Current guidelines do not recommend the removal of the testis as long as the ultrasound findings are normal

Extragenital Germ Cell Cancer Testicular biopsy and removal testis

- ☐ Metachronous testicular GCT most commonly occurred in seminomatous EGCT with a cumulative risk of 10% within 10 years
- ☐ Secondary testicular tumors are quite easy to detect and, especially in the case of seminoma, highly curable
- ☐ Regular ultrasound of the testis during follow-up seems reasonable
- ☐ Routine bilateral testicular biopsy in EGCT patients cannot be routinely justified

Seminomatous Extragonadal Germ Cell Cancer Treatment

- ❑ Patients with seminomatous EGCT should be treated according to the IGCCCG classification prognostic group
- ❑ 3 cycles of bleomycin, etoposide, cisplatin (BEP) for good prognosis
- ❑ 4 cycles of BEP for intermediate prognosis patients
- ❑ In case of contraindications to bleomycin in good prognosis patients is 4 cycles of etoposide, cisplatin
- ❑ Substituting bleomycin by ifosfoamide if a subsequent pulmonary operation is planned

Non-seminomatous Extragonadal Germ Cell Cancer Treatment

- ❑ The standard chemotherapy regimen for patients with a mediastinal non-seminomatous EGCT consists of four cycles of cisplatin-based combination chemotherapy
- ❑ Patients with retroperitoneal non-seminomatous EGCT are classified according to the serum tumor marker of the IGCCCG classification
- ❑ Retroperitoneal non-seminomatous EGCT are treated analogously to metastatic testicular non-seminomatous GCT
- ❑ Several studies corroborated retroperitoneal non-seminomatous EGCT outcome are same primarily testicular GCT

Non-seminomatous Extragonadal Germ Cell Cancer Treatment with intermediate-poor prognosis

Clinical Trial > Br J Cancer. 1998 Sep;78(6):828-32. doi: 10.1038/bjc.1998.587.

Four cycles of BEP vs four cycles of VIP in patients with intermediate-prognosis metastatic testicular non-seminoma: a randomized study of the EORTC Genitourinary Tract Cancer Cooperative Group. European Organization for Research and Treatment of Cancer

R de Wit¹, G Stoter, D T Sleijfer, J P Neijt, W W ten Bokkel Huinink, L de Prijck, L Collette, R Sylvester

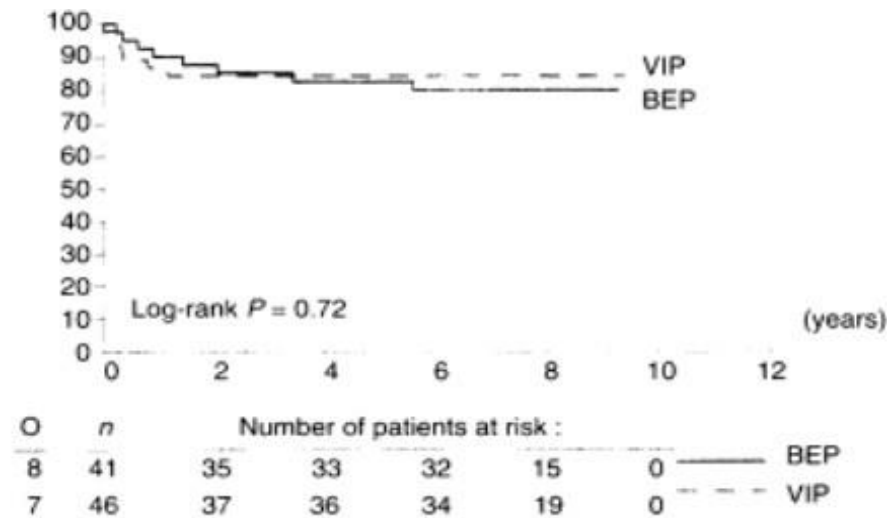


Figure 1 Progression-free survival

4 BEP vs 4 VIP

- ❑ 84 patients, median follow-up of 7.7 years
- ❑ 5-year-PFS 85% vs 83%
- ❑ Treatment related death 2 vs 1 patients
- ❑ Grade 3-4 hematological toxicity 37% vs 89%

Combination of cisplatin, etoposide and bleomycin remains the standard induction chemotherapy and that ifosfamide should not replace bleomycin

Extragonadal Germ Cell Cancer Treatment with poor and intermediate risk

Clinical Trial > Cancer. 2003 Apr 15;97(8):1869-75. doi: 10.1002/cncr.11271.

