Family Medicine & Primary Care Review 2024; 26(2): 251–260, https://doi.org/10.5114/fmpcr.2024.139038

REVIEWS

ISSN 1734-3402, eISSN 2449-8580

Hodgkin's lymphoma in adults – diagnosis and treatment

ANNA GRUSZCZYŃSKA[1, A–F], KRZYSZTOF KOWALIK[2, D, E], DAGMARA JABŁOŃSKA[3, A–F],
ORCID ID: 0000-0001-8928-7578
KATARZYNA HETMAN[4, C–F], ANDRZEJ MODRZEJEWSKI[2, D]

[1] Department of Forensic Medicine of the Pomeranian Medical University, Szczecin, Poland
[2] Clinical Department of General Surgery of the Pomeranian Medical University, Szczecin, Poland
[3] Clinical Department of Nephrology with Dialysis Station the Regional Hospital in Kielce, Kielce, Poland
[4] Department of Clinical Oncology Western Pomeranian Oncology Center in Szczecin, Szczecin, Poland

A – Study Design, **B** – Data Collection, **C** – Statistical Analysis, **D** – Data Interpretation, **E** – Manuscript Preparation, **F** – Literature Search, **G** – Funds Collection

Summary Hodgkin's lymphoma (HL) is a malignant disease of the lymphatic system with two peaks of incidence. Often one of the first symptoms of the disease is non-painful enlargement of the lymph nodes. The development of diagnostic techniques has allowed more efficient evaluation of the lesions. Classification of patients according to stage and the presence of risk factors has made it possible to tailor treatment regimes to the individual patient. The article discusses the diagnosis and contemporary treatment options for HL.
Key words: Hodgkin disease, diagnosis, treatment, drug therapy.

Gruszczyńska A, Kowalik K, Jabłońska D, Hetman K, Modrzejewski A. Hodgkin's lymphoma in adults – diagnosis and treatment. *Fam Med Prim Care Rev* 2024; 26(2): 251–260, doi: https://doi.org/10.5114/fmpcr.2024.139038.

Background

Hodgkin's lymphoma (HL) belongs to tumors of the lymphatic system. The disease is characterized by clonal proliferation of Reed-Sternberg giant cells and mononuclear Hodgkin cells. They induce a reactionary proliferation of lymphocytes, monocytes and other cells.

Epidemiology

In Europe, the incidence of Hodgkin's lymphoma is estimated at 2–3/100,000 cases per year. It is slightly more frequently diagnosed in men. There are two peaks of incidence: the first around age 20–30, and the second after age 55 [1].

Etiopathogenesis

No direct risk factors for the disease or its causes have been defined. Important in the pathogenesis of the disease is the presence of giant Reed-Sternberg (RS) cells with a multilobed nucleus and large mononuclear Hodgkin cells. RS cells occupy a small portion of the affected lymph node. They are monoclonal in nature and originate from mature B lymphocytes [2]. These cells have the ability to produce immunoglobulins as a result of downregulation of transcription factors typical of B lymphocytes, including OCT2, BOB1 and EBF1 [3]. They show high expression of nuclear transcription factor κB and NOTCH 1 pathway activity [4].

A key role in the diagnosis of lymphoma is played by the CD30 antigen localized on RS cells. It is a transmembrane protein that functions as a cytokine receptor from the tumor necrosis factor α group [5]. It is characterized by low expression in healthy tissues. Anti-CD30 and anti-CD20 staining has been used to distinguish histologic subtypes of Hodgkin's lymphoma, including classical (cHL, classical HL) CD30+, CD20- and nodular lymphocyte predominant HL (NLPHL, nodular lymphocyte predominant HL) CD30-, CD20+ forms [6].

There are epidemiological factors that may show an association with the incidence of HL. These factors include family predisposition, exposure to certain viruses and immunosuppression. Same-sex siblings of HL patients have a 10-fold increased risk of developing the disease [7]. In monozygotic twins of HL patients, the risk of siblings developing the disease is much higher than in dizygotic twins [8].

There is a higher risk of developing the disease when the socioeconomic situation is worse. However, this does not apply to the group of young adults, in whom the trend is the opposite [9].

Another important factor is compulsive smoking, which doubles the risk of the disease [6]. Infection with human immunodeficiency virus (HIV) also contributes to an increased likelihood of HL compared to the general population [10]. Immunocompromised individuals, including HIV positive individuals, have advanced disease at the time of diagnosis. In addition, this group often has atypical localization of the disease and a worse prognosis after initial therapy [11].

The EBV virus has been linked to the pathogenesis of Hodgkin's lymphoma. People who have had infectious mononucleosis have a fourfold increased risk of developing the disease [12]. In about 40% of cases of this lymphoma, latent infection with the virus is found [13]. Identification of EBV DNA may reflect lymphoblastoid cell proliferation. Due to decreased immune competence (often observed in Hodgkin's disease). Identification of EBV DNA may also indicate the presence of EBV genomes in Reed-Sternberg cells [14]. A history of childhood infectious diseases such as chicken pox, measles, mumps, rubella and pertussis decreases the risk of HL [15].

Symptoms

The most characteristic symptom of HL is non-painful enlargement of lymph nodes. Most often these are lymph nodes above the diaphragm (cervical, supraclavicular and axillary), less often inguinal and retroperitoneal. The disease tends to spread through continuity, occupying successive groups of lymph

nodes according to the direction of lymph flow. Less frequently, it spreads via the bloodstream [16]. Tumor masses can reach large sizes before a diagnosis is established. Symptoms associated with enlarged lymph nodes depend on their location. If the condition involves the mediastinum, there is shortness of breath, cough, superior vena cava syndrome or pressure on the airways and difficulty breathing. In cases of retroperitoneal space involvement, abdominal discomfort, obstruction of urinary outflow, bloating, constipation and symptoms of obstruction occur.

The extraperitoneal form is rare. The lungs, liver, bone marrow and bones are most commonly involved in this variety. Rarely, the Waldeyer ring and gastrointestinal tract are also involved. Very rarely, there are neurological symptoms of paraneoplastic syndromes [17]. There may be general symptoms in the form of weakness, excessive fatigability, lymph node pain after alcohol consumption and so-called B symptoms – fever, chills, night sweats or unexplained weight loss > 10% of body weight. B-symptoms occur in about 30% of patients and are common in those with advanced stage or massive disease. They show a prognostic character and are therefore included in the staging system. Severe, unremitting pruritus without apparent skin pathology on physical examination may be refractory to topical and systemic agents and may indicate the presence of clinically latent HL [18].

Diagnostics

In addition to subject and physical examination, laboratory and imaging tests are used in the diagnosis. The panel of laboratory tests for Hodgkin's lymphoma includes morphology, erythrocyte sedimentation rate (ESR), electrolytes (sodium, potassium), urea, creatinine, calcium, ALT, ASTcom, bilirubin, alkaline phosphatase, lactate dehydrogenase, uric acid and phosphorus. Computed tomography (CT) scans of the neck, chest, abdomen and pelvis are most commonly performed during diagnostic imaging. Other methods used are PET-CT (fluorine F 18-fludeoxyglucose positron emission tomography) and PET MRI [19]. Virological tests for HIV, HBV and HCV infection are also performed. PET-CT is routinely used to determine the stage of disease [20]. Formerly, a bone marrow biopsy was performed, as 5% of HL patients had a disease involving the marrow. This has now been replaced by PET-CT, as focal bone lesions seen on the scan predicted marrow involvement with high sensitivity and specificity [21]. There are various diagnostic methods to diagnose massive mediastinal disease. Some investigators use the thoracic ratio of the maximum diameter of the transverse mass to the internal thoracic transverse diameter (measured at the level of the Th5/6 intervertebral disc on thoracic radiography) [22]. Some researchers measure the maximum width of the mediastinal mass, which they divide by the maximum intrathoracic diameter [23]. Others measure the mass of lymph nodes at their greatest dimension [24].

The prognostic factors evaluated are the presence or absence of general symptoms, the so-called B-symptoms, the stage of the lymphoma, the presence of large masses and the type and effectiveness of the treatment used. Other important factors are age, gender, erythrocyte sedimentation rate (ESR), hematocrit, size of lesions present in the abdominal cavity and number of lymph nodes involved [25–27]. A PET-CT scan is performed after two cycles of chemotherapy to assess the effectiveness of treatment [28, 29]. Biomarkers and calculation of metabolic tumor volume are also used to better determine the prognostic course of the disease [28, 30–32].

Pathomorphological diagnosis

The diagnosis is based on histopathological evaluation of the entire lymph node or other suspicious infiltrated tissue. To establish a definitive diagnosis, it is necessary to identify Reed-Sternberg cells pathognomonic for the condition. Aspiration biopsy is not a reliable diagnostic method due to the negligible percentage of RS cells present in the tumor mass. Therefore, a small biopsy sample may not contain a sufficient number of malignant cells [33, 34]. Reed-Sternberg cells are large cells with multiple cell nuclei or a single biplanar nucleus. Both variants have a large prominent nucleus [35]. The diagnosis is confirmed by immunophenotypic examination of the tumor cells.

