EUROPEAN HEMATOLOGY ASSOCIATION

# EHA-MSH Hematology Tutorial

## Self-assessment Case – Session 4: Hodgkin Lymphoma

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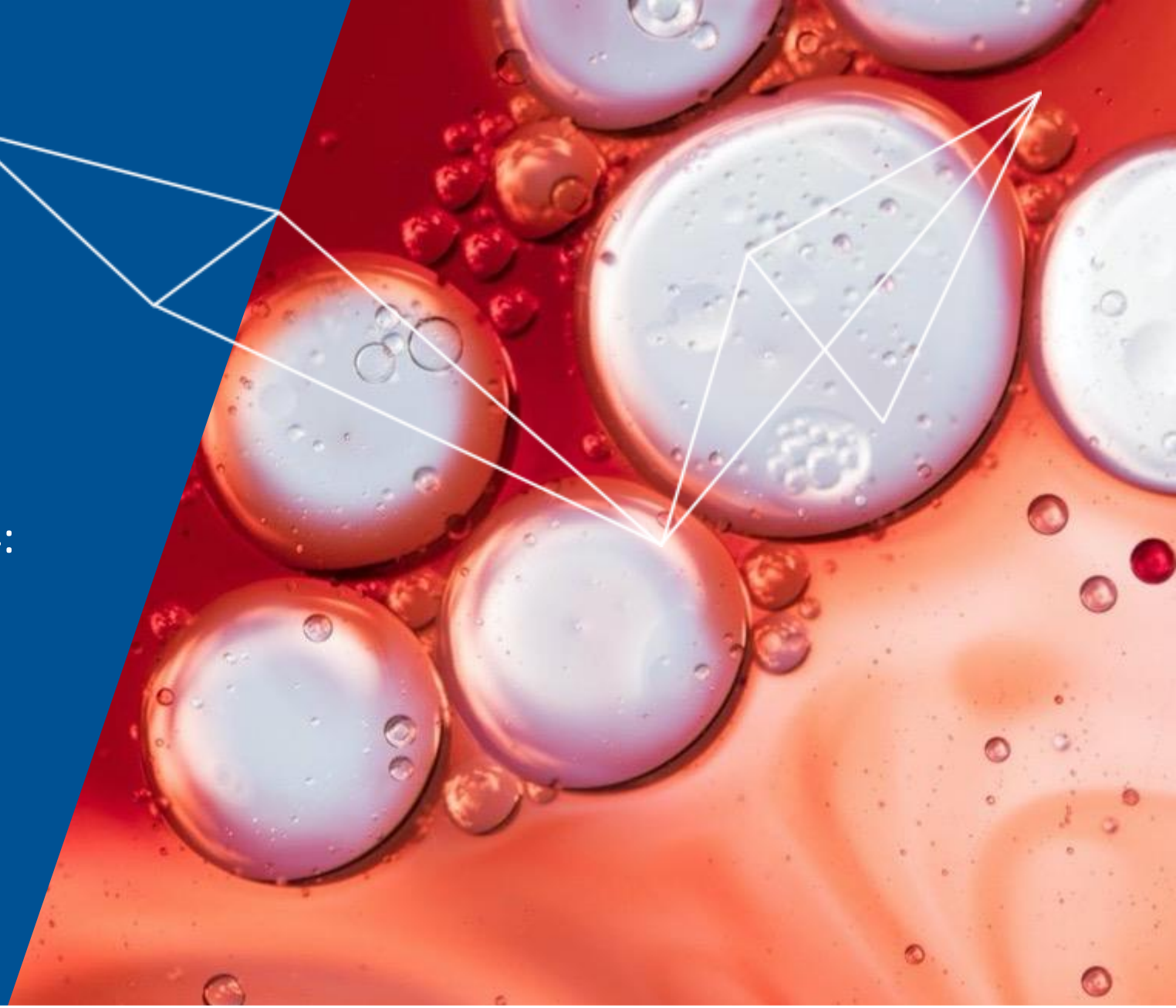


