Testicular germ cell tumors

Introduction

- **Most common solid tumor in young adult men** with 3-6 new cases/100,000 men/year.
- **They account for 1.5% of male malignancies** and 5% of urological tumors.
- **Bilateral** in 1-2% of cases.
- **The peak incidence** is in the 3rd decade of life for nonseminomatous tumors and in the 4th decade for pure seminomas.
- **Prior history of cryptorchidism in 10% of cases.**
- **Associated with alterations** of chromosome 12 (isochromosome 12p) and also with changes in the p53 locus in intratubular germ cell neoplasia (Tin).
- **The following are considered to be epidemiological risk factors:**
  - Cryptorchidism (10% of testicular tumors have a history of cryptorchidism).
  - Klinefelter syndrome.
  - Family history of testicular cancer in 1st degree relatives.
  - Presence of Tin or contralateral tumor.
  - Infertility.

Histological classification (WHO 2004)

- **Germ cell tumors (90-95%):**
  - Intratubular germ cell neoplasia, unclassified type (Tin).
  - Seminoma (35% of the total).
    - Classic (85%).
    - Anaplastic (10%): the most aggressive.
    - Spermatocytic (5%): tends not to metastasize.
  - Nonseminomatous germ cell tumor (NSGCT).
    - Embryonal carcinoma (20%).
    - Teratoma (5%).
    - Teratocarcinoma (20%): combines the two aforementioned types. Produces $\beta$-HCG and $\alpha$-FP.
    - Choriocarcinoma (<1%).
    - Yolk sac tumor (<1%).
    - Mixed tumor (polyembryoma).
- **Sex cord-gonadal stromal tumors:** see chapter on Sex cord-gonadal stromal tumors.
  - Leydig cell tumor (or interstitial cell tumor).
  - Malignant Leydig cell tumor.
  - Sertoli cell tumor (or androblastoma): the classic type is a calcifying and sclerosing large cell tumor.
  - Malignant Sertoli cell tumor.
  - Granulosa cell tumor: adult and juvenile variants.
  - Thecoma-fibroma group tumors.
  - Other gonadal stromal tumors: incompletely differentiated and mixed variants.
  - Germ cell and gonadal stromal cell tumors (gonadoblastoma).
- **Nonspecific stromal tumors:**
  - Epithelial ovarian tumors: from Müllerian remnants.
  - Tumors of the collecting ducts and rete testis.
  - Other tumors (benign and malignant), nonspecific stromal tumors: sarcomas.
- **Secondary tumors:**
  - Metastatic.
  - Leukemic infiltration.
  - Lymphomatous infiltration.
Age of onset

- **Children:** yolk sac tumor.
- **20-30 years:** choriocarcinoma.
- **25-30 years:** embryonal carcinoma or teratocarcinoma.
- **30-40 years:** seminoma.
- **>50 years:** lymphomas.

Symptoms

- **Painless testicular nodule:** the most common symptom.
- **Intense scrotal pain** due to bleeding or necrosis (20%). **Low back pain** (11%). Symptoms similar to those of orchitis in 10% of cases.
- **Gynecomastia** in 7%, especially in choriocarcinoma.
- **Weight loss.**
- Sometimes the first sign arises from abdominal or lung metastases.

