Grupo Português
Génito - Urinário

XXVIII Workshop
Urologia Oncológica

Germ Cell Tumors

Non-Seminoma – Stage II and negative biomarkers

Clinical case

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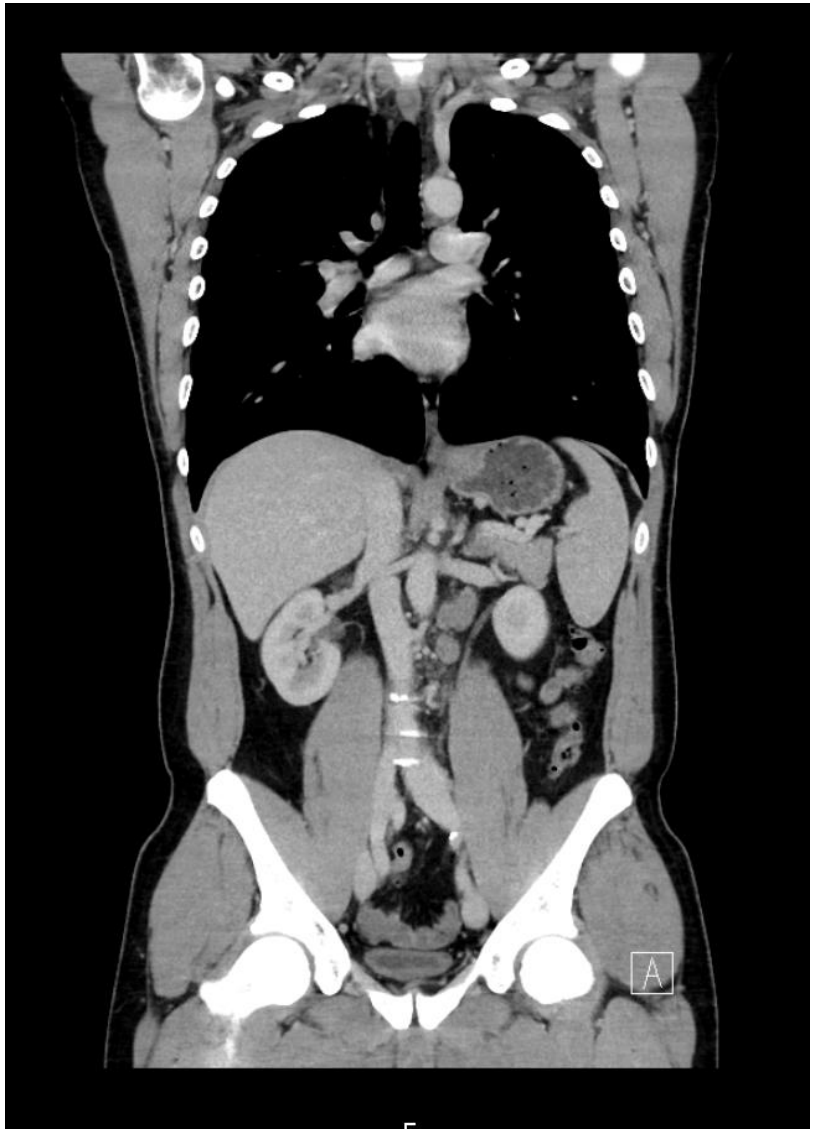
EAU Guidelines Panel on Chronic Pelvic Pain