# Diagnosis

- A 33-year-old Italian man presented with fever, night sweats, and weight loss of 6 kg in two months
- Former smoker
- No relevant medical history
- CT and PET scans revealed:
  - Bulky mediastinal mass measuring 11 × 9 cm
  - Adenopathies in the neck, thorax, and abdomen measuring up to 3 cm (max. diameter)
  - Spleen involvement (multiple lesions measuring up to 5 cm [max. diameter])
  - Lesions in the right lung (multiple lesions measuring up to 1.5 cm [max. diameter])
- Lymph-node biopsy reveals classical Hodgkin lymphoma with nodular sclerosis
  - Ann Arbor stage IVEB
  - IPS score of 4 (male, anemia, leukocytosis, stage)

# First-line treatment

## July 2020

- No new drugs approved in Italy for first-line treatment
- 2 cycles of ABVD
- PET scan after 2 cycles of ABVD
  - PET-negative (Deauville score of 2)
- 4 cycles of A(B)VD
- PET scan after 6 cycles of ABVD
  - PET-negative (Deauville Score of 2)
- CT scan after 6 cycles of ABVD
  - Residual mediastinal mass measuring 5 × 1.5 cm

## February 2021 follow-up

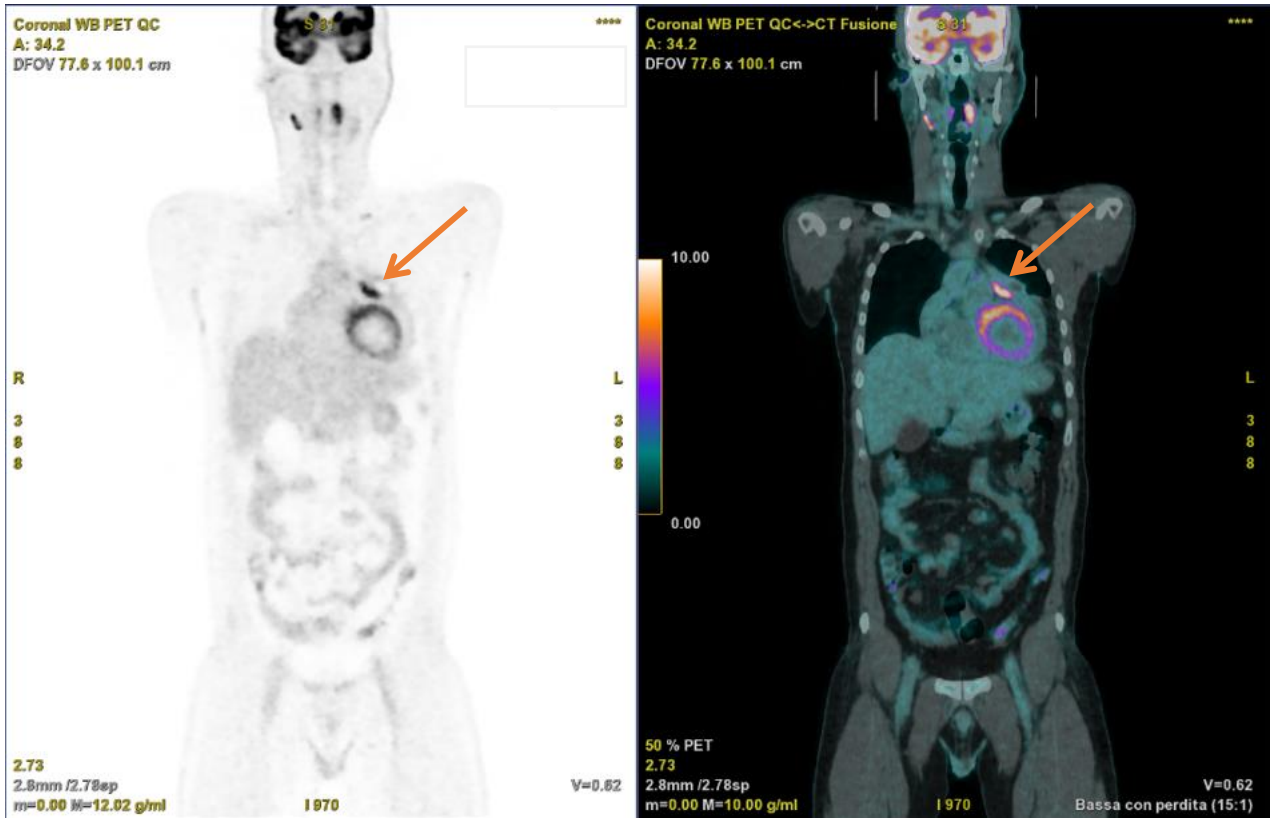
- First complete metabolic response

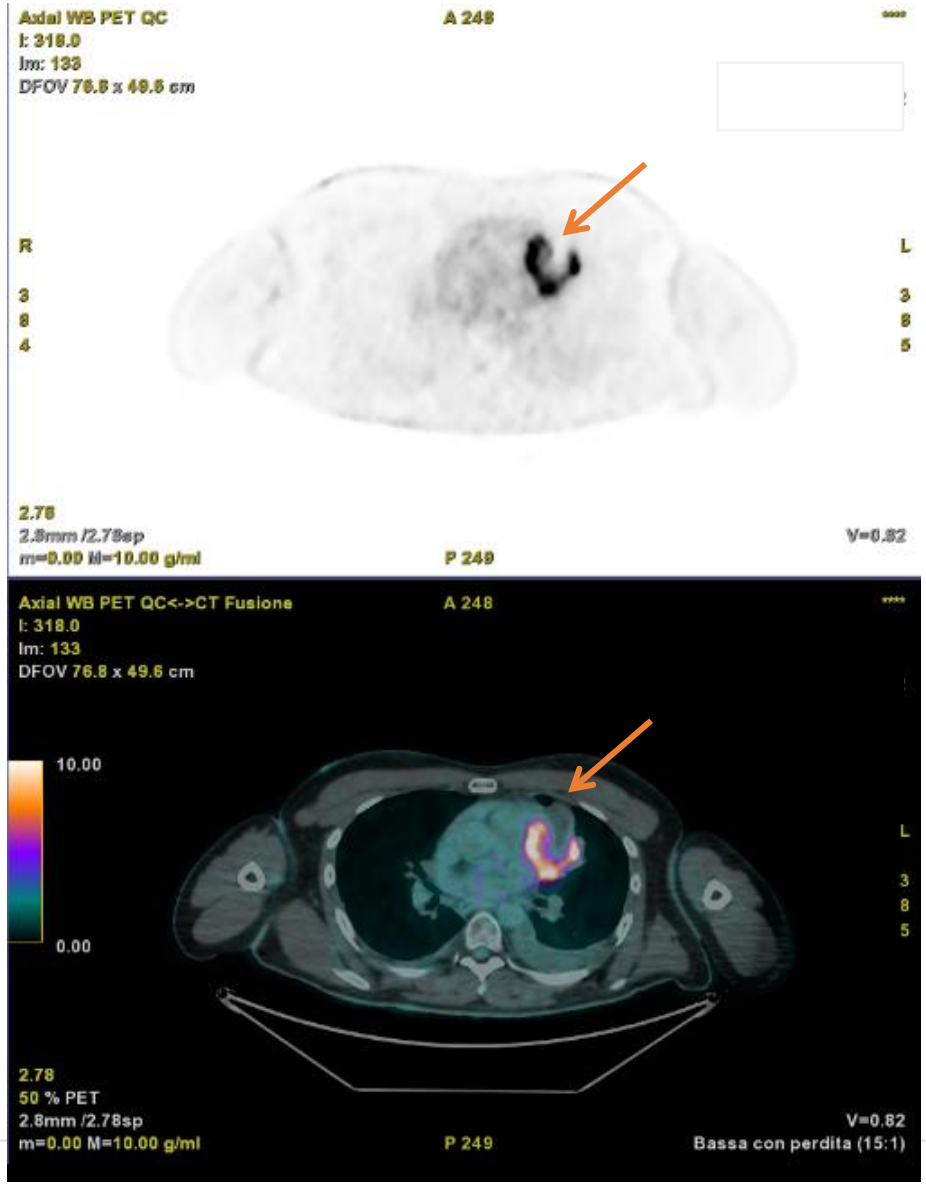
# First relapse

**June 2021 (after 4 months)**

- Cough and fever (37.5°C)
- CT scan
  - Increase in mediastinal mass (6 × 3.5 cm) and non-bulky supradiaphragmatic adenopathies
- PET scan
  - PET-positive due to mediastinal mass and multiple thoracic adenopathies (Deauville Score of 5)