Diagnosis

- **Testicular tumor markers:** elevated in 51% of testicular tumors (in 90% of NSGCT and 30% of seminomas).
  - **β-HCG:** indicates the presence of trophoblasts. Normal levels <5 mIU/mL. Elevated in 100% of choriocarcinomas, 50% of embryonal carcinomas, and 10% of seminomas. Half-life of 24 hours (should not be tested until at least 1 week after orchiectomy).
  - **α-feto-protein** (AFP): produced by yolk sac cells. Normal levels <15 ng/mL. Elevated in 60% of nonseminomatous tumors. Half-life of 6 days (should not be tested until at least 1 month after surgery).
  - **LDH:** a marker of tissue destruction. Elevated in 80% of advanced tumors.
  - Other less clinically useful markers:
    - **PLAP** (placental alkaline phosphatase): may rise in cases of pure seminoma.
    - **NSE** (neuron specific enolase).
    - **GTCM-2** (superficial anti-proteoglycan antibody).
- **Scrotal ultrasound/MRI:** assesses the size of the lesion and its extension to neighboring structures as well as its echoic pattern. Displays heterogeneous images with anechoic (cystic) and other hypoechoic or hyperechoic areas. Seminomas have a more homogeneous pattern of a well-defined hypoechoic mass. An ultrasound finding of testicular microlithiasis is associated with a tumor in 46% of cases and calls for rigorous monitoring, which includes: instructing the patient in self-examination, measuring markers, and performing an ultrasound, physical exam, and a biopsy in case of doubt. MRI is more specific than ultrasound in the diagnosis of testicular cancer and can distinguish a seminoma from a nonseminomatous tumor. Because of its high cost, however, it is only indicated in cases of diagnostic doubt.
- **Inguinal surgical exploration:** in cases of doubtful ultrasound/MRI findings, the testicle should be explored. If a tumor is found, an orchiectomy is performed. In cases of doubt, an intraoperative biopsy can be carried out.
- **Biopsy of the contralateral testicle:** to rule out T1n. Should be performed in cases of contralateral atrophy, a history of cryptorchidism or severe azoospermia/oligozoospermia, and in patients ≤40 years. Double biopsy is recommended to increase sensitivity. The low incidence of T1n (9%) or contralateral tumors (2.5%) makes routine biopsies controversial.
- **Abdominal-pelvic CT or MRI:** crucial for tumor staging.
- **Chest CT/X-ray:** to detect lung and mediastinal metastases. A chest X-ray is sufficient in seminomas if an abdominal CT shows no lymphadenopathy. In NSGCT and seminomas with abdominal lymphadenopathy, a chest CT should be performed.
- **PET:** only indicated in seminomas to assess residual post-chemotherapy masses to decide between observation and active treatment.
- **Fertility study and cryopreservation of semen:** should always be offered to all younger patients with a desire for future fertility before starting chemo/radiotherapy.
**Staging**

- **Primary tumor (pT):** classified after radical orchiectomy. Without orchiectomy, the tumor should be classified as Tx, unless it is Tis or T4.

- **Regional nodes (N and pN):** interaortocaval, para-aortic, paracaval, preaortic, precaval, retroaortic, and retrocaval. If there is epididymal infiltration, there may be external iliac lymphadenopathy. In cases of prior scrotal/inguinal surgery or invasion of the scrotal wall, there may be inguinal lymphadenopathy. Other nodes are considered as outside the region.

- **Distant metastasis (M):** the most common locations are the non-regional lymph nodes, lungs, liver, bones, and other organs.

- **Serum markers (S):** β-HCG, AFP, and LDH are determined prior to surgery to assign S value.

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**TNM classification (UICC 2009, 7th edition)**