Histological types of HL

There are two main types of the disease: the classical form (cHL, classical Hodgkin lymphoma), which accounts for 95% of cases, and the nodular lymphocyte-predominant Hodgkin's lymphoma (NLPHL) subtype in about 5% of cases [36]. In classical Hodgkin's lymphoma, 4 subtypes are distinguished due to the differentiation of the cellular environment surrounding the tumor cells [6, 34, 37, 38]:

1. Nodular sclerosis Hodgkin's lymphoma (NSHL) occurs in 60–80% of patients with classical Hodgkin's lymphoma. It is found mainly in young people and adults.
2. Mixed cellularity Hodgkin's lymphoma (MCHL) is present in 15–20% of cases. The most common form is in patients over 50 years of age, mostly found in men. Compared to nodular sclerosis and lymphocyte-predominant forms, the mixed form is often associated with advanced disease and the presence of general symptoms. It is characterized by a worse prognosis compared to NS.
3. Lymphocyte depleted Hodgkin's lymphoma (LDHL) is another form that occurs in 5% of patients.
4. Lymphocyte rich classic Hodgkin's lymphoma (LRCHL) accounts for < 1% of cases. It occurs mainly in the elderly and patients with immune disorders, such as those infected with HIV. The disease often presents with general symptoms and rarely occupies peripheral lymph nodes. The prognosis is worse compared to HF.

Nonclassical Hodgkin's lymphoma (nodular lymphocyte-majority lymphoma) most often affects young people, mostly men. It appears mainly in peripheral nodes without mediastinal involvement, is usually diagnosed in the early stages and progresses slowly without signs of progression [13]. Transformation of the nodular form with lymphocyte predominance into diffuse large B-cell lymphoma (DLBCL) is possible [38].

Table 1. Staging of primary nodal lymphomas (Lugano 2014) – modified Ann Arbor classification [39]

Stage	Characteristics
I	one lymph node or one group of adjacent lymph nodes or a single extranodal lesion without lymph node involvement
IIa	≥ 2 groups of lymph nodes on the same side of the diaphragm or grade I or II for nodal lesions with limited extranodal organ involvement through continuity
III	lymph nodes on both sides of the diaphragm or lymph nodes above the diaphragm with simultaneous involvement of the spleen
IV	involvement of extra-symphatic organ not through continuity with involved lymph nodes

The tonsils, Waldeyer's ring and spleen are considered nodal tissue.
Additionally, in Hodgkin's lymphoma: A – general symptoms absent; B – general symptoms present: fever (> 38°C) with no apparent cause, night sweats or loss of > 10% of body weight in the past 6 months.
Massive grade II – grade II as mentioned above and a massive nodal (bulky) lesion, i.e. a single nodal lesion ≥ 10 cm in size or covering > 1/3 of the width of the thoracic spine evaluated on CT at any height of the thoracic spine.

Classification of patients

Patients are divided into groups taking into account the stage of the disease (according to the modified Ann Arbor classification) and clinical and biological factors. The classification includes patients with early, favorable classical type HL; early, unfavorable type HL; and advanced type HL [40].

Adverse prognostic factors include the presence of B symptoms, extranodal disease, a tumor greater than or equal to 10 cm in size on CT or greater than 1/3 of the chest diameter on chest X-ray, involvement of three or more lymph node groups and a sedimentation rate greater than 50 mm/h for stage A or greater than 30 mm/h for stage B. Cases of stage I or II disease without co-morbid adverse factors constitute early, favorable Hodgkin's lymphoma.

When one or more risk factors are present in stage I or II, the disease is referred to as early, unfavorable, classical HL type. An index describing adverse prognostic factors with scoring for patients according to the stage of HL has also been developed. The International Prognostic Index includes: albumin less than 4.0 g/L, hemoglobin less than 10.5 g/L, male gender, age greater than or equal to 45 years, stage IV disease, WBC greater than 15,000/mm^3, absolute lymphocyte count less than 600/mm^3 or lymphocyte count greater than 8% of the total WBC count [41, 42]. Low risk is present when up to two risk factors are present, and high risk above three factors [43]. Each of the aforementioned groups is characterized by a different treatment regimen.

Treatment

The main treatment modality is various chemotherapy regimens with or without radiotherapy. An extratherapeutic effect is achieved in 75% of newly diagnosed adult patients [44]. The treatment modality for adults with Hodgkin's lymphoma mainly depends on the clinical stage of the disease. If low-stage disease is present, an ABVD chemotherapy regimen is used, which consists of doxorubicin, bleomycin, vinblastine and dacarbazine. In addition, radiation therapy may be used. Higher stage lymphoma is an indication for treatment with chemotherapy alone. A combination of chemotherapy and radiotherapy can be used in exceptional situations, such as large tumor size, i.e. in the mediastinum above 10 cm, and when a tumor above 2.5 cm remains after chemotherapy [45].

The choice of treatment also depends on the patient's age. In patients older than 60 years who would not be able to receive standard doses of chemotherapy, brentuximab vedotin can be used [46]. It can be combined with dacarbazine or with doxorubicin, vinblastine or dacarbazine (AVD) [47, 48].

Radiation therapy is not routinely used as the sole treatment for patients with Hodgkin's lymphoma. The radiation dose applied to the involved lymph nodes ranges from 30 to 36 Gy [49–51]. Tumor infiltration that localizes close to important organs is an indication to consider proton therapy, which will limit radiation and protect important structures [52]. The usual radiation therapy regimen involves consecutive irradiation of three groups of lymph nodes. The first group consists of neck, thoracic and axillary lymph nodes, the second group consists of nodes around the aorta and spleen, and the third group consists of pelvic lymph nodes [49–51].

In patients with early favorable HL, an ABVD regimen (doxorubicin, bleomycin, vinblastine and dacarbazine) for 3 to 6 cycles or an ABVD regimen for 2 to 4 cycles with the additional use of IFRT at a dose of 20 Gy or 30 Gy is used. When there are contraindications to chemotherapy (mainly in the elderly), radiation therapy alone may be used [53–55]. The National Cancer Institute of Canada conducted a study comparing the efficacy of an ABVD regimen for 4–6 cycles with subtotal lymph node irradiation [56]. The median follow-up period was 11.3 years. During follow-up, no differences were seen in disease-free survival rates of 89% and 86% (p = 0.64) and overall survival (OS) of 98% versus 98% (p = 0.95). GHSG's HD10 study, which compared the use of 2 or 4 cycles of ABVD with the additional use of 30 or 20 Gy IFRT, showed no differences in 10-year progression-free survival (PFS) or OS rates among the aforementioned patient groups. PFS was 87%, OS was 94%, and the median follow-up period was 8.2 years [57, 58]. In another study conducted by GHSG, the ABVD regimen was modified by excluding dacarbazine, bleomycin or both drugs from treatment in combination with the use of 30 Gy radiotherapy. After 5 years, significantly worse treatment outcomes were observed in patients in the groups without dacarbazine and/or bleomycin [59]. The use of PET-CT to modify the treatment regimen is described in the RAPID, EORTC H10F and HD16 studies [60–62]. Patients without disease features on PET-CT after the second or third cycle of chemotherapy ended treatment after the fourth cycle. In contrast, patients with HL exponents on PET-CT receive additional cycles of chemotherapy and nodal radiotherapy [63]. When treating patients older than 60 years with early, favorable HL type who needed more than 2 cycles of ABVD, bleomycin was omitted due to its toxic effects on the lungs. Studies HD10 and HD13 showed that the use of 2 cycles of ABVD with IFRT causes 2% lung damage, 2 cycles of AVD with IFRT also causes 2% pulmonary toxicity. In cases where 4 cycles of ABVD with IFRT are used, negative pulmonary sequelae occur in 10% of patients [64].

Patients with early, unfavorable Hodgkin lymphoma type are treated with 4 cycles of ABVD chemotherapy and involved-field radiotherapy (IFRT) (20 Gy to 30 Gy) [65–67] or 6 cycles of ABVD [57, 60]. The National Cancer Institute of Canada (NCIC) conducted a randomized, prospective study comparing ABVD therapy for 4 to 6 cycles with ABVD for 2 cycles combined with extended field radiotherapy (EFRT). The progression-free rate was more favorable in the combination therapy group at 94% versus 86% (p = 0.006), but OS was better in patients using ABVD alone at 92% versus 81% in combination therapy (p = 0.04) [60]. During the HD11 trial conducted by GHSG, the following therapies were compared: 4 cycles of ABVD with 30 Gy IFRT, 4 cycles of ABVD with 20 Gy IFRT, 4 cycles of BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone) with 30 Gy IFRT, 4 cycles of BEACOPP with 20 Gy IFRT. At follow-up (with a median follow-up of 8.8 years), there was no difference in OS rates (93–96%) in the aforementioned groups [62]. After treatment regimens with 30 Gy IFRT, no difference was seen between therapies. However, after administration of 20 Gy IFRT, it was noted that the PFS of the ABVD regimen was 76% compared to 84% for therapy with BEACOPP ((HR) 1.5 and 95% confidence interval (CI) 1.0–2.1) [68]. Based on this study, a treatment regimen of four cycles of ABVD combined with 30 Gy IFRT or BEACOPP with 20 Gy radiotherapy was established. Another HD14 GHSG study comparing the use of four cycles of ABVD in combination with 30 Gy IFRT or two cycles of BEACOPP followed by two cycles of ABVD with 30 Gy IFRT showed that the first treatment regimen was the preferred therapy. No difference in OS was observed during follow-up (median 43 months) [66]. Another study indicating the use of 4 cycles of ABVD with IFRT due to the toxicity of other therapies is H9-U conducted by the European Organization for Research and Treatment of Cancer (EORTC). It compared 3 therapies: 6 cycles of ABVD combined with 36 Gy IFRT, 4 cycles of ABVD with 36 Gy IFRT, and 4 cycles of BEACOPP with 36 Gy IFRT. No differences were observed during follow-up (median 64 months). EFS (adverse event-free survival rate) ranged from 89% to 92% (p = 0.38) and OS rate 91–96% (p = 0.89) [67]. When a PET-CT scan performed after 2 cycles of chemotherapy showed HL, brentuximab vedotin was added to the therapy regimen and bleomycin was abandoned. In case of side effects after bleomycin, a regimen of A + AVD therapy (brentuximab vedotin, doxorubin, vinblastine and dacarbazine) with radiotherapy is