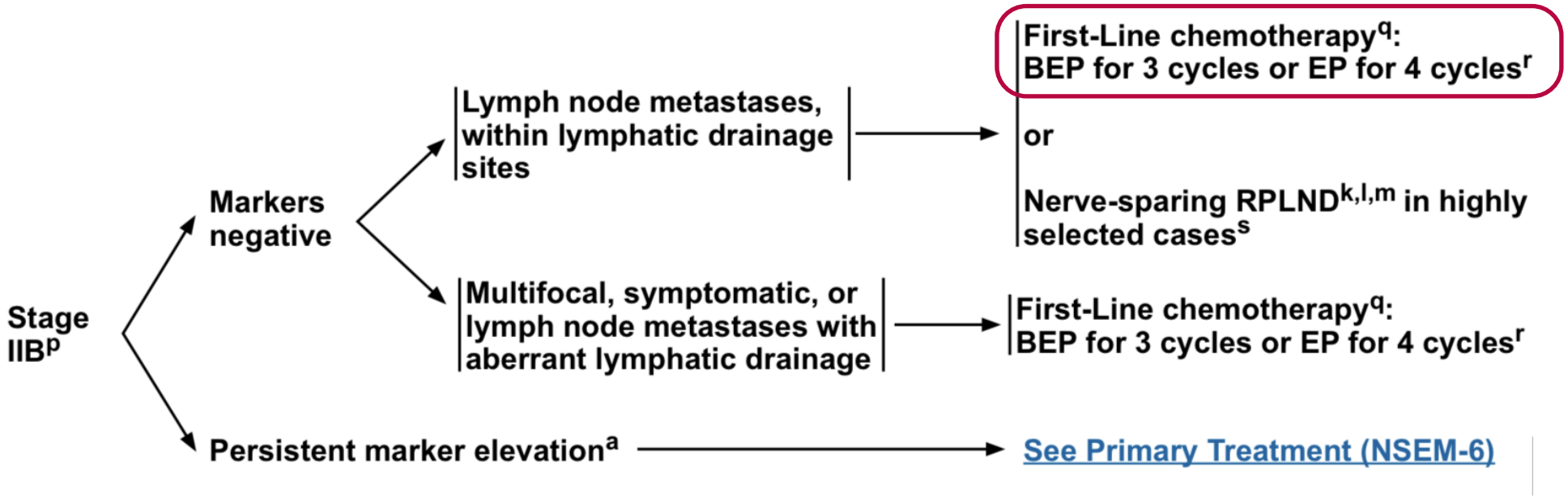
Right NSGCT

- Bilateral microcalcifications
- 90% Embrional; 10% Yolk sac
- Vascular invasion
- Pre op tumour markers elevated
- Pos op serum tumour markers S0
- Retroperitoneal gg 2-5 cm



pT2 cN2 cM0 R0 S0 with vascular invasion/> 50 % embryonal, AJCC IIb, good prognosis

What to do?



NCCN Guidelines 2023

pT2 cN2 cM0 R0 S0 with vascular invasion/> 50 % embryonal, AJCC IIb, good prognosis

What to do?

Primary treatment for patients with stage IIB nonseminoma depends on post-orchiectomy tumor marker levels and radiographic findings. When tumor marker levels are normal, the CT findings determine the proper course of treatment. If abnormal radiographic findings are limited to lymph node metastases within lymphatic drainage sites in the retroperitoneum (ie, the landing zone), patients may receive primary chemotherapy with either three cycles of BEP or four cycles of EP (both preferred) or primary nerve-sparing RPLND (reserved for highly selected cases; ie, stage II tumors with teratoma predominance in patients with normal markers). RPLND is also recommended for stage II tumors with somatic type malignancy (previously referred to as transformed teratoma).

NCCN Guidelines 2023

pT2 cN2 cM0 R0 S0 with vascular invasion/> 50 % embryonal, AJCC IIb, good prognosis

What to do?

For patients with negative markers and lymph node metastases within the primary landing zones, both primary chemotherapy or nerve-sparing RPLND are options per NCCN guidelines (10). A prospective study by Weissbach *et al.* compared RPLND or primary chemotherapy in CS IIA/B patients and found no difference in relapse rates at 36 months. No differences in quality of life were noted between groups, and 12% of patients treated with RPLND were reclassified as pathologic stage I disease (40). Therefore, upfront RPLND remains an option for patients wishing to avoid or unable to tolerate chemotherapy. Importantly, the cure rate for CS IIB disease is high (with survival from 88–95%) (26,64,65) with either RPLND or induction chemotherapy

Cheriyan SK, Nicholson M, Aydin AM, Azizi M, Peyton CC, Sexton WJ, Gilbert SM. Current management and management controversies in early- and intermediate-stage of nonseminoma germ cell tumors. Transl Androl Urol. 2020 Jan;9(Suppl 1)

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What to do?