# PET scan at relapse




- PET scan reveals suspected nodal mediastinal classical Hodgkin lymphoma (early relapse, after 4 months)

# Question 1:
# Based on the clinical history and PET findings after 6 cycles of ABVD, how do you suggest to proceed?

1. Involved-field radiotherapy
2. Evaluate patient for feasibility of biopsy
3. Extended-field radiotherapy
4. Salvage chemotherapy
5. Follow-up

# Question 1:
# Based on the clinical history and PET findings after 6 cycles of ABVD, how do you suggest to proceed?

1. Involved-field radiotherapy
2. **Evaluate patient for feasibility of biopsy**
3. Extended-field radiotherapy
4. Salvage chemotherapy
5. Follow-up

# Feedback to Question 1

- The gold standard for diagnosis of classical Hodgkin lymphoma is histological confirmation, especially after achievement of complete response
- Feasibility of biopsy at relapse should be evaluated by a multidisciplinary team and depends on target lesion site, patient characteristics, and need for treatment

# Biopsy of PET-positive lesions

- After multidisciplinary discussion (hematologist, radiologist, nuclear medicine physician, thoracic surgeon):
  - Mammary and paratracheal lymph-node lesions were excluded as targets for biopsy due to their small dimensions
  - Mediastinal mass was evaluated as a potential suitable target
    - Both for CT-guided needle biopsy and surgical biopsy