implemented [69]. In patients with no features of HL on PET-CT, it is possible to terminate radiotherapy after 2 cycles of chemotherapy. A randomized, prospective study conducted by EORTC HIOU analyzed the use of PET-CT to modify treatment after 2 cycles of therapy [64]. In the absence of HL features on PET-CT after two cycles of therapy, patients were randomly assigned to a group receiving six cycles of ABVD or four cycles of ABVD combined with radiotherapy to the involved lymph nodes. PFS of patients in the first group was 94.7% compared to 99.2% of patients in the second group (p = 0.026). No difference in OS was observed. If features of HL were found on PET-CT after two cycles of ABVD, patients were randomly assigned to a group of 4 cycles of ABVD combined with 30 Gy of radiotherapy or to a group receiving 2 cycles of ABVD followed by 2 cycles of escalated BEACOPP with 30 Gy of radiotherapy [70]. The percentage of 5-year PFS was 91% for the regimen with BEACOPP, and 77% for therapy with ABVD (p = 0.002). The percentage of 5-year OS reached 96% when treatment with BEACOPP was administered and 89% when ABVD was given (p = 0.02). This study indicates a beneficial effect of adding BEACOPP to ABVD in patients with early, unfavorable HL type with detectable HL features on PET-CT after 2 cycles. A randomized prospective study of HD17 was conducted by the GHSG. The aim of the study was to determine whether radiation therapy could be omitted from the treatment regimen for patients with complete disease regression on PET-CT. The results of patients undergoing 2 cycles of BEACOPP with gradual dose escalation were analyzed in comparison to a group of patients who received a typical dose of BEACOPP. One group underwent the described regimen in combination with radiotherapy, while the other group was divided into two subgroups after receiving the PET-CT result. Patients with HL features on PET-CT in addition to the chemotherapy regimen received radiotherapy to the involved lymph nodes. Patients whose PET-CT scan showed HL were treated with chemotherapy alone [71]. The median follow-up period was 46.2 months. In combination therapy, the 5-year PFS rate was 97.3% (95% CI: 94.5–98.7), and in therapy, the use of PET-CT PES control reached 95.1% (95% CI: 92.0–97) (HR 0.523; 95% CI: 0.23–1.21) [71]. It was concluded that omitting radiotherapy in patients with complete metabolic response after 4 cycles of BEACOPP-based chemotherapy does not significantly affect PFS.

In patients with advanced classical Hodgkin's lymphoma, the treatment replaced the formerly used ABVD regimen with A + AVD chemotherapy (brentuximab vedotin (antibody-drug conjugate targeting DC30), doxorubicin, vinblastine, dacarbazine). This treatment was given in 6 cycles [72, 73]. A randomized prospective study involving patients with previously untreated advanced HL was conducted that compared the ABVD regimen with A + AVD therapy. The 6-year OS rate was 93.9% in the A + AVD group (95% confidence interval (CL) 91.6–95.5) and 89.4% compared to the ABVD groups (95% CI: 86.6–91.7) (hazard ratio (HR) 0.59; CI: 0.40–0.88; p = 0.009) [74]. Median follow-up was 73 months. The 6-year PFS was 82.3% in patients who received A + AVD (95% CI: 79.1–85.0) and 74.5% when ABVD was used (95% CI: 70.8–77.7) (HR 0.68; 95% CI: 0.53–0.86; p = 0.002). Use of A + AVD was associated with a higher incidence of grade 3 or 4 peripheral neuropathy compared to the ABVD regimen. 67% with A + AVD and 43% with ABVD [75]. Use of the A + AVD regimen resulted in a partial or complete cure in about 80% of patients. Lung lesions caused by ABVD contributed to 11 deaths. The use of ABVD for 6–8 months is considered the standard of care for patients with advanced Hodgkin's lymphoma. The OS rate is the same with other regimens such as: BEACOPP (bleomycin, etoposide, doxorubicin, procarbazine and prednisone), BEACOPP in increasing doses, Stanford V (doxorubicin, vinblastine, mechloretamine, etoposide, vincristine, bleomycin and prednisone) and MOPP-ABV (mechlorethamine, vincristine, procarbazine, prednisone/doxorubicin, bleomycin and vinblastine) [76–83]. Three prospective studies have failed to show a benefit of chemotherapy along with radiotherapy on OS [84–87]. For patients with advanced stage HL, the use of PET-CT after 2 cycles of ABVD to modify therapy has been studied. During the randomized, prospective RATHL trial, patients without HL features on PET-CT were divided into two groups. The first received 4 consecutive cycles of ABVD, and the second received 4 cycles of AVD (doxorubicin, vinblastine and dacarbazine). At follow-up (median 41 months), there was no difference in the 3-year OS rate. The ABVD regimen had an OS of 97.2%; 95% CI: 95.1–98.4, while the AVD group had an OS of 97.6%; 95% CI: 95.6–98.7 [52]. The absolute difference between ABVD and AVD in 3-year PFS was 1.6% (95% CI: 3.2 to 5.3). Continuation of bleomycin treatment resulted in a slight increase in PFS. However, the ABVD regimen resulted in significant lung changes. We also studied the use of BEACOPP regimen after 2 cycles of ABVD in patients with HL features on PET-CT. No better effect of the BEACOPP regimen was demonstrated compared to typical ABVD treatment. The median follow-up was 41 months. With BEACOPP therapy, the 3-year PFS rate was 67.5%, and the OS rate was 87.8%. Treatment with brentuximab vedotin was studied. Two doses of the drug were administered. 6 cycles of AVD were followed by four more doses of brentuximab vedotin. In patients over 60 years of age. The 2-year event-free survival rate was 80%, PFS rate 84%, OS 93% [52]. Grade 3 and 4 toxicity as a result of treatment occurred in 42% of patients.

Risk factors for recurrence of HL in patients with the recurrent, classic type of this disease are: lack of positive effect after treatment, relapse in less than 12 months, lack of clinical complete remission after reinduction, presence of B symptoms at the time of relapse, extranodal disease, use of more than two salvage regimens beforehand [88–90]. The following drugs are recommended for such patients: nivolumab or pembrolizumab, brentuximab vedotin, brentuximab vedotin with nivolumab, chemotherapy with stem cell transplantation, combination chemotherapy, radiation therapy. Nivolumab and pembrolizumab are among the monoclonal antibodies directed against the PD-1 receptor. The drugs are immune checkpoint inhibitors. Both drugs are used to achieve complete clinical remission of the disease prior to autologous or allogeneic bone marrow transplantation. The randomized, prospective study compared the efficacy of pembrolizumab and brentuximab vedotin in the treatment of patients with relapsed HL or refractory HL who were ineligible for autologous hematopoietic cell transplantation (SCT). The median follow-up period was 25.7 months. The PFS of patients taking pembrolizumab was 13.2 months (95% CI: 10.9–19.4), and that of patients taking brentuximab vedotin was 8.3 months (95% CI: 5.7–8.8) (HR 0.65; 95% CI: 0.48–0.88; p = 0.0027) [91]. 16% of patients taking pembrolizumab and 11% of patients taking brentuximab vedotin experienced treatment-related serious adverse events. Other studies of pembrolizumab indicate an overall response rate in the 64–74% range and an overall response rate of 22.4% (95% CI: 6.9–28.6) [92, 93]. An efficacy study of nivolumab showed an overall response rate in the range of 65–87% and an overall response rate of 16–28% [94–96]. A combination of nivolumab and brentuximab vedotin was also studied. The objective response rate was 82%, and the overall response rate was 61% [97]. Brentuximab vedotin is a combination of an antibody that detects CD30 with a drug directed against it [98–100]. The CD30 antigen is mainly found on Reed-Sternberg cells of Hodgkin lymphoma. Studies of the use of brentuximab vedetin in patients with HL relapse have shown response rates as high as 75%, with complete remissions of about 50% and a median PFS of 4 to 8 months [98–102]. The use of brentuximab vedotin was studied in patients over 60 years of age who could not receive chemotherapy due to poor health. The overall response rate in these patients was 92%, and the complete remission rate was 73% [50]. The AETHERA trial evaluated the efficacy of brentuximab vedotin compared with a placebo. The median follow-up was 5 years. The 5-year PFS rate