<table>
<thead>
<tr>
<th>Primary tumor</th>
<th>pTx</th>
<th>Primary tumor cannot be assessed.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>pT0</td>
<td>No evidence of primary tumor (e.g. histological scar in testis).</td>
</tr>
<tr>
<td></td>
<td>pTis</td>
<td>Intratubular germ cell neoplasia (testicular intraepithelial neoplasia, Tin).</td>
</tr>
<tr>
<td></td>
<td>pT1</td>
<td>Tumor limited to testis and epididymis without vascular/lymphatic invasion: tumor may invade tunica albuginea but not tunica vaginalis.</td>
</tr>
<tr>
<td></td>
<td>pT2</td>
<td>Tumor limited to testis and epididymis with vascular/lymphatic invasion, or tumor extending through tunica albuginea with involvement of tunica vaginalis.</td>
</tr>
<tr>
<td></td>
<td>pT3</td>
<td>Tumor invades spermatic cord with or without vascular/lymphatic invasion.</td>
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<tr>
<td></td>
<td>pT4</td>
<td>Tumor invades scrotum with or without vascular/lymphatic invasion.</td>
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<table>
<thead>
<tr>
<th>Regional lymph nodes</th>
<th>N0</th>
<th>Regional lymph nodes cannot be assessed.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N1</td>
<td>Metastasis with a lymph node mass &lt;2 cm in greatest dimension or multiple lymph nodes, but none &gt;2 cm in greatest dimension.</td>
</tr>
<tr>
<td></td>
<td>N2</td>
<td>Metastasis with a lymph node mass 2-5 cm in greatest dimension, or multiple lymph nodes with any one mass 2-5 cm in greatest dimension.</td>
</tr>
<tr>
<td></td>
<td>N3</td>
<td>Metastasis with a lymph node mass &gt;5 cm in greatest dimension.</td>
</tr>
<tr>
<td></td>
<td>pNx</td>
<td>Regional lymph nodes cannot be assessed.</td>
</tr>
<tr>
<td></td>
<td>pN0</td>
<td>No regional lymph node metastasis.</td>
</tr>
<tr>
<td></td>
<td>pN1</td>
<td>Metastasis with a lymph node mass &lt;2 cm in greatest dimension and 5 or fewer positive nodes, none &gt;2 cm in greatest dimension.</td>
</tr>
<tr>
<td></td>
<td>pN2</td>
<td>Metastasis with a lymph node mass 2-5 cm in greatest dimension; or more than 5 positive nodes, none &gt;5 cm; or evidence of extranodal extension of tumor.</td>
</tr>
<tr>
<td></td>
<td>pN3</td>
<td>Metastasis with a lymph node mass &gt;5 cm in greatest dimension.</td>
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</table>

<table>
<thead>
<tr>
<th>Distant metastasis</th>
<th>M0</th>
<th>No distant metastasis.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M1</td>
<td>Distant metastasis (M1a non-regional lymph nodes or lung; M1b other sites).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Serum markers</th>
<th>Sx</th>
<th>Serum marker studies not available or not performed.</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>S0</td>
<td>Serum marker study levels within normal limits.</td>
</tr>
<tr>
<td></td>
<td>S1</td>
<td>LDH &lt;1.5 x N and β-HCG &lt;5000 mU/l/mL and α-FP &lt;1000 ng/mL.</td>
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<tr>
<td></td>
<td>S2</td>
<td>LDH 1.5-10 x N or β-HCG 5000-50000 mU/l/mL or α-FP 1000-10000 ng/mL.</td>
</tr>
<tr>
<td></td>
<td>S3</td>
<td>LDH &gt;10 x N or β-HCG &gt;50000 mU/l/mL or α-FP &gt;10000 ng/mL.</td>
</tr>
</tbody>
</table>

(N indicates the upper limit of normal for the LDH assay)

<table>
<thead>
<tr>
<th>Stage grouping</th>
<th>Stage 0</th>
<th>Stage I</th>
<th>Stage II</th>
<th>Stage III</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>pTisN0M0S0</td>
<td>pT1N0M0S0</td>
<td>pT4N0M0S0</td>
<td>pT0-4/T1N0M0S0</td>
</tr>
<tr>
<td></td>
<td>pT1N0M0S0</td>
<td>pT2N0M0S0</td>
<td>pT3N0M0S0</td>
<td>pT0-4/T2N0M0S0</td>
</tr>
<tr>
<td></td>
<td>pT2N0M0S0</td>
<td>pT3N0M0S0</td>
<td>pT4N0M0S0</td>
<td>pT0-4/T3N0M0S0</td>
</tr>
<tr>
<td></td>
<td>pT3N0M0S0</td>
<td>pT4N0M0S0</td>
<td>pT0-4/T4N0M0S0</td>
<td>pT0-4/T4N0M0S0</td>
</tr>
</tbody>
</table>

(Stage grouping includes all possible combinations of primary tumor, regional nodes, and distant metastasis states. Each stage is further divided based on the specific combinations of pT, N, and M states.)
Testicular tumor surgery

- **Radical inguinal orchiectomy**: the standard treatment. In cases of prior scrotal violation (biopsy, puncture, or trans-scrotal orchiectomy) a hemiscrotectomy is recommended simultaneously with retroperitoneal lymphadenectomy.