- A CT-guided needle biopsy was performed, and relapse of classical Hodgkin lymphoma was confirmed

# Question 2:
# After histological confirmation of refractory classical Hodgkin lymphoma, how do you suggest to proceed?

1. Involved-field radiotherapy
2. Upfront ASCT
3. Extended-field radiotherapy
4. Salvage chemotherapy and ASCT
5. Follow-up

# Question 2:
# After histological confirmation of refractory classical Hodgkin lymphoma, how do you suggest to proceed?

1. Involved-field radiotherapy
2. Upfront ASCT
3. Extended-field radiotherapy
4. **Salvage chemotherapy and ASCT**
5. Follow-up

# Feedback to Question 2

- Standard treatment of a young transplant-eligible patient with refractory/relapsed classical Hodgkin lymphoma is second-line polychemotherapy followed by ASCT consolidation
- Upfront ASCT is not an option since post-transplant outcomes are clearly superior in patients achieving a complete metabolic response before transplantation
- Radiotherapy, regardless of dosage and fields, is not a suitable option for a young patient refractory to first-line therapy
  - Should be candidate for a potentially curative systemic treatment

# Question 3:
# What kind of salvage chemotherapy would you offer to this patient?

1. ICE (ifosfamide, carboplatin, etoposide)
2. DHAP (dexamethasone, Ara-C, cisplatin)
3. Bendamustine and brentuximab vedotin
4. BEGEV (bendamustine, gemcitabine, vinorelbine)
5. In the absence of randomized trials, all the above options are correct