with brentuximab vedotin was 59% (95% CI: 51–66) versus 41% (95% CI: 33–49) in the placebo group (HR 0.52; 95% CI: 0.379–0.717) [103, 104]. The use of brentuximab vedotin and bendamustine was tested. After 2 cycles, objective response rates were 93% and 78%, and overall remission rates were 74% and 32% [105, 106]. Brentuximab vedotin is used for the same purpose as nivolumab and pembrolizumab. High doses of chemotherapy are administered, followed by autologous or allogeneic bone marrow transplantation [107–109]. Allogeneic transplantation is indicated in patients with primary refractory disease. It is estimated that using standard chemotherapy followed by bone marrow transplantation will achieve long-term disease-free survival in approximately 50% of patients with relapsed HL [107]. A randomized trial was conducted that compared the use of conventional chemotherapy and a combination of chemotherapy and autologous hematopoietic SCT. This observation was carried out for patients with recurrent chemosensitive HL type [110]. The 3-year freedom from failure of combination therapy was 55% in transplant patients, and the rate of positive results of chemotherapy alone reached 34% of patients. There were no differences in OS nother study is a Cochrane meta-analysis, which showed that autologous stem cell transplantation after reinduction chemotherapy improved relapse-free survival by 20–30% compared to the use of chemotherapy alone. No differences in OS were observed [111]. The AETHERA trial evaluated PFS in two groups of patients after autologous stem cell transplantation. The first group received brentuximab vedotin, and the second group received a placebo. The median follow-up was 5 years. The 5-year PFS rate in patients after brentuximab vedotin was 59% (95% CI: 51–66), and 41% (95% CI: 33–49) in the placebo group (HR 0.521; 95% CI: 0.379–0.717) [103, 104]. The majority of patients did not receive treatment lasting 16 months because they developed progressive peripheral neuropathy. Its resolution after brentuximab vedotin withdrawal was not complete. An important element of treatment efficacy is the evaluation of the initial effect of chemotherapy. Long-term survival of up to 22–71% has been demonstrated in patients who experienced remission of more than one year [98, 112]. Long-term survival of 11–46% was observed in patients who experienced a remission of less than one year after chemotherapy [98, 99, 113]. It has been shown that patients over 60 years of age tolerated the combination of chemotherapy and radiotherapy better than high-dose chemotherapy with subsequent bone marrow transplantation [114]. Patients with relapsed HL who received only high-dose radiotherapy as initial treatment have a good prognosis. The use of combination chemotherapy in them results in a 10-year DFS rate of 57–81%, and OS reaches 57–89% [98, 115, 116]. In a small group of selected patients, the use of radiotherapy alone can achieve long-term survival in about 50% of cases [117]. Two chemotherapy regimens are used to treat relapsed HL. The first includes ifosfamide, carboplatin and etoposide (ICE), and the second includes GVD therapy (gemcitabine, vinorelbine, liposomal doxorubicin). If this treatment is not effective, pembrolizumab or nivolumab is introduced.

Treatment of Hodgkin's lymphoma in pregnant patients differs from the generally accepted regimen. The method used to assess the stage of the disease is MRI. The early stage, the location above the diaphragm and the slow growth of the tumor make it possible to limit ourselves only to vigilant observation and to consider inducing early labor (at 32–36 weeks) in order to undertake appropriate therapy [118]. Supra-diaphragmatic radiotherapy with lead shielding can be used for treatment [119, 120]. The administration of chemotherapy (usually the ABVD regimen) during the first trimester of pregnancy is inadvisable, as it is associated with birth defects in the child [121, 122]. Later in pregnancy, short-term radiation therapy can be administered before delivery when there is a rapidly enlarging tumor in the mediastinum that threatens the life of the mother. Beginning in the second trimester of pregnancy, when necessary, intravenous vinblastine is usually given at a dose of 6 mg/m^2 every 2 weeks until delivery [123, 124]. The use of the ABVD regimen in the second half of pregnancy seems safe [125]. Steroids are often used, which not only reduce the tumor mass but also accelerate lung maturation in the fetus.

Nodular lymphocyte-predominant lymphoma (NLPHL) differs immunophenotypically from classical HL. NLPHL cells have CD15-, CD20+, CD30-, while classic HL cells have CD15+, CD20-, CD30+ receptors [126, 127]. The prognosis of NLPHL lymphoma types is favorable. In some patients, follow-up and observation of the patient is sufficient [128]. A retrospective study comparing active observation with treatment showed a 5-year PFS rate of 77% in the untreated group versus 85% when chemotherapy was given [129]. The most commonly used treatment for early-stage patients is radiation therapy [130–133]. This is usually IFRT (involved-field radiation therapy) [134]. Another treatment modality is the combination of chemotherapy and radiation therapy. In early disease, an ABVD regimen (doxorubicin, bleomycin, vinblastine, dacarbazine) for 2–3 cycles together with IFRT is used [130, 135].

In the advanced state, R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone) or R-CVP (rituximab, cyclophosphamide, vincristine and prednisone) therapy is chosen [136–138]. Rituximab can be used as the sole drug for initially diagnosed or relapsed NLPHL lymphoma. The study (median follow-up – 9.8 years) showed that the PFS rate was 3 years after induction of the drug. PFS reached 5.6 years when maintenance therapy was given in addition to initial therapy [139].

Long-term follow-up of patients and biopsies are needed if relapse occurs. 10% of patients with NLPHL develop tumor transformation to diffuse large B-cell lymphoma (DLBCL) or T-cell/histiocyte-rich large B-cell lymphoma (THRLBCL, T-cell/histiocyte-rich large B-cell lymphoma) within 10 years [139–141].

CT is the most commonly used follow-up method in patients with HL, as the radiation dose associated with it is lower than that of PET-CT [142]. The absence of HL features on post-treatment PET-CT indicates a low risk of Hodgkin's lymphoma recurrence. Follow-up imaging is not recommended for patients with this result [143]. Disturbing symptoms or abnormalities on laboratory or imaging studies are an indication for diagnostic imaging. The 5-year risk of recurrence is 5.6% for patients remaining in remission for 2 years after treatment [144].

A 2015 U.S. study indicates that the 5-year survival rate for patients with HL undergoing treatment is 90% [145].

Complications

The treatment used to eradicate Hodgkin's lymphoma is associated with the possibility of long-term side effects for the patient. The drugs used can cause damage to internal organs and subsequent impairment or loss of function. The therapy also weakens the immune system. It is observed that patients who have undergone treatment for lymphoma are more likely to develop another malignancy. Regular screening is recommended to detect cancer at an early stage. Cardiovascular disease and pulmonary fibrosis are also more common in this group of patients [146, 147].

The alkylating drugs used may contribute to the development of acute myeloid leukemia (AML) in a patient with Hodgkin's lymphoma in remission. The risk of AML within 10 years of completion of therapy is 3% in patients treated with a regimen containing mechlorethamine, vincristine, procarbazine and prednisone (MOPP) [148, 149]. The use of doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) is associated with a 10-year AML risk of less than 1% [150].

The increased risk of developing AML after treatment with chemotherapy and/or radiotherapy for solid tumors is particularly true for pleural mesothelioma, cancers of the lung, breast, head and neck, thyroid, gastrointestinal tract (esophagus, stom-

ach, colon and rectum), bone and soft tissue and cervix [148, 151–155]. The main cause of these cancers is radiation therapy. With the passage of time, the risk of the disease increases. At 15 years, it is 13%, [148], and at 40 years, it is as high as 48% [156].

Autologous stem cell transplantation is associated with the occurrence of distant complications such as second malignancies, hypothyroidism, hypogonadism, heart disease, hemiplegia and depression [157].

Other symptoms that occur after HL treatment include chronic fatigue [158], impaired lung function [159, 160] and bone necrosis [161].

Summary

The modern approach to the patient strives to individualize therapy. The choice of the best treatment for patients with Hodgkin's lymphoma depends on, among other things, the histological type of HL, the presence of adverse prognostic factors, the clinical stage, the patient's age and performance status. After treatment, regular follow-up of patients plays an important role. It makes it possible to detect recurrence of the disease and determine whether the patient has developed complications after therapy.

Source of funding: This work was funded from the author's own resources.
Conflicts of interest: The authors declare no conflicts of interest.