- **Conservative surgery (lumpectomy)**: can be considered in synchronous or metachronous bilateral tumors and in monorchid patients with normal testosterone levels if the tumor volume does not occupy >30% of the testis. Since tin is present in 82% of bilateral tumors, all patients should receive adjuvant radiotherapy (20 Gy) after surgery. Because radiation may produce testosterone deficiency and infertility, it can be delayed in younger patients.

- **Retroperitoneal lymphadenectomy (RLA)**: can be performed laparoscopically and with preservation of the sympathetic chains to prevent ejaculatory disorders. In Europe it is used for treating post-CHTH residual masses of NSGCT. In the US, it precedes chemotherapy in patients with stage IB/IIA NSGCT and negative markers.

Treatment of stage I seminoma

- **Radical orchiectomy**: with orchiectomy only, the 5-year relapse rate due to subclinical retroperitoneal metastasis is 15-20%. For tumors >4 cm and with rete testis invasion, the relapse rate is 32%. Without these risk factors, the relapse rate is 12%.

- **Treatment options after orchiectomy**:
  - *Watchful waiting*: if there are no risk factors and patients can be followed closely. Of the 15-20% of post-orchiectomy relapses, 70% can be treated with salvage RT. Of these patients, only 20% will suffer a relapse and require salvage CHTH. With this strategy, the cancer-specific survival rate is 97-100%.
  - *Prophylactic CHTH*: 1-2 cycles of Carboplatin reduce relapse rates to 1-3%. Chemotherapy after orchiectomy is thus a good alternative to observation and prophylactic RT, especially if there are risk factors when monitoring is difficult.
  - *Prophylactic RT*: 20-24 Gy to the para-aortic chains or in a hockey stick pattern (para-aortic + ipsilateral iliac) reduces relapse rates to 1-3%. It is a cheap treatment option with delayed side-effects in less than 2% of patients with risk factors.

Treatment of stage I NSGCT

- **Orchiectomy**: excluding cases of stage IS tumors, up to 30% of patients who only undergo testicle removal will have a relapse. 80% will relapse within 1 year, 12% in the 2nd year, 6% in the 3rd year, and 2% in each successive year. The best predictor of relapse is the presence of vascular invasion in the primary tumor: without invasion (pT1) the relapse rate is 15-20%, with invasion (pT2+4) it is 50%. 35% of patients have normal markers at the time of relapse.

- **Treatment options after orchiectomy**:
  - *Watchful waiting*: a valid option in low risk patients (no vascular invasion) because of the high efficacy of salvage CHTH and RLA in treating post-CHTH residual masses. Not indicated in stage IS tumors, for which the first option is CHTH with 3-4 cycles of Bleomycin, Etoposide, and Cisplatin (BEP); the alternative is RLA.
  - *Prophylactic CHTH*: in high risk patients (with vascular invasion) or when monitoring is difficult and patients do not want to take the risk of follow-up. 2 cycles of BEP lower the relapse rate to 3%. There is a risk of mature teratoma after CHTH and also of late chemo-resistant relapse. In those cases, RLA of the residual mass is indicated.
  - *Retroperitoneal lymphadenectomy (RLA)*: an alternative to CHTH in high risk patients who do not want to take the risk of follow-up or in whom monitoring is difficult. Can be performed laparoscopically and with preservation of the sympathetic chains to prevent ejaculatory disorders. The risk of recurrence after this surgery is 7%, slightly higher than for prophylactic CHTH. If the pathology is positive, CHTH is recommended with 2 cycles of BEP, which lowers the risk of recurrence to 2%.
Treatment of stage I seminoma after orchiectomy

- Easy follow-up and no risk factors
  - Watchful waiting
    - cured
  - relapse
    - Salvage RT or CHTH
      - cured
      - relapse
        - Salvage CHTH
- Difficult follow-up, tumor >4 cm or rete testis invasion
  - Prophylactic RT or CHTH
    - cured
Treatment of stage I TCGNS after orchiectomy

- Easy follow-up and no vascular invasion (pT1)
  - Watchful waiting
    - cured
    - relapse

- Difficult follow-up or vascular invasion (pT2-4)
  - 1st option
    - CHTH (2 cycles of BEP)
      - relapse
        - Salvage CHTH (3-4 cycles of BEP)
          - relapse
            - Salvage RLA (residual mass)
          - cured
        - pN0
      - pN1-2
  - alternative
    - Primary RLA
      - cured
      - CHTH (2 cycles of BEP)
Treatment of metastatic germ cell tumors