Non-seminoma

Metastatic stage IIA, marker-positive and stage IIB-III non-seminoma

- Good-prognosis patients should receive 3 cycles of BEP
  - 4 cycles of EP can be used if there are contraindications against bleomycin
- Intermediate- or poor-prognosis patients should receive 4 cycles of BEP
  - 4 cycles of VIP with granulocyte colony-stimulating factor (G-CSF) support can be used if there are contraindications against bleomycin

EAU Guidelines 2022

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Tumors **larger than 2 centimeters**, involvement of more than 6 lymph nodes with cancer and evidence of **vascular invasion** of the primary tumor are all associated with an increased risk of cancer recurrence.
The relapse rate after retroperitoneal lymph node dissection has been reported to be approximately 60% in patients who had microscopic evidence of vascular invasion in the primary tumor.

EAU Guidelines 2022

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When to do imaging?

3.2. Response to Therapy and Post Therapeutic Changes

Patients with stage II or III TGCT are commonly treated with poly-chemotherapy regimens. CT imaging remains the standard modality for monitoring therapeutic response by measuring the diameter of the different lesions over several consecutive examinations [14,15]. The EGCCCG guidelines recommend that CT assessment must be performed at the end of first-line chemotherapy. An intermediate assessment must also be performed earlier in cases of poor-risk NSGCT patients treated according the GETUG 13 protocol [39].

The Role of CT in the Staging and Follow-Up of Testicular Tumors: Baseline, Recurrence and Pitfalls; Thibaut Pierre Et all, Cancers 2022, 14, 3965.

pT2 cN2 cM0 R0 S0 with vascular invasion/> 50 % embryonal, AJCC IIb, good prognosis

VADs?

cN > IIb (RPLN>3.5/5 cm) increase risk of TEE

Fankhauser CD et al, Eur Urol Focus 2021

BEP ChT significantly increase TEEs within the first year (6.3x myocardial infarction, 6.0x cerebrovascular accident 24.7x venous thromboembolism)

Lauritsen J et al, J Clin Oncol 2020

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VADs?

Recommendations	Strength rating
Balance the individual patients' potential benefits and risks of thromboprophylaxis during first-line chemotherapy in men with metastatic germ cell tumours.	Weak
Avoid use of central venous-access devices during first-line chemotherapy whenever possible.	Weak

EAU Guidelines 2022

pT2 cN2 cM0 R0 S0 with vascular invasion/> 50 % embryonal, AJCC IIb, good prognosis

VADs?

Despite lacking level I evidence…
- **TEE prevention** should be considered in GCT patients receiving cisplatin-based ChT for metastatic disease (>RPLN>3.5 cm; poor-risk features)
- **Vascular Access Devices** should be **avoided** whenever possible!

Fankhauser CD et al, European Association of Urology Testicular Cancer Panel Position 2021

Peripheral venous access should be used instead of an indwelling vascular access device

ESMO-EURACAN Clinical Practice Guideline for diagnosis 2022

pT2 cN2 cM0 R0 S0 with vascular invasion/> 50 % embryonal, AJCC IIb, good prognosis

PET/CT-FDG?

Non-seminoma

There is no recommendation for primary staging or restaging with F-FDG PET/CT in non-seminomas in the current EAU Guidelines because of its similar sensitivity and specificity to conventional restaging in the follow up (13,14). Its ability to predict viable residual masses was evaluated in a prospective clinical trial with 45 patients with poor prognosis non-seminomas. F-FDG PET/CT was compared to conventional radiologic monitoring with CT scans and changes in serum tumor markers. F-FDG PET/CT showed a sensitivity of 59% and a specificity of 92%. CT scan had a sensitivity of 55% and a specificity of 86% and change in serum tumor markers a sensitivity of 42% and a specificity of 100% (15).