References

1. Eichenauer DA, Engert A, André M, et al. Hodgkin's lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2014; 25(Suppl. 3): iii70–iii75, doi: 10.1093/annonc/mdu181.
2. Kanzler H, Küppers R, Hansmann ML, et al. Hodgkin and Reed-Sternberg cells in Hodgkin's disease represent the outgrowth of a dominant tumor clone derived from (crippled) germinal center B cells. *J Exp Med* 1996; 184(4): 1495–1505, doi: 10.1084/jem.184.4.1495.
3. Stein H, Marafioti T, Foss HD, et al. Down-regulation of BOB.1/OBF.1 and Oct2 in classical Hodgkin disease but not in lymphocyte predominant Hodgkin disease correlates with immunoglobulin transcription. *Blood* 2001; 97(2): 496–501, doi: 10.1182/blood.v97.2.496.
4. Schwarzer R, Jundt F. Notch and NF-κB signaling pathways in the biology of classical Hodgkin lymphoma. *Curr Mol Med* 2011; 11(3): 236–245, doi: 10.2174/156652411795243423.
5. Diehl V, Burrichter H, Schaadt M, et al. Hodgkin's disease cell lines: characteristics and biological activities. *Haematol Blood Transfus* 1983; 28: 411–417.
6. Ansell SM. Hodgkin lymphoma: 2016 update on diagnosis, risk-stratification, and management. *Am J Hematol* 2016; 91(4): 434–442, doi: 10.1002/ajh.24272.
7. Grufferman S, Cole P, Smith PG, et al. Hodgkin's disease in siblings. *N Engl J Med* 1977; 296(5): 248–250.
8. Mack TM, Cozen W, Shibata DK, et al. Concordance for Hodgkin's disease in identical twins suggesting genetic susceptibility to the young-adult form of the disease. *N Engl J Med* 1995; 332(7): 413–418, doi: 10.1056/NEJM199502163320701.
9. Rezaei N, ed. *Hodgkin's Lymphoma* [Internet]. *InTech* 2012, doi: 10.5772/1469.
10. Franceschi S, Dal Maso L, La Vecchia C. Advances in the epidemiology of HIV-associated non-Hodgkin's lymphoma and other lymphoid neoplasms. *Int J Cancer* 1999; 83(4): 481–485.
11. Andrieu JM, Roithmann S, Tourani JM, et al. Hodgkin's disease during HIV1 infection: the French registry experience. French Registry of HIV-associated Tumors. *Ann Oncol* 1993; 4(8): 635–641.
12. DeVita VT, Lawrence TS, Rosenberg SA. *Devita, Hellman & Rosenberg's Cancer: Principles & Practice of Oncology.* 8th ed. Philadelphia: Lippincott Williams & Wilkins; 2008.
13. Küppers R. Molecular biology of Hodgkin lymphoma. *Hematology Am Soc Hematol Educ Program* 2009: 491–496, doi: 10.1182/asheducation-2009.1.491.
14. Weiss LM, Strickler JG, Warnke RA, et al. Epstein-Barr viral DNA in tissues of Hodgkin's disease. *Am J Pathol* 1987; 129(1): 86–91.
15. Alexander FE, Jarrett RF, Lawrence D, et al. Risk factors for Hodgkin's disease by Epstein-Barr virus (EBV) status: prior infection by EBV and other agents. *Br J Cancer* 2000; 82(5): 1117–1121.
16. Smithers DW, Lillicrap SC, Barnes A. Patterns of lymph node involvement in relation to hypotheses about the modes of spread of Hodgkin's disease. *Cancer* 1974; 34: 1779–1786.
17. Musshoff K. Prognostic and therapeutic implications of staging in extranodal Hodgkin's disease. *Cancer Res* 1971; 31: 1814–1827.
18. Gobbi PG, Cavalli C, Gendarini A, et al. Reevaluation of prognostic significance of symptoms in Hodgkin's disease. *Cancer* 1985; 56(12): 2874–2880.
19. Picardi M, Cavaliere C, Della Pepa R, et al. PET/MRI for staging patients with Hodgkin lymphoma: equivalent results with PET/CT in a prospective trial. *Ann Hematol* 2021; 100(6): 1525–1535.
20. Barrington SF, Kirkwood AA, Franceschetto A, et al. PET-CT for staging and early response: results from the Response-Adapted Therapy in Advanced Hodgkin Lymphoma study. *Blood* 2016; 127(12): 1531–1538.
21. Adams HJ, Kwee TC, de Keizer B, et al. Systematic review and meta-analysis on the diagnostic performance of FDG-PET/CT in detecting bone marrow involvement in newly diagnosed Hodgkin lymphoma: is bone marrow biopsy still necessary? *Ann Oncol* 2014; 25(5): 921–927.
22. Lister TA, Crowther D, Sutcliffe SB, et al. Report of a committee convened to discuss the evaluation and staging of patients with Hodgkin's disease: Cotswolds meeting. *J Clin Oncol* 1989; 7(11): 1630–1636.
23. Mauch P, Goodman R, Hellman S. The significance of mediastinal involvement in early stage Hodgkin's disease. *Cancer* 1978; 42(3): 1039–1045.
24. Bradley AJ, Carrington BM, Lawrance JA, et al. Assessment and significance of mediastinal bulk in Hodgkin's disease: comparison between computed tomography and chest radiography. *J Clin Oncol* 1999; 17(8): 2493–2498.
25. American Cancer Society: Cancer Facts and Figures 2022. American Cancer Society, 2022 [cited 7.10.2022]. Available from URL: tu musi byc konkretny link.
26. Cosset JM, Henry-Amar M, Meerwaldt JH, et al. The EORTC trials for limited stage Hodgkin's disease. The EORTC Lymphoma Cooperative Group. *Eur J Cancer* 1992; 28A(11): 1847–1850.
27. Evens AM, Helenowski I, Ramsdale E, et al. A retrospective multicenter analysis of elderly Hodgkin lymphoma: outcomes and prognostic factors in the modern era. *Blood* 2012; 119(3): 692–695.
28. Agostinelli C, Gallamini A, Stracqualursi L, et al. The combined role of biomarkers and interim PET scan in prediction of treatment outcome in classical Hodgkin's lymphoma: a retrospective, European, multicentre cohort study. *Lancet Haematol* 2016; 3(10): e467–e479.
29. Gallamini A, Rossi A, Patti C, et al. Interim PET-adapted chemotherapy in advanced Hodgkin lymphoma: results of the second interim analysis of the Italian GITIL/FIL DH0607 trial. *Hematol Oncol* 2015; 33(Suppl. 1): 100–180.

30. Spina V, Bruscaggin A, Cuccaro A, et al. Circulating tumor DNA reveals genetics, clonal evolution, and residual disease in classical Hodgkin lymphoma. *Blood* 2018; 131(22): 2413–2425.
31. Cottereau AS, Versari A, Loft A, et al. Prognostic value of baseline metabolic tumor volume in early-stage Hodgkin lymphoma in the standard arm of the H10 trial. *Blood* 2018; 131(13): 1456–1463.
32. Akhtari M, Milgrom SA, Pinnix CC, et al. Reclassifying patients with early-stage Hodgkin lymphoma based on functional radiographic markers at presentation. *Blood* 2018; 131(1): 84–94.
33. Swerdlow SH, Campo E, Harris NL, et al. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*. 4th ed. Lyon: IARC Press; 2008.
34. Stein H, Delsol G, Pileri SA. *Hodgkin Lymphoma*. In: Jaffe ES, Harris NL, Stein H, et al. eds. *World Health Organization (WHO) Classification of Tumours: Pathology & Genetics; Tumours of Haematopoietic and Lymphoid Tissues*. Lyon: IARC Press; 2001: 237–253.
35. Weidner N, Cote RJ, Suster S, et al. *Modern Surgical Pathology*. Elsevier Health Sciences; 2009: 1461–1462.
36. Krzakowski M, Potemski P, Warzocha K, et al. *Onkologia kliniczna*. T. III. Gdańsk: Via Medica; 2015 (in Polish).
37. Kumar V, Cotran RS, Robins SL. *Robins Patologia*. Wrocław: Elsevier Urban & Partner; 2005: 495–498 (in Polish).
38. Mughal TI, Mughal T, Goldman J, et al. *Understanding Leukemias, Lymphomas and Myelomas*. 2nd ed. Boca Raton (FL): CRC Press; 2009.
39. Cheson BD, Fisher RI, Barrington SF, et al. Alliance, Australasian Leukaemia and Lymphoma Group; Eastern Cooperative Oncology Group; European Mantle Cell Lymphoma Consortium; Italian Lymphoma Foundation; European Organisation for Research; Treatment of Cancer/Dutch Hemato-Oncology Group; Grupo Español de Médula Ósea; German High-Grade Lymphoma Study Group; German Hodgkin's Study Group; Japanese Lymphorra Study Group; Lymphoma Study Association; NCIC Clinical Trials Group; Nordic Lymphoma Study Group; Southwest Oncology Group; United Kingdom National Cancer Research Institute. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. *J Clin Oncol* 2014; 32(27): 3059–3068, doi: 10.1200/JCO.2013.54.8800.
40. Jost LM, Stahel RA, ESMO Guidelines Task Force. ESMO Minimum Clinical Recommendations for diagnosis, treatment and follow-up of Hodgkin's disease. *Ann Oncol* 2005; 16(Suppl. 1): i54–i55.
41. Hasenclever D, Diehl V. A prognostic score for advanced Hodgkin's disease. International Prognostic Factors Project on Advanced Hodgkin's Disease. *N Engl J Med* 1998; 339(21): 1506–1514.
42. Moccia AA, Donaldson J, Chhanabhai M, et al. International Prognostic Score in advanced-stage Hodgkin's lymphoma: altered utility in the modern era. *J Clin Oncol* 2012; 30(27): 3383–3388.
43. Eichenauer DA, Aleman BMP, Andre M, et al. Hodgkin's lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment, and follow-up. *Ann Oncol* 2018; 29(Suppl. 4): ii19–ii29.
44. Brenner H, Gondos A, Pulte D. Ongoing improvement in long-term survival of patients with Hodgkin disease at all ages and recent catch-up of older patients. *Blood* 2008; 111(6): 2977–2983.
45. Engert A, Haverkamp H, Kobe C, et al. Reduced-intensity chemotherapy and PET-guided radiotherapy in patients with advanced stage Hodgkin's lymphoma (HD15 trial): a randomised, open-label, phase 3 non-inferiority trial. *Lancet* 2012; 379(9828): 1791–1779.
46. Forero-Torres A, Holkova B, Goldschmidt J, et al. Phase 2 study of frontline brentuximab vedotin monotherapy in Hodgkin lymphoma patients aged 60 years and older. *Blood* 2015; 126(26): 2798–2804.
47. Friedberg JW, Forero-Torres A, Bordoni RE, et al. Frontline brentuximab vedotin in combination with dacarbazine or bendamustine in patients aged ≥ 60 years with HL. *Blood* 2017; 130(26): 2829–2837.
48. Evens AM, Advani RH, Helenowski IB, et al. Multicenter Phase II Study of Sequential Brentuximab Vedotin and Doxorubicin, Vinblastine, and Dacarbazine Chemotherapy for Older Patients With Untreated Classical Hodgkin Lymphoma. *J Clin Oncol* 2018; 36(30): 3015–3022.
49. Herst J, Crump M, Baldassarre FG, et al. Management of Early-stage Hodgkin Lymphoma: A Practice Guideline. *Clin Oncol* (*R Coll Radiol*) 2017; 29(1): e5–e12.
50. Dühmke E, Franklin J, Pfreundschuh M, et al. Low-dose radiation is sufficient for the noninvolved extended-field treatment in favorable early-stage Hodgkin's disease: long-term results of a randomized trial of radiotherapy alone. *J Clin Oncol* 2001; 19(11): 2905–2914.
51. Mendenhall NP, Rodrigue LL, Moore-Higgs GJ, et al. The optimal dose of radiation in Hodgkin's disease: an analysis of clinical and treatment factors affecting in-field disease control. *Int J Radiat Oncol Biol Phys* 1999; 44(3): 551–561.
52. Dabaja BS, Hoppe BS, Plastaras JP, et al. Proton therapy for adults with mediastinal lymphomas: the International Lymphoma Radiation Oncology Group guidelines. *Blood* 2018; 132(16): 1635–1646.
53. Canellos GP, Abramson JS, Fisher DC, et al. Treatment of favorable, limited-stage Hodgkin's lymphoma with chemotherapy without consolidation by radiation therapy. *J Clin Oncol* 2010; 28(9): 1611–1615.
54. Landgren O, Axdorph U, Fears TR, et al. A population-based cohort study on early-stage Hodgkin lymphoma treated with radiotherapy alone: with special reference to older patients. *Ann Oncol* 2006; 17(8): 1290–1295.
55. Backstrand KH, Ng AK, Takvorian RW, et al. Results of a prospective trial of mantle irradiation alone for selected patients with early-stage Hodgkin's disease. *J Clin Oncol* 2001; 19(3): 736–741.
56. Meyer RM, Gospodarowicz MK, Connors JM, et al. ABVD alone versus radiation-based therapy in limited-stage Hodgkin's lymphoma. *N Engl J Med* 2012; 366(5): 399–408.
57. Engert A, Plütschow A, Eich HT, et al. Reduced treatment intensity in patients with early-stage Hodgkin's lymphoma. *N Engl J Med* 2010; 363(7): 640–652.
58. Sasse S, Bröckelmann PJ, Goergen H, et al. Long-Term Follow-Up of Contemporary Treatment in Early-Stage Hodgkin Lymphoma: Updated Analyses of the German Hodgkin Study Group HD7, HD8, HD10, and HD11 Trials. *J Clin Oncol* 2017; 35(18): 1999–2007.
59. Behringer K, Goergen H, Hitz F, et al. Omission of dacarbazine or bleomycin, or both, from the ABVD regimen in treatment of early-stage favourable Hodgkin's lymphoma (GHSG HD13): an open-label, randomised, non-inferiority trial. *Lancet* 2015; 385(9976): 1418–1427.
60. Raemaekers JM, André MP, Federico M, et al. Omitting radiotherapy in early positron emission tomography-negative stage I/II Hodgkin lymphoma is associated with an increased risk of early relapse: Clinical results of the preplanned interim analysis of the randomized EORTC/LYSA/FIL H10 trial. *J Clin Oncol* 2014; 32(12): 1188–1194.
61. Radford J, Illidge T, Counsell N, et al. Results of a trial of PET-directed therapy for early-stage Hodgkin's lymphoma. *N Engl J Med* 2015; 372(17): 1598–1607.
62. Fuchs M, Goergen H, Kobe C, et al. Positron Emission Tomography-Guided Treatment in Early-Stage Favorable Hodgkin Lymphoma: Final Results of the International, Randomized Phase III HD16 Trial by the German Hodgkin Study Group. *J Clin Oncol* 2019; 37(31): 2835–2845.
63. Bröckelmann PJ, Sasse S, Engert A. Balancing risk and benefit in early-stage classical Hodgkin lymphoma. *Blood* 2018; 131(15): 1666–1678.
64. Böll B, Goergen H, Behringer K, et al. Bleomycin in older early-stage favorable Hodgkin lymphoma patients: analysis of the German Hodgkin Study Group (GHSG) HD10 and HD13 trials. *Blood* 2016; 127(18): 2189–2192.