- Prognostic groups of metastatic germ cell tumors (IGCCCG classification from 1997):
  - Good prognosis:
    - **NSGCT** (56% of cases): 5-year survival rate of 92%. All of the following:
      - Primary testicular or retroperitoneal tumor.
      - Absence of non-pulmonary visceral metastasis.
      - **AFP** <1000 ng/mL.
      - β-HCG <5000 IU/L (1000 ng/mL).
      - **LDH** <1.5 x upper limit of normal.
    - **Seminoma** (90% of cases): 5-year survival rate of 86%. All of the following:
      - All primary tumor locations.
      - Absence of non-pulmonary visceral metastasis.
      - Normal **AFP**.
      - All β-HCG values.
      - All **LDH** values.
  - Intermediate prognosis:
    - **NSGCT** (28% of cases): 5-year survival rate of 80%. All of the following:
      - Primary testicular or retroperitoneal tumor.
      - Absence of non-pulmonary visceral metastasis.
      - **AFP** 1000-10000 ng/mL or β-HCG 5000-50000 IU/L or **LDH** 1.5-10 x upper limit of normal.
    - **Seminoma** (10% of cases): 5-year survival rate of 72%. When any of the criteria for a good prognosis are not met:
      - All primary tumor locations.
      - Absence of non-pulmonary visceral metastasis.
      - Normal **AFP**.
      - All β-HCG values.
      - All **LDH** values.
  - Poor prognosis:
    - **NSGCT** (16% of cases): 5-year survival rate of 48%. Any of the following:
      - Primary mediastinal tumor.
      - Non-pulmonary visceral metastasis.
      - **AFP** >10000 or β-HCG >50000 or **LDH** >10 x upper limit of normal.
    - **Seminoma** (0%): no patients are classified as having a poor prognosis.

- PRIMARY TREATMENT based on histology and IGCCCG prognostic group:
  - Low volume metastatic tumor (stages IIA/B):
    - **Seminoma IIA/B**: RT with 30 Gy in *hockey stick* pattern (para-aortic + ipsilateral iliac) is the standard treatment for stage IIA tumors (36 Gy for IIB). In stage IIB the alternative is CHTH with 3 cycles of BEP or 4 cycles of EP.
    - **NSGCT IIA/B**: standard treatment is CHTH with 3 cycles of BEP followed by RLA in cases of residual masses. Alternatives in NSGCT IIA with negative markers are:
      - Observation: reevaluation at 6 weeks. If the lymph nodes shrink, they are probably not malignant and should be monitored; if they are the same or larger, RLA should be performed (if pathology shows mature teratoma, no further Tx is needed; if there is malignancy, CHTH with 2 cycles of BEP are indicated).
      - Primary RLA with conservation of the sympathetic chains; if pathology is positive for tumor, 2 cycles of BEP are recommended.
  - Advanced metastatic tumor (stages IIC, IIIA/B/C): the treatment of choice is primary CHTH with 3-4 cycles of BEP.
    - IGCCCG good prognosis group: 3 cycles of BEP or 4 of EP if *Bleomycin* is contraindicated.
    - IGCCCG intermediate prognosis group: 4 cycles of BEP.
    - IGCCCG poor prognosis group: 4 cycles of BEP or clinical trial in the reference center.
• **Restaging after primary CTHH and SALVAGE TREATMENT:** after primary CTHH the tumor should be restaged with imaging tests and markers. There are various possibilities:
  - *Decreasing markers and stable tumor or tumor in regression:*
    - If there is no residual mass: monitoring.
    - If there is a residual mass of a seminoma it should not be resected, but controlled with imaging techniques and markers. PET can be performed to distinguish fibrosis from an active tumor in the residual mass. If there is progression of the mass, salvage CTHH with 4 cycles of PEI/VIP (Cisplatin, Etoposide, Ifosfamide), TIP (Paclitaxel, Ifosfamide, Cisplatin), or VeIP (Vinblastin, Ifosfamide, Cisplatin) is indicated with RLA of the residual mass or RT.
    - If there is a residual mass of an NSGCT: RLA should be performed even if markers have normalized. The risk of a residual tumor is 10%, of a mature teratoma 40%, and of necrosis-fibrosis 50%. Neither PET nor any prognostic model can predict the pathology of the residual mass. Consolidation CTHH after resection of the mass is indicated only after incomplete resection of an immature teratoma or viable carcinoma, but not in cases of complete resection of a tumor occupying <10% of the mass, nor in mature teratomas or in cases of fibrosis/necrosis.
  - *Decreasing markers with metastasis progression:* RLA with preservation of sympathetic chains, if possible.
  - Increasing markers after 2 cycles of BEP: salvage CTHH with 4 cycles of PEI/VIP, TIP, or VeIP or clinical trials. With increasing markers, RLA is not indicated.
• **Late relapses (>2 years after first-line treatment):** complete resection of all lesions should be attempted. If technically unfeasible, a biopsy should be performed along with salvage CTHH, depending on the pathology. If the patient responds to salvage CTHH and if possible, secondary surgery is indicated; if not, RT should be performed.