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# Feedback to Question 3

- Randomized trials comparing different salvage chemotherapies for classical Hodgkin lymphoma are lacking; centers can choose one of the strategies tested in phase 2 trials
- The optimal salvage treatment should be effective, feasible, and support blood stem-cell mobilization
- 2 to 4 cycles of second-line treatments are usually given as bridge to ASCT

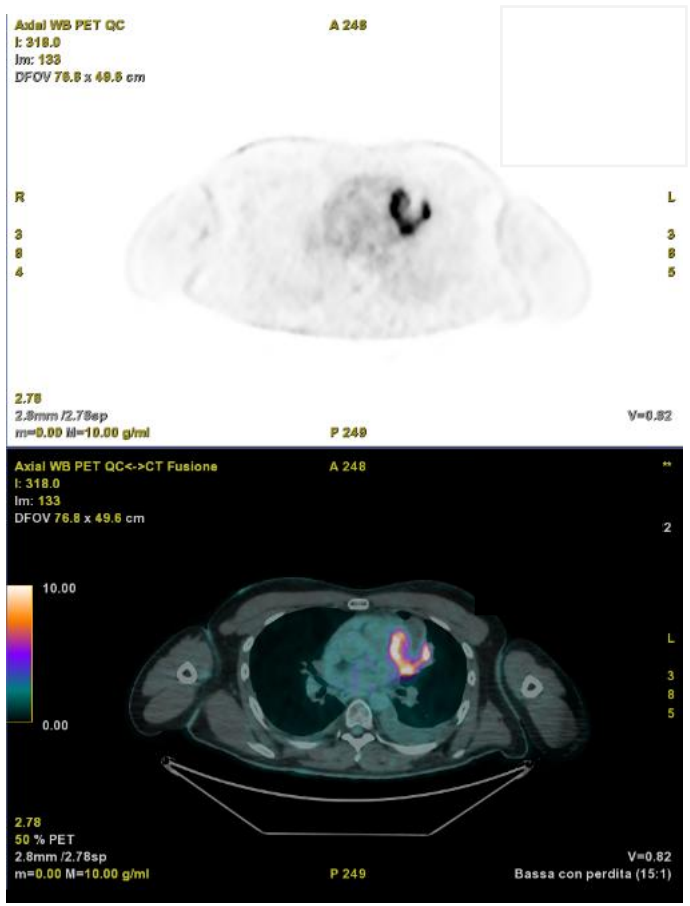
# First salvage

- 2 cycles of BEGEV
  - Well tolerated except for grade 2 skin rash after cycle 1
  - Steroids pre-medication from cycle 2
- PET after 2 cycles
  - PET-negative (Deauville Score of 3)
- 1 cycle of BEGEV plus G-CSF and leukapheresis
  - Day + 10
  - 5.8 x $10^6$ $CD34^+$ cells/kg
- 1 more cycle of BEGEV (in total 4 cycles of BEGEV)
- PET after 4 cycles of BEGEV
  - PET-negative (Deauville Score of 2)
- CT after 4 cycles of BEGEV
  - Residual mediastinal mass measuring 5.2 × 2 cm