65. Gunther JR, Fanale MA, Reddy JP, et al. Treatment of Early-Stage Unfavorable Hodgkin Lymphoma: Efficacy and Toxicity of 4 Versus 6 Cycles of ABVD Chemotherapy with Radiation. *Int J Radiat Oncol Biol Phys* 2016; 96(1): 110–118.
66. Tresckow B, von, Plütschow A, Fuchs M, et al. Dose-intensification in early unfavorable Hodgkin's lymphoma: final analysis of the German hodgkin study group HD14 trial. *J Clin Oncol* 2012; 30(9): 907–913.
67. Fermé C, Thomas J, Brice P, et al. ABVD or BEACOPPbaseline along with involved-field radiotherapy in early-stage Hodgkin Lymphoma with risk factors: Results of the European Organisation for Research and Treatment of Cancer (EORTC)-Groupe d'Étude des Lymphomes de l'Adulte (GELA) H9-U intergroup randomised trial. *Eur J Cancer* 2017; 81: 45–55.
68. Eich HT, Diehl V, Görgen H, et al. Intensified chemotherapy and dose-reduced involved-field radiotherapy in patients with early unfavorable Hodgkin's lymphoma: final analysis of the German Hodgkin Study Group HD11 trial. *J Clin Oncol* 2010; 28(27): 4199–4206.
69. Kumar A, Casulo C, Yahalom J, et al. Brentuximab vedotin and AVD followed by involved-site radiotherapy in early stage, unfavorable risk Hodgkin lymphoma. *Blood* 2016; 128(11): 1458–1464.
70. André MPE, Girinsky T, Federico M, et al. Early Positron Emission Tomography Response – Adapted Treatment in Stage I and II Hodgkin Lymphoma: Final Results of the Randomized EORTC/LYSA/FIL H10 Trial. *J Clin Oncol* 2017; 35(16): 1786–1794.
71. Borchmann P, Plütschow A, Kobe C, et al. PET-guided omission of radiotherapy in early-stage unfavourable Hodgkin lymphoma (GHSG HD17): a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol* 2021; 22(2): 223–234.
72. Connors JM, Jurczak W, Straus DJ, et al. Brentuximab Vedotin with Chemotherapy for Stage III or IV Hodgkin's Lymphoma. *N Engl J Med* 2018; 378(4): 331–344.
73. Straus DJ, Długosz-Danecka M, Alekseev S, et al. Brentuximab vedotin with chemotherapy for stage III/IV classical Hodgkin lymphoma: 3-year update of the ECHELON-1 study. *Blood* 2020; 135(10): 735–742.
74. Ansell SM, Radford J, Connors JM, et al. Overall Survival with Brentuximab Vedotin in Stage III or IV Hodgkin's Lymphoma. *N Engl J Med* 2022; 387(4): 310–320.
75. Evens AM, Connors JM, Younes A, et al. Older patients (aged ≥ 60 years) with previously untreated advanced-stage classical Hodgkin lymphoma: a detailed analysis from the phase III ECHELON-1 study. *Haematologica* 2022; 107(5): 1086–1094, doi: 10.3324/haematol.2021.278438.
76. Canellos GP, Niedzwiecki D. Long-term follow-up of Hodgkin's disease trial. *N Engl J Med* 2002; 346(18): 1417–1418.
77. Duggan DB, Petroni GR, Johnson JL, et al. Randomized comparison of ABVD and MOPP/ABV hybrid for the treatment of advanced Hodgkin's disease: report of an intergroup trial. *J Clin Oncol* 2003; 21(4): 607–614.
78. Federico M, Luminari S, Iannitto E, et al. ABVD compared with BEACOPP compared with CEC for the initial treatment of patients with advanced Hodgkin's lymphoma: results from the HD2000 Gruppo Italiano per lo Studio dei Linfomi Trial. *J Clin Oncol* 2009; 27(5): 805–811.
79. Viviani S, Zinzani PL, Rambaldi A, et al. ABVD versus BEACOPP for Hodgkin's lymphoma when high-dose salvage is planned. *N Engl J Med* 2011; 365(3): 203–312.
80. Bauer K, Skoetz N, Monsef I, et al. Comparison of chemotherapy including escalated BEACOPP versus chemotherapy including ABVD for patients with early unfavourable or advanced stage Hodgkin lymphoma. *Cochrane Database Syst Rev* 2011; 8: CD007941, doi: 10.1002/14651858.CD007941.pub2.
81. Chisesi T, Bellei M, Luminari S, et al. Long-term follow-up analysis of HD9601 trial comparing ABVD versus Stanford V versus MOPP/EBV/CAD in patients with newly diagnosed advanced-stage Hodgkin's lymphoma: a study from the Intergruppo Italiano Linfomi. *J Clin Oncol* 2011; 29(32): 4227–4233.
82. Carde P, Karrasch M, Fortpied C, et al. Eight Cycles of ABVD Versus Four Cycles of BEACOPPescalated Plus Four Cycles of BEACOPPbaseline in Stage III to IV, International Prognostic Score ≥ 3, High-Risk Hodgkin Lymphoma: First Results of the Phase III EORTC 20012 Intergroup Trial. *J Clin Oncol* 2016; 34(17): 2028–2036.
83. Mounier N, Brice P, Bologna S, et al. ABVD (8 cycles) versus BEACOPP (4 escalated cycles ≥ 4 baseline): final results in stage III-IV low-risk Hodgkin lymphoma (IPS 0-2) of the LYSA H34 randomized trial. *Ann Oncol* 2014; 25(8): 1622–1628.
84. Fabian CJ, Mansfield CM, Dahlberg S, et al. Low-dose involved field radiation after chemotherapy in advanced Hodgkin disease. A Southwest Oncology Group randomized study. *Ann Intern Med* 1994; 120(11): 903–912.
85. Aleman BM, Raemaekers JM, Tirelli U, et al. Involved-field radiotherapy for advanced Hodgkin's lymphoma. *N Engl J Med* 2003; 348(24): 2396–2406.
86. Fermé C, Mounier N, Casasnovas O, et al. Long-term results and competing risk analysis of the H89 trial in patients with advanced-stage Hodgkin lymphoma: a study by the Groupe d'Etude des Lymphomes de l'Adulte (GELA). *Blood* 2006; 107(12): 4636–4642.
87. Johnson P, Federico M, Kirkwood A, et al. Adapted Treatment Guided by Interim PET-CT Scan in Advanced Hodgkin's Lymphoma. *N Engl J Med* 2016; 374(25): 2419–2429.
88. Josting A, Franklin J, May M, et al. New prognostic score based on treatment outcome of patients with relapsed Hodgkin's lymphoma registered in the database of the German Hodgkin's lymphoma study group. *J Clin Oncol* 2002; 20(1): 221–230.
89. Bonfante V, Santoro A, Viviani S, et al. Outcome of patients with Hodgkin's disease failing after primary MOPP-ABVD. *J Clin Oncol* 1997; 15(2): 528–534.
90. Garcia-Carbonero R, Paz-Ares L, Arcediano A, et al. Favorable prognosis after late relapse of Hodgkin's disease. *Cancer* 1998; 83(3): 560–565.
91. Kuruvilla J, Ramchandren R, Santoro A, et al. Pembrolizumab versus brentuximab vedotin in relapsed or refractory classical Hodgkin lymphoma (KEYNOTE-204): an interim analysis of a multicentre, randomised, open-label, phase 3 study. *Lancet Oncol* 2021; 22(4): 512–524.
92. Armand P, Shipp MA, Ribrag V, et al. Programmed Death-1 Blockade with Pembrolizumab in Patients with Classical Hodgkin Lymphoma After Brentuximab Vedotin Failure. *J Clin Oncol* 2016; 34(31): 3733–3739.
93. Chen R, Zinzani PL, Lee HJ, et al. Pembrolizumab in relapsed or refractory Hodgkin lymphoma: 2-year follow-up of KEYNOTE-087. *Blood* 2019; 134(14): 1144–1153.
94. Ansell SM, Lesokhin AM, Borrello I, et al. PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma. *N Engl J Med* 2015; 372(4): 311–319.
95. Younes A, Santoro A, Shipp M, et al. Nivolumab for classical Hodgkin's lymphoma after failure of both autologous stem-cell transplantation and brentuximab vedotin: a multicentre, multicohort, single-arm phase 2 trial. *Lancet Oncol* 2016; 17(9): 1283–1294.
96. Armand P, Engert A, Younes A, et al. Nivolumab for Relapsed/Refractory Classic Hodgkin Lymphoma After Failure of Autologous Hematopoietic Cell Transplantation: Extended Follow-Up of the Multicohort Single-Arm Phase II CheckMate 205 Trial. *J Clin Oncol* 2018; 36(14): 1428–1439.
97. Herrera AF, Moskowitz AJ, Bartlett NL, et al. Interim results of brentuximab vedotin in combination with nivolumab in patients with relapsed or refractory Hodgkin lymphoma. *Blood* 2018; 131(11): 1183–1194.
98. Gopal AK, Ramchandren R, O'Connor OA, et al. Safety and efficacy of brentuximab vedotin for Hodgkin lymphoma recurring after allogeneic stem cell transplantation. *Blood* 2012; 120(3): 560–568.