Dotzauer R, Thomas C, Jäger W. The use of F-FDG PET/CT in testicular cancer. *Transl Androl Urol*. 2018;7(5):875-878.

cT2 N2 M0 R0 S0 with vascular invasion/> 50 % embryonal, AJCC IIb, good prognosis

What to do?

- 3 BEP

When to do imaging?

- 4-6 weeks after chemotherapy

CVC?

- As minimum as possible

PET-FDG?

- Not applicable

EAU Guidelines 2022, ESMO-EURACAN Clinical Practice Guideline for diagnosis 2022

<1 cm RPLN after 2 BEP, what to do?

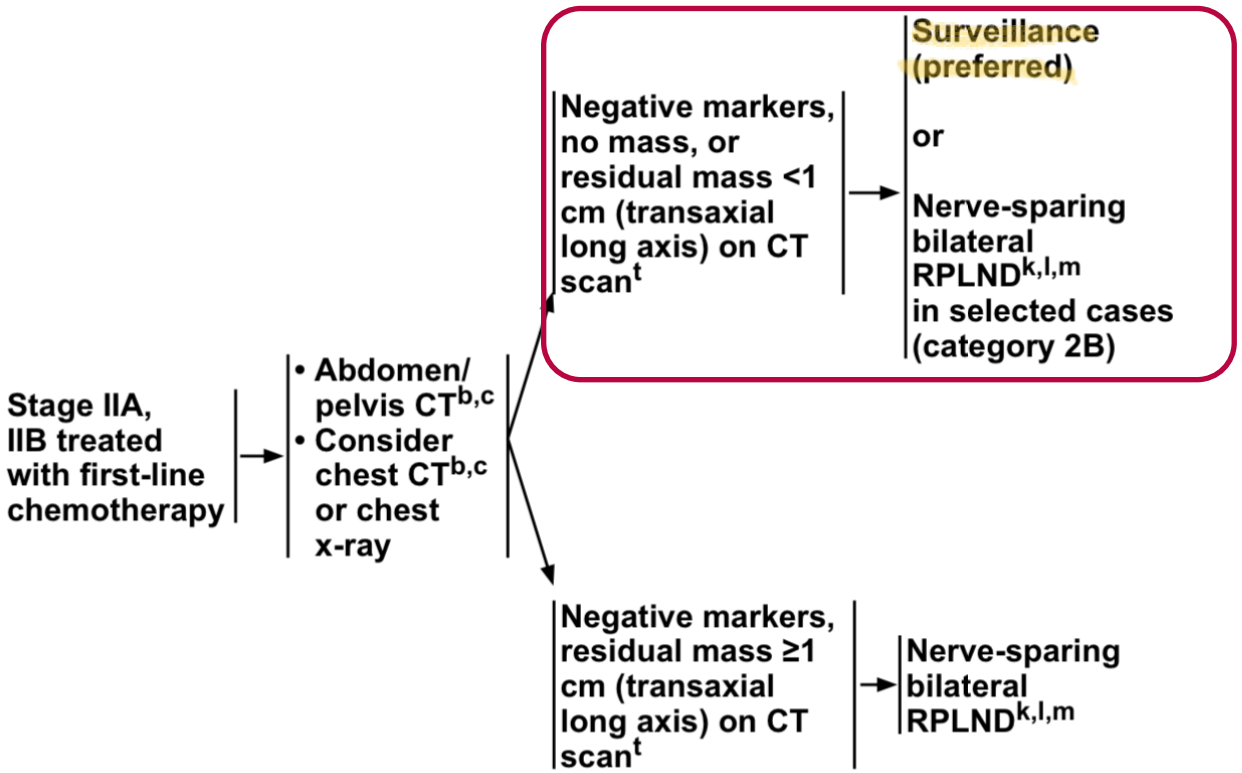
- 3 BEP *versus* 2 BEP?

<1 cm RPLN after 2 BEP, what to do?

- 3 BEP *versus* 2 BEP?