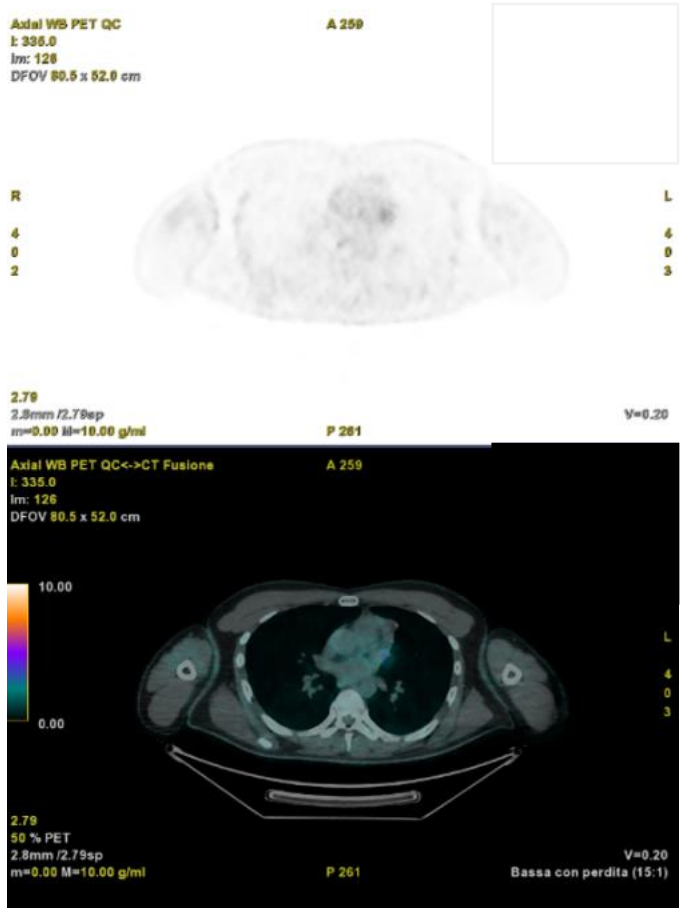
# PET scan after 4 cycles of BEGEV


PET scan after 4 cycles of BEGEV reveals complete metabolic response (Deauville score of 2)

# PET scan at relapse and after 4 cycle of BEGEV




At relapse
(Deauville score of 5)




After 4 cycles of BEGEV
(Deauville score of 2)

# Question 4:
# What kind of consolidation would you offer to this patient?

1. None
2. Radiotherapy (36 Gy) on residual mediastinal mass
3. ASCT
4. Radiotherapy (24 Gy) on residual mediastinal mass
5. Brentuximab vedotin

# Question 4:
# What kind of consolidation would you offer to this patient?

1. None
2. Radiotherapy (36 Gy) on residual mediastinal mass
3. **ASCT**
4. Radiotherapy (24 Gy) on residual mediastinal mass
5. Brentuximab vedotin

# Feedback to Question 4

- In chemosensitive patients with relapse and who achieve a complete metabolic response after second-line treatment, ASCT consolidation should be performed whenever possible
- ASCT consolidation is associated with superior overall survival in comparison to chemotherapy alone in patients with relapsed/refractory classical Hodgkin lymphoma
- None of the combination strategies that integrate new therapies into salvage regimens have been proven to be superior to ASCT consolidation
  - New therapies: Brentuximab vedotin, immune checkpoint inhibitors, etc.

# ASCT

**June 2021**

- BEAM chemotherapy

**June 23, 2021**

- $5.8 \times 10^6$ $CD34^+$ cell/kg infused

- ASCT complicated by:
  - Mucositis (grade 2)
  - Febrile neutropenia (grade 2)
    - 4 days' duration
    - No microbiological positive tests
    - Effective piperacillin/tazobactam therapy
  - No red cell transfusions required
  - 2 platelet transfusions
- Engraftment
  - + 9 days after ASCT

# Question 5:
# What kind of post-ASCT consolidation would you offer to this patient?

1. None
2. Consolidation radiotherapy (36 Gy) on residual mediastinal mass
3. Immune checkpoint inhibitor consolidation
4. Consolidation radiotherapy (30 Gy) on residual mediastinal mass
5. Brentuximab vedotin consolidation

# Question 5:
# What kind of post-ASCT consolidation would you offer to this patient?

1. None
2. Consolidation radiotherapy (36 Gy) on residual mediastinal mass
3. Immune checkpoint inhibitor consolidation
4. **Consolidation radiotherapy (30 Gy) on residual mediastinal mass**
5. Brentuximab vedotin consolidation