Cisplatin, etoposide and either bleomycin or ifosfamide in the treatment of disseminated germ cell tumors: final analysis of an intergroup trial

Stuart Hinton ¹, Paul J Catalano, Lawrence H Einhorn, Craig R Nichols, E David Crawford, Nicholas Vogelzang, Donald Trump, Patrick J Loehrer Sr

5-Year Survivals by Treatment Arm^a

	Overall survival (%)		Progression-free survival (%)	
	BEP	VIP	BEP	VIP
Good prognosis (<i>n</i> = 37)	88	92	75	92
Intermediate prognosis (<i>n</i> = 65)	84	77	73	72
Poor prognosis (<i>n</i> = 181)	57	62	49	56

BEP: bleomycin, etoposide, and cisplatin; VIP: etoposide, ifosfamide, and cisplatin.

^a None of the *P* values between arms were statistically significant.

304 patients with advanced-stage germ cell tumors (using the Indiana University staging system) were randomized to 4 BEP vs 4VIP

PFS rates were 64% vs 58% and the OS rates were 69% vs 67% in the VIP and BEP arms

Grade 3/4 hematologic toxicity for BEP 39.3% and 37.1% vs for VIP 28.3% and 62 % More primarily hematologic toxicity, occurred on the VIP arm

In most patients with poor and intermediate risk germ cell tumors, four cycles of BEP remain the standard therapy

When to consider VIP chemotherapy

- ☐ Patients not suitable for bleomycin
- ☐ In the presence of underlying lung disease (COPD)
- ☐ Over 50 years old
- ☐ If there are bulky lung metastases (resection may be required after treatment)
- ☐ Extensive tumor burden in the lung
- ☐ Primary mediastinal EGCT (resection may be required for residual mediastinal mass after chemotherapy)

High-Dose Chemotherapy and Autologous Hematopoietic Stem-Cell Rescue for EGCT

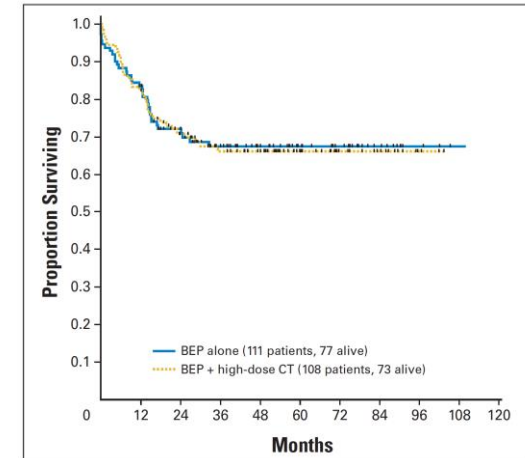
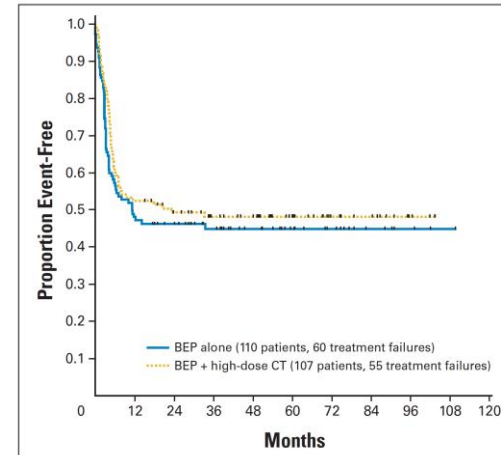
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ORIGINAL REPORT