FIRST: COMPLETE 3 CICLES OF BEP

<1 cm RPLN after 3 BEP, what to do?



NCCN Guidelines 2023

<1 cm RPLN after 2 BEP, what to do?

Management of postchemotherapy residual masses ≤1 cm

After induction chemotherapy for CS II patients, further management depends on the size of residual masses. There is a clear consensus that for masses ≥1 cm, post-chemotherapy is recommended as there is a significant rate of both viable malignancy (11–17%) and teratoma (39–42%) (45,46). However, the management of residual masses <1 cm after induction chemotherapy is controversial as the histology of PC-RPLND masses <1 cm is 71% fibronecrosis, 24% teratoma, and 4% viable malignancy (47). Though imaging with FDG PET plays a role in the management of seminoma, a prospective trial demonstrated a false negative rate of 40% in NSGCT and furthermore, all cases of teratoma resulted in false-negative PET scans (48). Both surveillance and nerve-sparing RPLND are options for residual masses <1 cm

Cheriyan SK, Nicholson M, Aydin AM, Azizi M, Peyton CC, Sexton WJ, Gilbert SM. Current management and management controversies in early- and intermediate-stage of nonseminoma germ cell tumors. Transl Androl Urol. 2020 Jan;9(Suppl 1)

<1 cm RPLN after 2 BEP, what to do?

- 3 BEP and surveillance

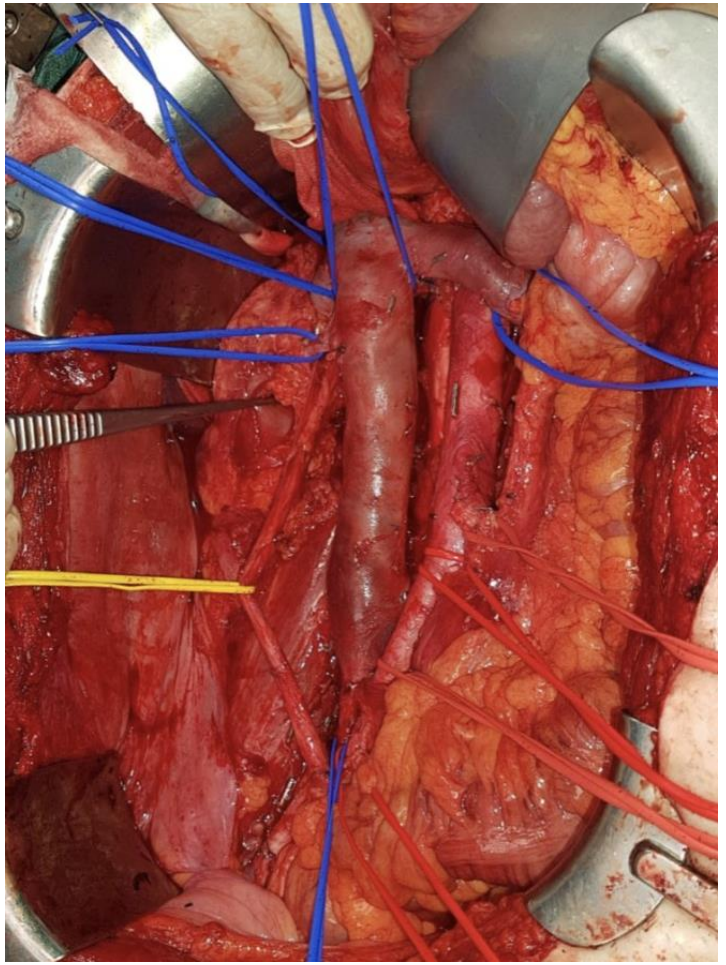
Despite the lack of randomized data, survival appears to be comparable between those who underwent RPLND and those who chose surveillance (over 90 percent among men with stage II or good-risk stage III disease).

Management of stage II nonseminomatous germ cell tumors, uptodate 2023

1-2 cm RPLN after 3 BEP, what to do?