# Feedback to Question 5

- Consolidation radiotherapy can be considered; brentuximab vedotin consolidation after ASCT (AETHERA trial) is recommended in patients with ≥ 2 risk factors at relapse
- Conventional dose for consolidation radiotherapy on PET-negative lesions is 30 Gy; 36 Gy dose can be used as local salvage treatment on PET-positive lesions
- Data on immune checkpoint inhibitor consolidation after ASCT are available; this option can be considered in patients with high-risk disease
  - In Italy, post-ASCT immune checkpoint inhibitor consolidation is not allowed in immune checkpoint inhibitor-naive patients

# Consolidation radiotherapy

- Pulmonary function tests and echocardiogram were performed
  - Results were normal

**August 2021**

- Radiotherapy (30 Gy) on residual mediastinal mass
- Post-consolidation radiotherapy CT (after 4 weeks)
  - Residual mediastinal mass measuring 3 cm
- Post-consolidation radiotherapy PET scan (after 6 weeks)
  - PET-negative (Deauville Score of 2)
- Second complete metabolic remission after 4 cycles of BEGEV, ASCT, and consolidation radiotherapy
- Follow-up was started

# Question 6:
# What kind of post-ASCT surveillance would you offer to this patient?

1. Clinical evaluation
2. Clinical evaluation and PET scans with the aim of early detection of disease relapse
3. Clinical evaluation and CT alternated to ultrasonogram with the aim of early detection of disease relapse
4. Clinical evaluation and CT alternated to ultrasonogram with the aim of early detection of disease relapse and surveillance for late toxic effects
5. Periodical pulmonary function tests

# Question 6:
# What kind of post-ASCT surveillance would you offer to this patient?

1. Clinical evaluation
2. Clinical evaluation and PET scans with the aim of early detection of disease relapse
3. Clinical evaluation and CT alternated to ultrasonogram with the aim of early detection of disease relapse
4. **Clinical evaluation and CT alternated to ultrasonogram with the aim of early detection of disease relapse and surveillance for late toxic effects**
5. Periodical pulmonary function tests

# Feedback to Question 6

- In young patients with long life expectancy, post-treatment surveillance should be performed with the aim of early detection of possible disease relapse and late side effects
- PET surveillance is not recommended for follow-up evaluation
- CT surveillance does not translate into superior post-relapse outcomes when compared to follow-up (clinical examination, ultrasound tests)

# Follow-up

- The patient is alive and in complete remission 31 months after completion of salvage therapy
  - Last visit was February 29, 2024
- ECOG PS is 0; no significant side effects reported (so far…)
- Clinical evaluation for disease relapse and side-effects monitoring will be continued (up to…?)

# Discussion

- Relapsed/refractory classical Hodgkin lymphoma should be histologically confirmed wherever possible; interpretation of PET results should take into account the false-positive rate
- Standard therapy in younger patients (age ≤ 65 years) should be effective, feasible, and with good stem-cell mobilizing properties
- With the lack of randomized clinical trials, salvage therapies can be chosen from a wide group of options tested in phase 2 trials
  - Mainly gemcitabine-, platinum- or brentuximab vedotin-based treatment regimens

# Discussion

- ASCT should be performed as consolidation in all eligible, chemosensitive patients
  - Potentially curative
- Post-ASCT consolidation with brentuximab vedotin is recommended for patients considered at high risk (≥ 2 or more of the following risk factors at relapse):
  - Remission duration < 1 year
  - Extranodal involvement
  - PET-positive response at transplant
  - B symptoms
  - > 1 second-line/subsequent therapy regimen
- Post-ASCT consolidation radiotherapy (30 Gy) can be considered in high-risk situations
  - Especially in bulky disease

# Discussion

- Post-ASCT surveillance should be performed without PET, and with a limited number of CT scans in order to reduce exposure to radiation
- Monitoring for treatment-related adverse effects is one of the aims of follow-up
  - Especially for potentially cured patients with a long life expectancy

# References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