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

Robert J. Motzer, Craig J. Nichols, Kim A. Margolin, Jennifer Bacik, Paul G. Richardson, Nicholas J. Vogelzang, Dean F. Bajorin, Primo N. Lara Jr, Lawrence Einhorn, Madhu Mazumdar, and George J. Bosl

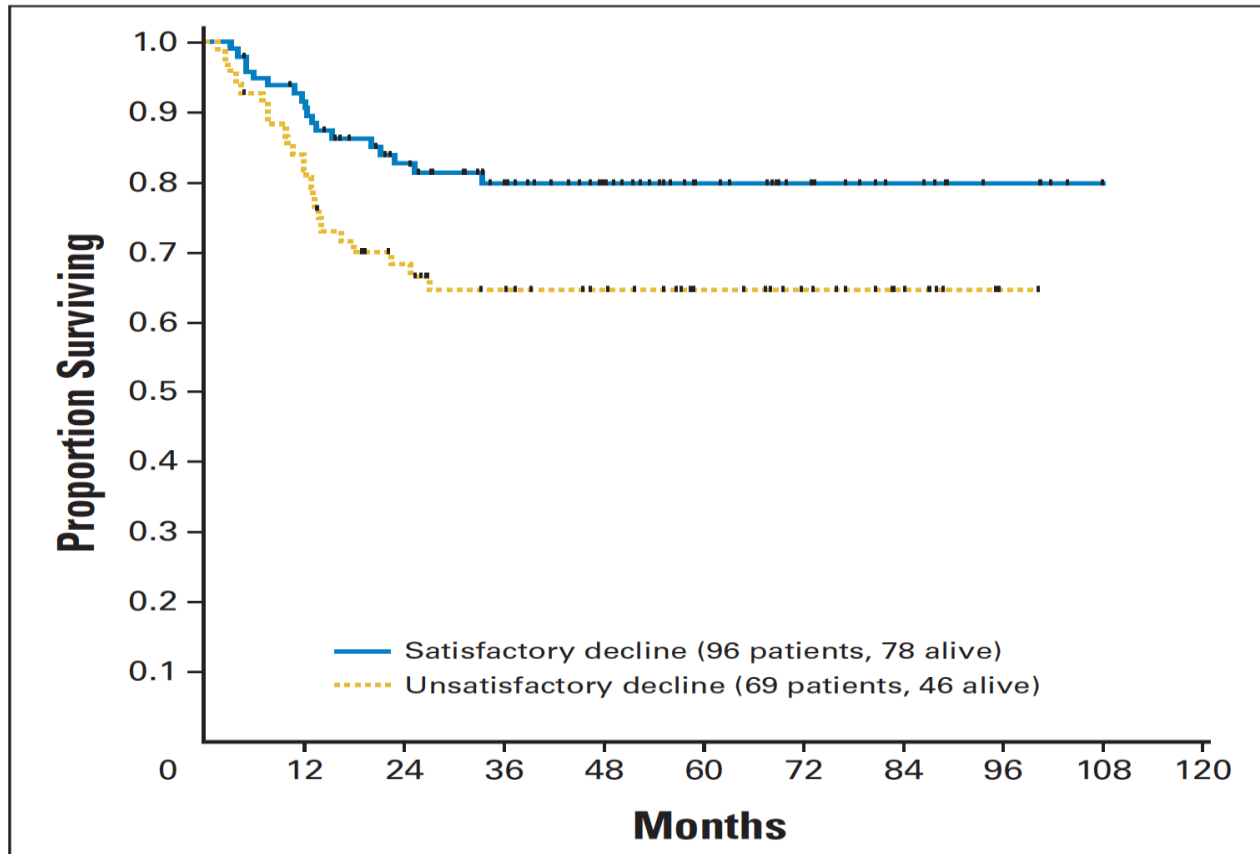


Two hundred nineteen patients were randomly assigned: 108 to BEP HDCT and 111 to BEP alone. **Primary location of 96(44%) patients was mediastinum.**

The 1-year durable complete response rate was 52% after BEP-HDCT and 48% after BEP alone (p: 0.53)

The proportion of all patients surviving at 2 years was 71%. There was no difference in survival for patients treated with BEP HDCT compared with treatment of BEP alone (p:0.94)