**Follow-up after curative treatment**

• **Follow-up of stage I seminoma:** physical examination and tumor markers every 4 m in the 1st and 2nd years, every 6 m in the 3rd and 4th years, and annually after 5 years. Abdominal and pelvic CT and chest X-ray every 6 m in the 1st and 2nd years and annually after the 3rd year.

• **Follow-up of stage I NSGCT:** physical examination and tumor markers every 3 m in the 1st and 2nd years, every 6 m in the 3rd and 4th years, and annually after the 5th year. Abdominal-pelvic CT and chest X-ray every 6 m in the 1st and 2nd years and annually after the 3rd year.

• **Follow-up of stage II and III metastatic tumors:** physical examination, tumor markers, and chest X-ray every 3 m in the 1st and 2nd year, every 6 m the 3rd and 4th years, and annually after the 5th year. Abdominal-pelvic CT every 6 m in the 1st and 2nd year and annually after the 3rd year. Chest CT if there is any abnormality in the chest X-ray or after resection of lung metastases. Brain CT in patients with headaches, neurological focality, or CNS symptoms.
Treatment of metastatic germ cell tumors

**Low volume (stage IIA/B)**
- **Seminoma**
  - Primary RT (alternative: 3 cycles of BEP in seminoma IIB)
    - 1st option
      - **Primary CHTH (2 cycles of BEP)**
        - Observation
          - residual mass
            - salvage RLA
          - no residual mass
            - no tumor
              - observation
            - 6 wks
              - no tumor
                - observation
              - tumor
                - Consolidation CHTH (2 cycles of BEP)
          - 6 wks
            - no tumor
              - observation
            - tumor
              - Salvage RLA

- **NSGCT**
  - Alternative in NSGCT IIA with ∅ markers
    - Observation
      - residual mass
        - salvage RLA
      - no residual mass
        - no tumor
          - observation
        - 6 wks
          - no tumor
            - observation
          - tumor
            - Consolidation CHTH (2 cycles of BEP)

**High volume (stage IIC or IIIA/B/C)**
- **Primary CHTH (3-4 cycles of BEP)**
  - markers ↑
    - Salvage CHTH (VIP, TIP OR VEIP)
      - progression
        - no progression
          - observation
        - seminoma residual mass
          - observation
          - tumor
            - Consolidation CHTH (2 cycles of BEP)
          - no tumor
            - observation
      - seminoma residual mass
        - observation
        - tumor
          - Consolidation CHTH (2 cycles of BEP)
    - markers ↓ metastasis ↑
      - observation
      - tumor
        - Consolidation CHTH (2 cycles of BEP)
    - markers ↓ metastasis ↓
      - observation
      - tumor
        - Consolidation CHTH (2 cycles of BEP)
  - no progression
    - observation
    - tumor
      - Consolidation CHTH (2 cycles of BEP)
  - NSCCT residual mass
    - observation
    - tumor
      - Consolidation CHTH (2 cycles of BEP)