99. Younes A, Bartlett NL, Leonard JP, et al. Brentuximab vedotin (SGN-35) for relapsed CD30-positive lymphomas. *N Engl J Med* 2010; 363(19): 1812–1821.
100. Younes A, Gopal AK, Smith SE, et al. Results of a pivotal phase II study of brentuximab vedotin for patients with relapsed or refractory Hodgkin's lymphoma. *J Clin Oncol* 2012; 30(18): 2183–2189.
101. Chen R, Palmer JM, Thomas SH, et al. Brentuximab vedotin enables successful reduced-intensity allogeneic hematopoietic cell transplantation in patients with relapsed or refractory Hodgkin lymphoma. *Blood* 2012; 119(26): 6379–6381.
102. Bazarbachi A, Boumendil A, Finel H, et al. Brentuximab vedotin for recurrent Hodgkin lymphoma after allogeneic hematopoietic stem cell transplantation: A report from the EBMT Lymphoma Working Party. *Cancer* 2019; 125(1): 90–98.
103. Moskowitz CH, Nademanee A, Masszi T, et al. Brentuximab vedotin as consolidation therapy after autologous stem-cell transplantation in patients with Hodgkin's lymphoma at risk of relapse or progression (AETHERA): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* 2015; 385(9980): 1853–1862.
104. Moskowitz CH, Walewski J, Nademanee A, et al. Five-year PFS from the AETHERA trial of brentuximab vedotin for Hodgkin lymphoma at high risk of progression or relapse. *Blood* 2018; 132(25): 2639–2642.
105. LaCasce AS, Bociek RG, Sawas A, et al. Brentuximab vedotin plus bendamustine: a highly active first salvage regimen for relapsed or refractory Hodgkin lymphoma. *Blood* 2018; 132(1): 40–48.
106. O'Connor OA, Lue JK, Sawas A, et al. Brentuximab vedotin plus bendamustine in relapsed or refractory Hodgkin's lymphoma: an international, multicentre, single-arm, phase 1–2 trial. *Lancet Oncol* 2018; 19(2): 257–266.
107. Holmberg L, Maloney DG. The role of autologous and allogeneic hematopoietic stem cell transplantation for Hodgkin lymphoma. *J Natl Compr Canc Netw* 2011; 9(9): 1060–1071.
108. Shah GL, Moskowitz CH. Transplant strategies in relapsed/refractory Hodgkin lymphoma. *Blood* 2018; 131(15): 1689–1697.
109. Martínez C, Gayoso J, Canals C, et al. Post-Transplantation Cyclophosphamide-Based Haploidentical Transplantation as Alternative to Matched Sibling or Unrelated Donor Transplantation for Hodgkin Lymphoma: A Registry Study of the Lymphoma Working Party of the European Society for Blood and Marrow Transplantation. *J Clin Oncol* 2017; 35(30): 3425–3432.
110. Schmitz N, Pfistner B, Sextro M, et al. Aggressive conventional chemotherapy compared with high-dose chemotherapy with autologous haemopoietic stem-cell transplantation for relapsed chemosensitive Hodgkin's disease: a randomised trial. *Lancet* 2002; 359(9323): 2065–2071.
111. Rancea M, Monsef I, Tresckow B, von, et al. High-dose chemotherapy followed by autologous stem cell transplantation for patients with relapsed/refractory Hodgkin lymphoma. *Cochrane Database Syst Rev* 2013; 6: CD009411.
112. Canellos GP, Petroni GR, Barcos M, et al. Etoposide, vinblastine, and doxorubicin: an active regimen for the treatment of Hodgkin's disease in relapse following MOPP. Cancer and Leukemia Group B. *J Clin Oncol* 1995; 13(8): 2005–2011.
113. Longo DL, Duffey PL, Young RC, et al. Conventional-dose salvage combination chemotherapy in patients relapsing with Hodgkin's disease after combination chemotherapy: the low probability for cure. *J Clin Oncol* 1992; 10(2): 210–218.
114. Böll B, Goergen H, Arndt N, et al. Relapsed hodgkin lymphoma in older patients: a comprehensive analysis from the German hodgkin study group. *J Clin Oncol* 2013; 31(35): 4431–4437.
115. Ng AK, Li S, Neuberg D, et al. Comparison of MOPP versus ABVD as salvage therapy in patients who relapse after radiation therapy alone for Hodgkin's disease. *Ann Oncol* 2004; 15(2): 270–275.
116. Horwich A, Specht L, Ashley S. Survival analysis of patients with clinical stages I or II Hodgkin's disease who have relapsed after initial treatment with radiotherapy alone. *Eur J Cancer* 1997; 33(6): 848–853.
117. Josting A, Nogová L, Franklin J, et al. Salvage radiotherapy in patients with relapsed and refractory Hodgkin's lymphoma: a retrospective analysis from the German Hodgkin Lymphoma Study Group. *J Clin Oncol* 2005; 23(7): 1522–1529.
118. Anselmo AP, Cavalieri E, Enrici RM, et al. Hodgkin's disease during pregnancy: diagnostic and therapeutic management. *Fetal Diagn Ther* 1999; 14(2): 102–105.
119. Mazonakis M, Varveris H, Fasoulaki M, et al. Radiotherapy of Hodgkin's disease in early pregnancy: embryo dose measurements. *Radiother Oncol* 2003; 66(3): 333–339.
120. Greskovich JF, Macklis RM. Radiation therapy in pregnancy: risk calculation and risk minimization. *Semin Oncol* 2000; 27(6): 633–645.
121. Thomas PR, Biochem D, Peckham MJ. The investigation and management of Hodgkin's disease in the pregnant patient. *Cancer* 1976; 38(3): 1443–1451.
122. Cardonick E, Iacobucci A. Use of chemotherapy during human pregnancy. *Lancet Oncol* 2004; 5(5): 283–291.
123. Jacobs C, Donaldson SS, Rosenberg SA, et al. Management of the pregnant patient with Hodgkin's disease. *Ann Intern Med* 1981; 95(6): 669–675.
124. Nisce LZ, Tome MA, He S, et al. Management of coexisting Hodgkin's disease and pregnancy. *Am J Clin Oncol* 1986; 9(2): 146–151.
125. Avilés A, Díaz-Maqueo JC, Talavera A, et al. Growth and development of children of mothers treated with chemotherapy during pregnancy: current status of 43 children. *Am J Hematol* 1991; 36(4): 243–248.
126. Harris NL. Hodgkin's lymphomas: classification, diagnosis, and grading. *Semin Hematol* 1999; 36(3): 220–232.
127. Shimabukuro-Vornhagen A, Haverkamp H, Engert A, et al. Lymphocyte-rich classical Hodgkin's lymphoma: clinical presentation and treatment outcome in 100 patients treated within German Hodgkin's Study Group trials. *J Clin Oncol* 2005; 23(24): 5739–5745.
128. Moskowitz AJ. NLP Hodgkin lymphoma: can we get away with less? *Blood* 2020; 135(26): 2329–2330.
129. Borchmann S, Joffe E, Moskowitz CH, et al. Active surveillance for nodular lymphocyte-predominant Hodgkin lymphoma. *Blood* 2019; 133(20): 2121–2129.
130. Eichenauer DA, Plütschow A, Fuchs M, et al. Long-Term Course of Patients with Stage IA Nodular Lymphocyte-Predominant Hodgkin Lymphoma: A Report From the German Hodgkin Study Group. *J Clin Oncol 2*015; 33(26): 2857–2862.
131. Chen RC, Chin MS, Ng AK, et al. Early-stage, lymphocyte-predominant Hodgkin's lymphoma: patient outcomes from a large, single-institution series with long follow-up. *J Clin Oncol* 2010; 28(1): 136–141.
132. Eichenauer DA, Engert A. How I treat nodular lymphocyte-predominant Hodgkin lymphoma. *Blood* 2020; 136(26): 2987–2993.
133. Binkley MS, Rauf MS, Milgrom SA, et al. Stage I-II nodular lymphocyte-predominant Hodgkin lymphoma: a multi-institutional study of adult patients by ILROG. *Blood* 2020; 135(26): 2365–2374.
134. Russell KJ, Hoppe RT, Colby TV, et al. Lymphocyte predominant Hodgkin's disease: clinical presentation and results of treatment. *Radiother Oncol* 1984; 1(3): 197–205.
135. Savage KJ, Skinnider B, Al-Mansour M, et al. Treating limited-stage nodular lymphocyte predominant Hodgkin lymphoma similarly to classical Hodgkin lymphoma with ABVD may improve outcome. *Blood* 2011; 118(17): 4585–4590.
136. Bartlett NL. Treatment of Nodular Lymphocyte Hodgkin Lymphoma: The Goldilocks Principle. *J Clin Oncol* 2020; 38(7): 662–668.
137. Xing KH, Connors JM, Lai A, et al. Advanced-stage nodular lymphocyte predominant Hodgkin lymphoma compared with classical Hodgkin lymphoma: a matched pair outcome analysis. *Blood* 2014; 123(23): 3567–373.