High-Dose Chemotherapy and Autologous Hematopoietic Stem-Cell Rescue for EGCT

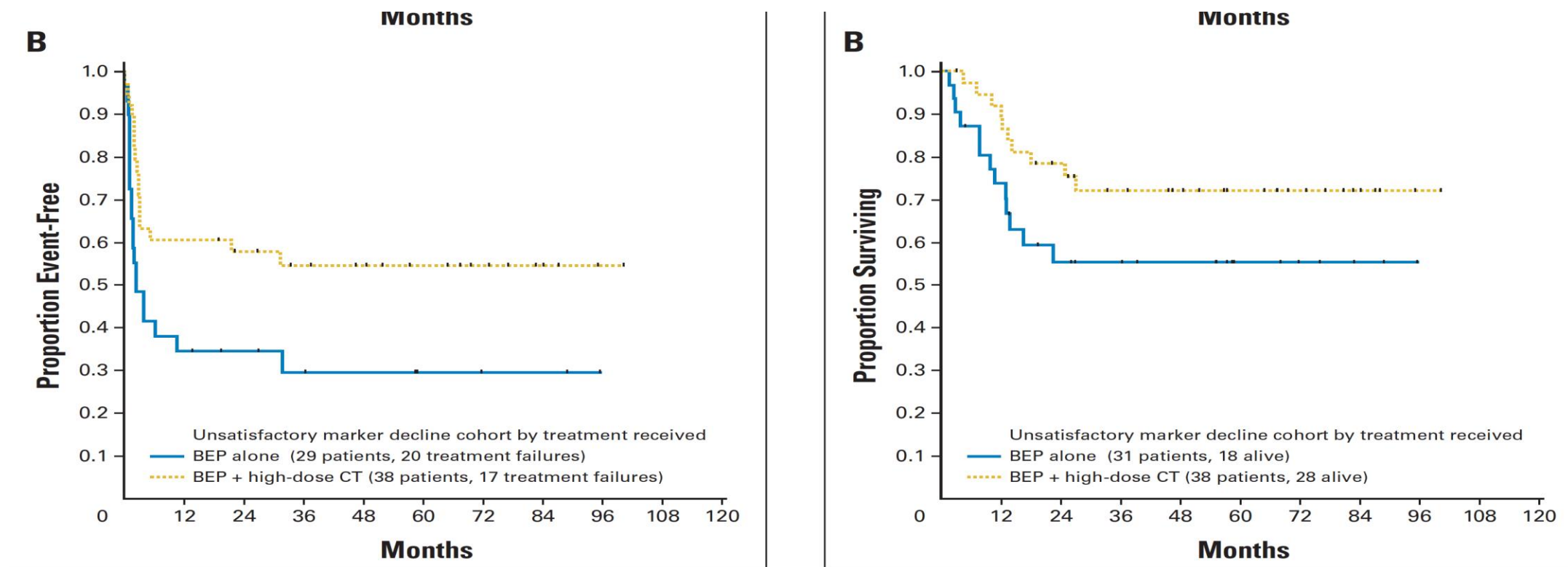


The marker decline was unsatisfactory if one or both markers demonstrated a slow decline (half-life 7 days for AFP or 3.5 days for HCG)

Marker decline was satisfactory in 96 patients (58%).

1-year durable response year 63% vs 49% in unsatisfactory patients

High-Dose Chemotherapy and Autologous Hematopoietic Stem-Cell Rescue for EGCT



The 1-year durable CR proportion for unsatisfactory-decline patients who received HDCT was 61% vs 34% for unsatisfactory-decline patients receiving BEP alone (p:0.03).