Nerve-sparing RPLND is indicated 6-8 weeks after the last cycle with previous imaging

ESMO-EURACAN Clinical Practice Guideline for diagnosis 2022, NCCN Guidelines 2023, EAU Guidelines 2022



If pT2 N1 M0 S0?

- **15-35% do not harbour metastasis!!!**

- TAP CT each 6 weeks until regression or progression resulting in observation only or treatment: chemotherapy, lymph node biopsy, RPLND in single progression lymph node

Weissbach L et al, Eur Urol 2000

ESMO-EURACAN Clinical Practice Guideline for diagnosis 2022

No RCTs between upfront NS-RPLND/BEPCh/Surveillance...

- Upfront BEPCh: higher 5-y recurrence free survival, but similar 5-y cancer specific survival

- Upfront NS-RPLND: lower BEPCh cycles number

Cheriyan SK et al, Transl Androl Urol 2020

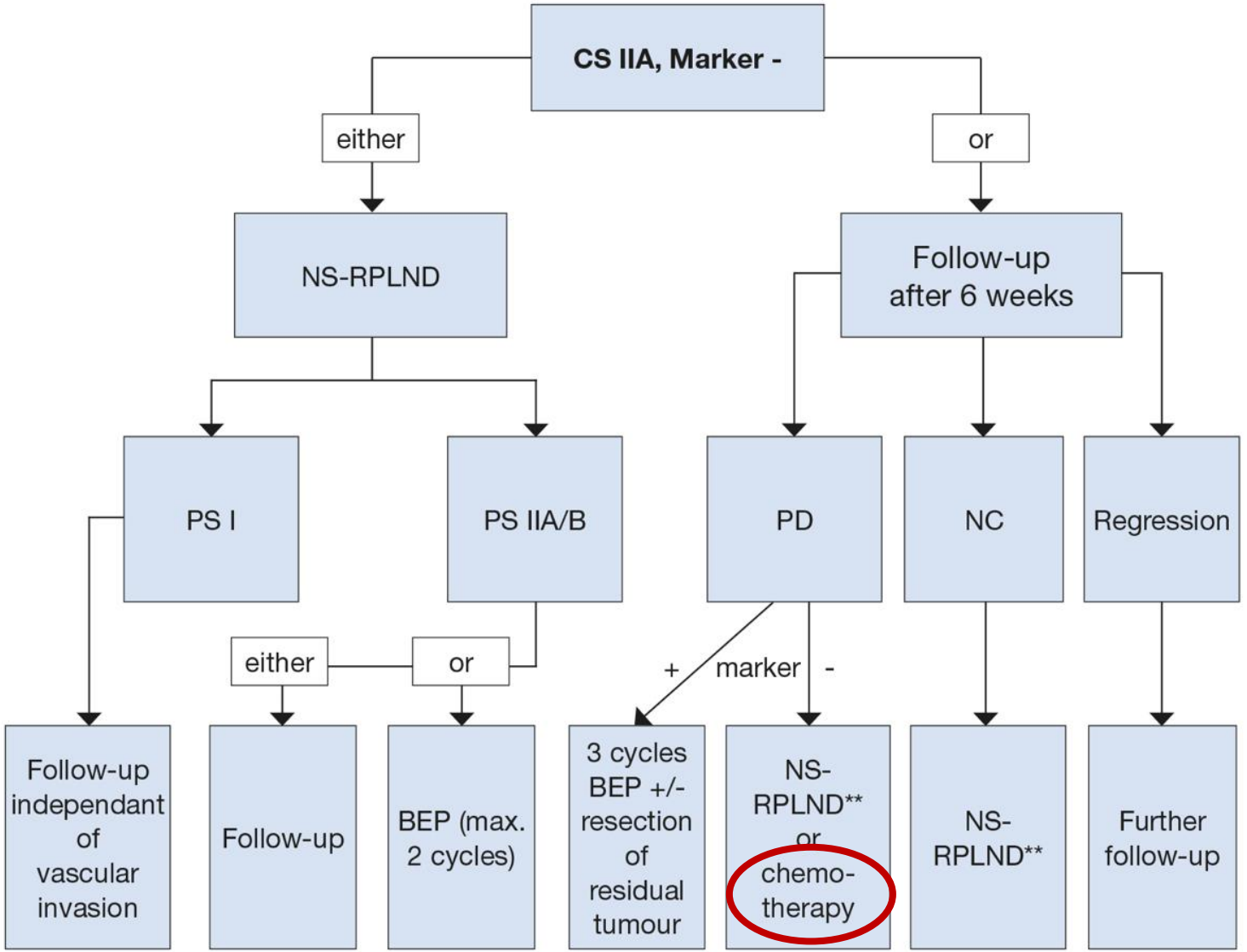
RPLND

Advantages	Not so good
Reduce number of BEPCh cycles	Risk of Infertility Risk of over-treatment

Chemotherapy

Advantages	Not so good