138. Fanale MA, Cheah CY, Rich A, et al. Encouraging activity for R-CHOP in advanced stage nodular lymphocyte-predominant Hodgkin lymphoma. *Blood* 2017; 130(4): 472–477.
139. Advani RH, Horning SJ, Hoppe RT, et al. Mature results of a phase II study of rituximab therapy for nodular lymphocyte-predominant Hodgkin lymphoma. *J Clin Oncol* 2014; 32(9): 912–918.
140. Eichenauer DA, Plütschow A, Fuchs M, et al. Long-Term Follow-Up of Patients with Nodular Lymphocyte-Predominant Hodgkin Lymphoma Treated in the HD7 to HD15 Trials: A Report From the German Hodgkin Study Group. *J Clin Oncol* 2020; 38(7): 698–705.
141. Kenderian SS, Habermann TM, Macon WR, et al. Large B-cell transformation in nodular lymphocyte-predominant Hodgkin lymphoma: 40-year experience from a single institution. *Blood* 2016; 127(16): 1960–1966.
142. El-Galaly TC, Mylam KJ, Brown P, et al. Positron emission tomography/computed tomography surveillance in patients with Hodgkin lymphoma in first remission has a low positive predictive value and high costs. *Haematologica* 2012; 97(6): 931–936.
143. Hartridge-Lambert SK, Schöder H, Lim RC, et al. ABVD alone and a PET scan complete remission negates the need for radiologic surveillance in early-stage, nonbulky Hodgkin lymphoma. *Cancer* 2013; 119(6): 1203–1209.
144. Hapgood G, Zheng Y, Sehn LH, et al. Evaluation of the Risk of Relapse in Classical Hodgkin Lymphoma at Event-Free Survival Time Points and Survival Comparison with the General Population in British Columbia. *J Clin Oncol* 2016; 34(21): 2493–2500.
145. SEER. Cancer Stat Facts: Hodgkin Lymphoma; National Cancer Institute: Bethesda, MD, USA [cited 29.09.2018]. Available from URL: https://seer.cancer.gov/statfacts/html/hodg.html.
146. Longo DL, Armitage JO. Controversies in the treatment of early-stage Hodgkin's lymphoma. *N Engl J Med* 2015; 372(17): 1667–1669.
147. Aleman BM, Belt-Dusebout AW, van den, Klokman WJ, et al. Long-term cause-specific mortality of patients treated for Hodgkin's disease. *J Clin Oncol* 2003; 21(18): 3431–3439.
148. Swerdlow AJ, Higgins CD, Smith P, et al. Second cancer risk after chemotherapy for Hodgkin's lymphoma: a collaborative British cohort study. *J Clin Oncol* 2011; 29(31): 4096–4104.
149. Koontz MZ, Horning SJ, Balise R, et al. Risk of therapy-related secondary leukemia in Hodgkin lymphoma: the Stanford University experience over three generations of clinical trials. *J Clin Oncol* 2013; 31(5): 592–598.
150. Valagussa P, Santoro A, Fossati-Bellani F, et al. Second acute leukemia and other malignancies following treatment for Hodgkin's disease. *J Clin Oncol* 1986; 4(6): 830–837.
151. Dores GM, Metayer C, Curtis RE, et al. Second malignant neoplasms among long-term survivors of Hodgkin's disease: a population-based evaluation over 25 years. *J Clin Oncol* 2002; 20(16): 3484–3494.
152. Franklin J, Pluetschow A, Paus M, et al. Second malignancy risk associated with treatment of Hodgkin's lymphoma: meta-analysis of the randomised trials. *Ann Oncol* 2006; 17(12): 1749–1760.
153. Chowdhry AK, McHugh C, Fung C, et al. Second primary head and neck cancer after Hodgkin lymphoma: a population-based study of 44,879 survivors of Hodgkin lymphoma. *Cancer* 2015; 121(9): 1436–1445.
154. Dores GM, Curtis RE, Leeuwen FE, van, et al. Pancreatic cancer risk after treatment of Hodgkin lymphoma. *Ann Oncol* 2014; 25(10): 2073–2079.
155. Rigter LS, Spaander MCW, Aleman BMP, et al. High prevalence of advanced colorectal neoplasia and serrated polyposis syndrome in Hodgkin lymphoma survivors. *Cancer* 2019; 125(6): 990–999.
156. Schaapveld M, Aleman BM, Eggermond AM, van, et al. Second Cancer Risk Up to 40 Years after Treatment for Hodgkin's Lymphoma. *N Engl J Med* 2015; 373(26): 2499–2511.
157. Lavoie JC, Connors JM, Phillips GL, et al. High-dose chemotherapy and autologous stem cell transplantation for primary refractory or relapsed Hodgkin lymphoma: long-term outcome in the first 100 patients treated in Vancouver. *Blood* 2005; 106(4): 1473–1478.
158. Kreissl S, Müller H, Goergen H, et al. Health-Related Quality of Life in Patients with Hodgkin Lymphoma: A Longitudinal Analysis of the German Hodgkin Study Group. *J Clin Oncol* 2020; 38(25): 2839–2848.
159. Horning SJ, Adhikari A, Rizk N, et al. Effect of treatment for Hodgkin's disease on pulmonary function: results of a prospective study. *J Clin Oncol* 1994; 12(2): 297–305.
160. Martin WG, Ristow KM, Habermann TM, et al. Bleomycin pulmonary toxicity has a negative impact on the outcome of patients with Hodgkin's lymphoma. *J Clin Oncol* 2005; 23(30): 7614–7620.
161. Prosnitz LR, Lawson JP, Friedlaender GE, et al. Avascular necrosis of bone in Hodgkin's disease patients treated with combined modality therapy. Cancer 1981; 47(12): 2793–2797.

Tables: 1
Figures: 0
References: 161

Received: 18.05.2023
Reviewed: 18.06.2023
Accepted: 18.07.2023

Address for correspondence:
Katarzyna Hetman, MD
Department of Clinical Oncology of the Western Pomeranian Oncology Center in Szczecin
22 Strzałowska St
71-730 Szczecin
Poland
Tel.: +48 914251501
E-mail: khetman@onkologia.szczecin.pl