Unsatisfactory decline patients who received HDCT had a 2-year survival rate of 78% vs 55% for unsatisfactory-decline patients receiving BEP alone, a difference of 23% (p:0.1)

Personalized chemotherapy based on tumor marker decline in poor prognosis germ-cell tumors

BEP vs T-BEP-oxaliplatin

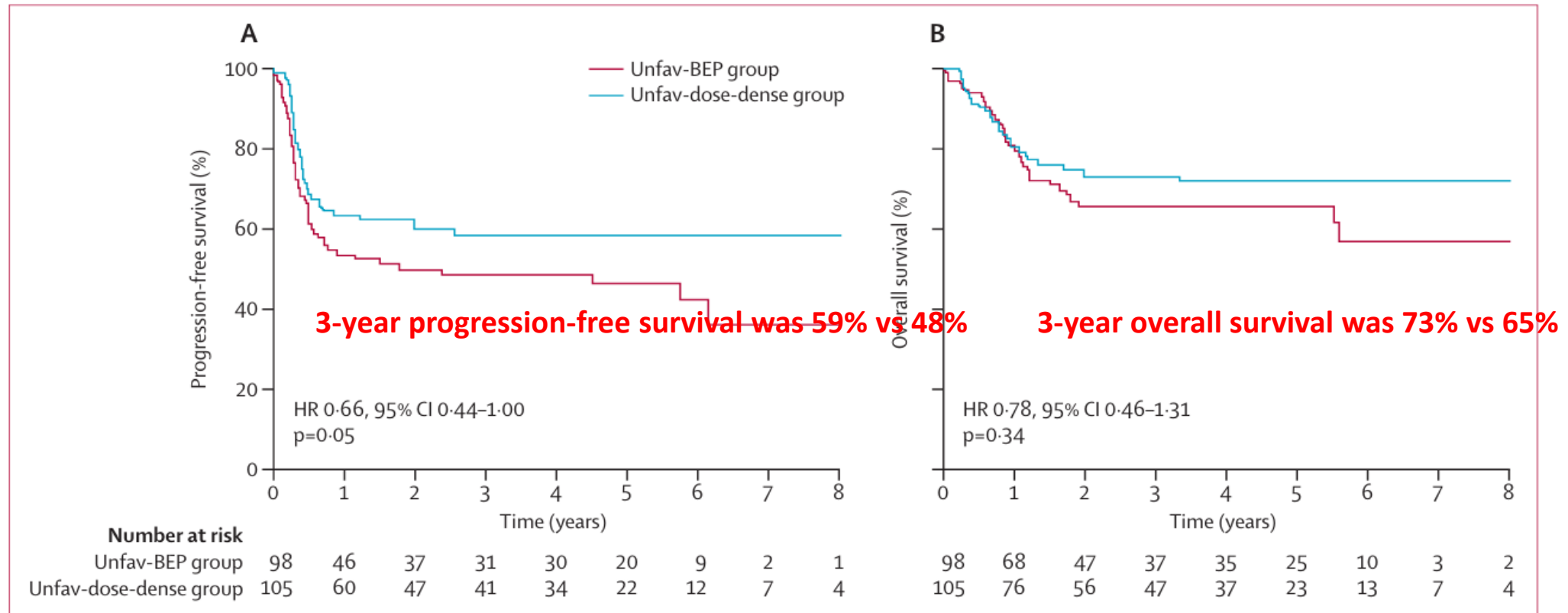


Figure 2: Progression-free survival (A) and overall survival (B) in patients with an unfavourable tumour marker decline

Unfav-dose-dense=patients with an unfavourable marker decline who were randomly assigned to receive a dose-dense regimen. Unfav-BEP=patients with an unfavourable marker decline who were randomly assigned to receive BEP.

Patients with poor-risk germ-cell tumour should benefit from treatment intensification in case of unfavorable tumour marker kinetics on BEP

After cisplatin-based chemotherapy Surgical Resection of Extragonadal Germ Cell Cancer