Effective against micrometastases Reduce de risk of recurrence but same survival	Risk of over-treatment Immediate side effects: Infertility Long term side effects: cardiovascular disease, hypertension, nephrotoxicity, neurotoxicity, vascular toxicity, high serum triglyceride levels

If pT2 N1 M0 S0?



EAU Guidelines 2022

Maximize cure while minimizing morbidity – How?

Genomics: Polygenic variation in the absence of a major high-penetrance susceptibility gene

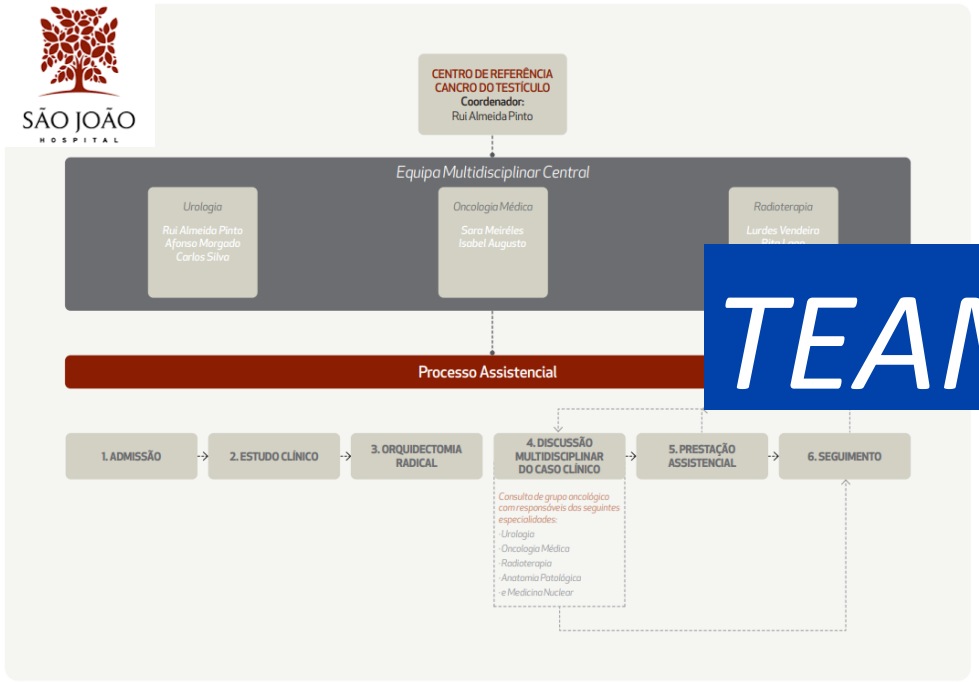
Epigenetic mechanisms: Chromatin remodeling; MicroRNA regulation; DNA promoter methylation

Genomics and therapy

- **Biomarkers for surgery/chemotherapy**
- **Potential targets:** TP53-MDM2, PI3 Kinase, MAPK signaling pathway, MSI/MMR (vinblastine, thalidomide, interferon-α, bevacizumab, pembrolizumab)

Maximize cure while minimizing morbidity – How?

Multidisciplinary Team



TEAM WORK

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