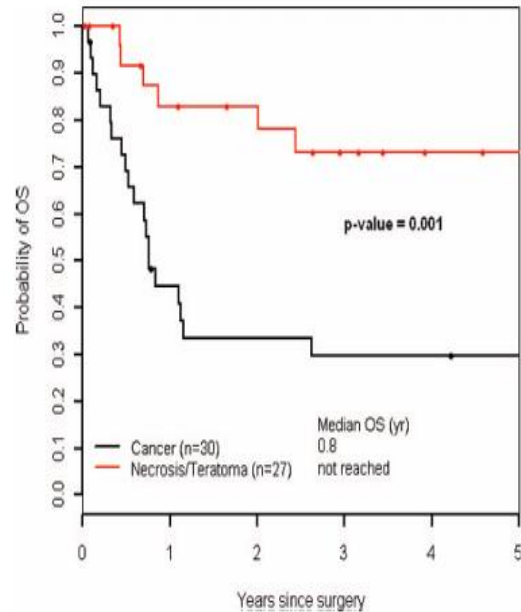


FIGURE 2. Overall survival by pathology in the final specimen (necrosis or teratoma versus residual carcinoma).

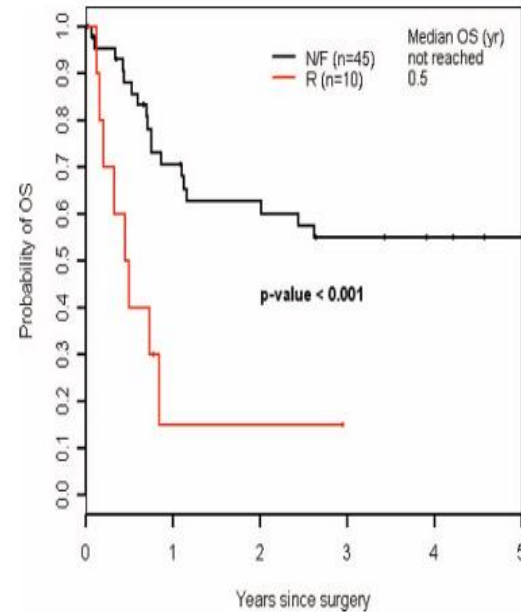


FIGURE 4. Overall survival by perioperative change in tumor markers (normalized or decreased versus increased).

- ❑ After cisplatin-based chemotherapy, preoperative tumor markers normalized or decreased in 79% of patients.
- ❑ An R0 resection was achieved in 91% of the patients with a major morbidity of 17.5% and no postoperative deaths.
- ❑ Factors correlating with better survival were necrosis or teratoma versus residual cancer on final pathology
- ❑ R0 resection
- ❑ Normalized or decreased postchemotherapy/preoperative tumor markers

Normalized or decreased postchemotherapy/preoperative tumor markers is the strongest independent predictor of improved survival

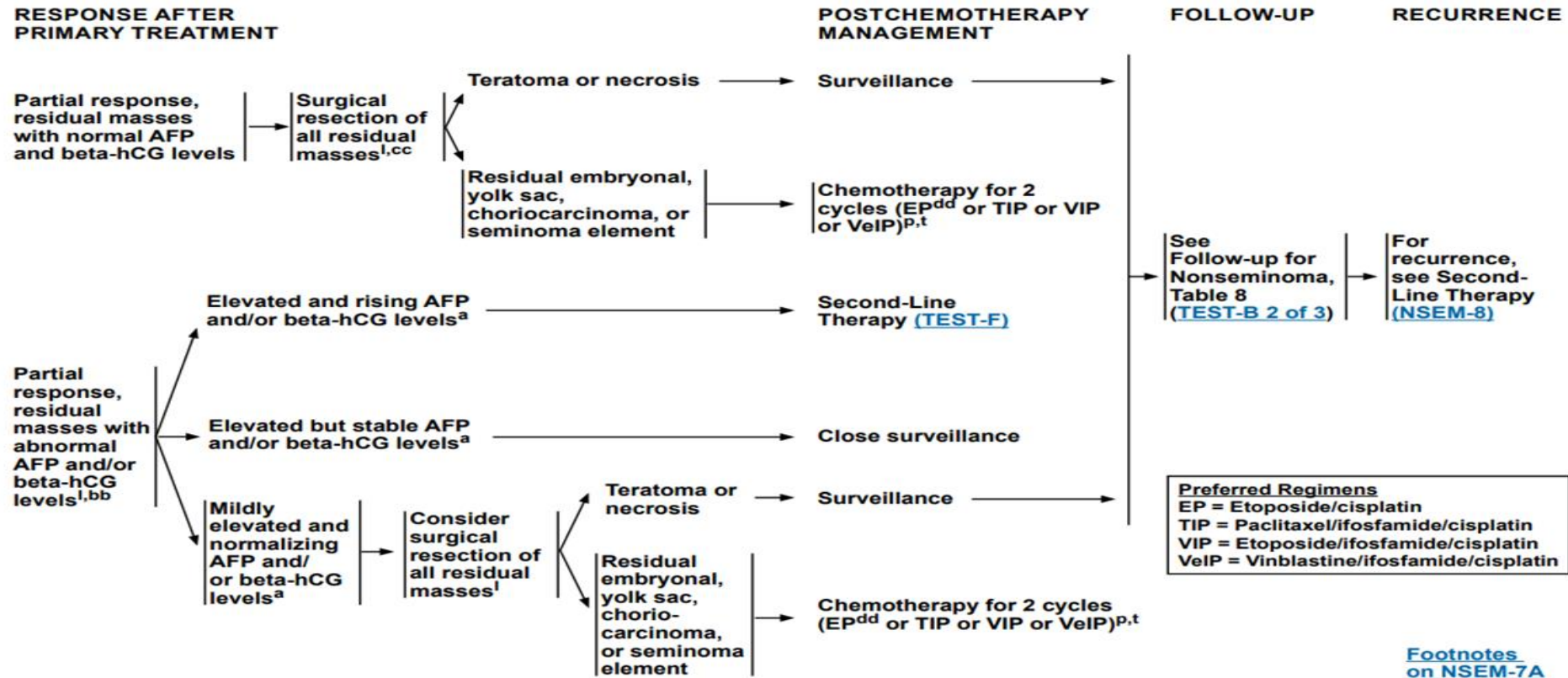
Adjuvant Treatment for After Surgical resection



National
Comprehensive
Cancer
Network®

NCCN Guidelines Version 1.2024 Testicular Cancer - Nonseminoma

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^a Mildly elevated, non-rising AFP levels may not indicate presence of germ cell tumor. Decisions to treat should not be based on AFP values. Decisions to treat should not be based on AFP values <20 ng/mL. More highly elevated AFP levels generally indicate the presence of nonseminomatous tumor elements. Further workup should be considered before initiating treatment for mildly elevated beta-hCG (generally <20 IU/L) since other factors, including hypogonadism and marijuana use, can cause false-positive results.

Patients with completely resected viable malignant tumour, comprising <10% of the specimen, do not benefit from adjuvant chemotherapy¹

¹Fizazi K, [Annals of Oncology](#) 2008.

Non-seminomatous Extragonadal Germ Cell Cancer Treatment with intermediate-poor prognosis

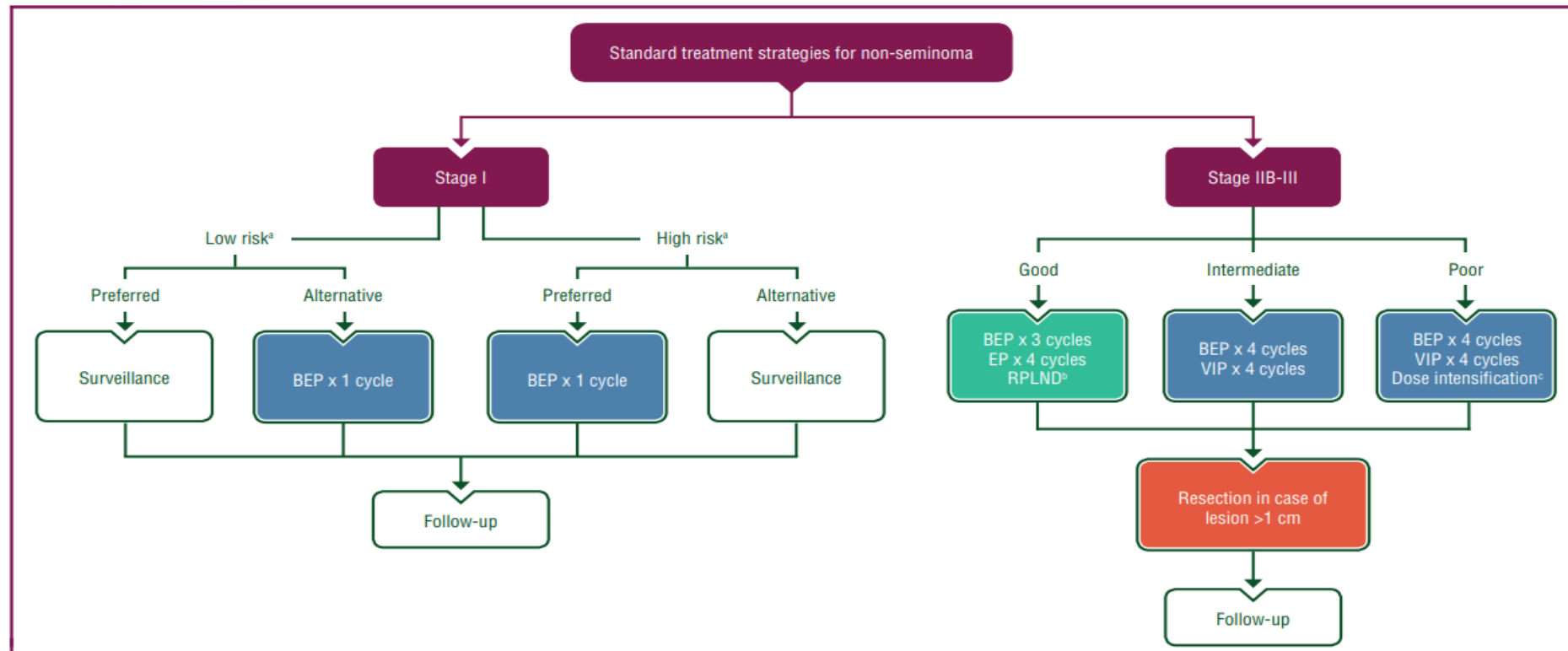


Figure 2. Standard treatment strategies for non-seminoma. Purple: general categories or stratification; blue: systemic anticancer therapy; turquoise: combination of treatments or other systemic treatments; red: surgery; white: other aspects of management. BEP, bleomycin—etoposide—cisplatin; EP, etoposide—cisplatin; RPLND, retroperitoneal lymph node dissection; VIP, etoposide—ifosfamide—cisplatin.

^a low risk and high risk based on absence and presence of vascular invasion, respectively.

^b (RPLND) marker-negative stage IIA/IIB.

^c (Dose intensification): In selected cases, e.g. poor marker decline.

ESMO-EURACAN Clinical Practice <https://doi.org/10.1016/j.annonc.2022.01.002>

Dose intensification should be consider in patients with poor marker decline

Conclusion

- ❑ EGCT are rare, comprise only 2–3% of all testicular germ cell tumors and located in the midline areas of the body.
- ❑ The majority of EGCT are located in the mediastinum, followed by the retroperitoneum
- ❑ Mediastinal nonseminomatous EGCT are related with poor prognosis
- ❑ Clinical presentation of EGCC varies widely dependent of anatomic locations
- ❑ Serum tumor markers might be elevated in about 40% to 60% of cases and demonstration of 12p chromosome change contributes to differential diagnosis in midline tumors if tumor marker does not elevate
- ❑ Current guidelines do not recommend the removal of the testis as long as the ultrasound findings are normalIn EGCT

Conclusion

- ❑ The standard chemotherapy regimen for patients with a mediastinal non-seminomatous EGCT consists of four cycles of cisplatin-based combination chemotherapy
- ❑ Patients with seminomatous EGCT should be treated according to the IGCCCG classification prognostic group
- ❑ Several studies corroborated retroperitoneal non-seminomatous and seminomatous EGCT outcomes are same primarily testicular GCT and treatment should be consider based on IGCCCG classification
- ❑ Patients with poor-risk EGCT, dose intensification should be considered for patients with unsatisfactory decline tumor marker