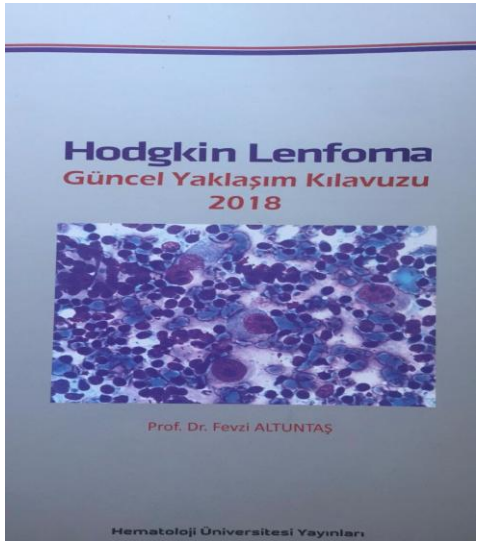
Hodgkin Lenfoma: Yeni Tanı Tedavi



Prof. Dr. Fevzi ALTUNTAŞ

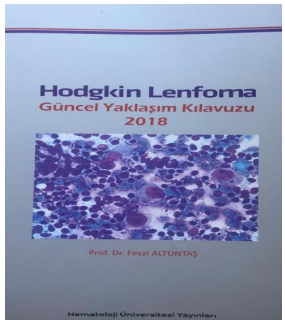
Yıldırım Beyazıt Üniversitesi Tıp Fakültesi Öğretim Üyesi

II. Hematolojik Nadir Hastalıklar Kongresi

2019, Magusa/KKTC

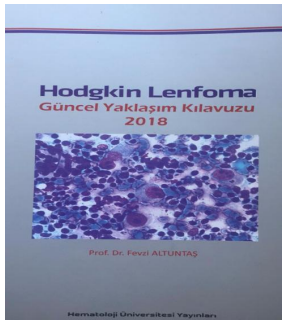
Sunum Planı

- Giriş
- Tedavi seçeneklerimiz
- Evreleme
- Prognostik kriteler
- Tedavi öncesi yapılması gerekenler
- Tedavi
- Prognoz
- Komplikasyonlar
- Takip



Hodgkin Lenfoma

- Hodgkin Lenfoma sıklığı yılda 2-3/100.0000 değişen bir lenfoma türüdür.
- Güncel kombine tedavilerle kür şansı %80'lerin üzerindedir.
- Kür şansının yüksek olması sebebi ile amaç sadece hastada kür elde etmek olmamalıdır. Bu sebeple amacımız maksimum yanıt elde etmenin yanında en az uzun dönem toksisite riski ve en iyi yaşam kalitesi olmalıdır.



Hodgkin Lenfoma- Sınıflama

Classification of Hodgkin lymphomas

Jackson and Parker	Lukes and Butler	Rye Conference	R.E.A.L. Classification	World Health Organization (WHO) Classification
Paragranuloma	Lymphocytic and/or histiocytic, nodular	Lymphocyte predominance	Nodular lymphocyte predominance	Nodular lymphocyte predominant HL
	Lymphocytic and/or histiocytic, diffuse		Classical Lymphocyte-rich HL*	Lymphocyte-rich classical HL
Granuloma	Nodular sclerosis	Nodular sclerosis	Classical Nodular sclerosis HL	Nodular sclerosis classical HL
	Mixed cellularity	Mixed cellularity	Classical Mixed cellularity HL	Mixed cellularity classical HL
Sarcoma	Diffuse fibrosis	Lymphocyte depletion	Classical Lymphocyte depletion HL	Lymphocyte depleted classical HL
	Reticular			

HL: Hodgkin lymphoma.
* Includes some L&H nodular cases.

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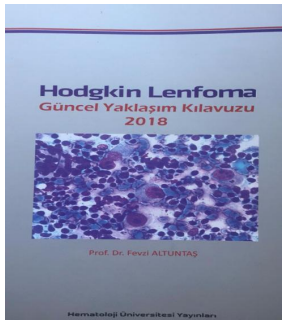

Hodgkin Lenfoma- Sınıflama

Nodular lymphocyte predominant Hodgkin lymphoma (NLPHL) and classical Hodgkin lymphoma (HL): Morphologic and immunophenotypic features

	Classical HL	NLPHL
Pattern	Diffuse, interfollicular, nodular	Nodular, at least in part
Tumor cells	Diagnostic RS cells; mononuclear or lacunar cells	"L&H" or "popcorn" cells
Background	Lymphocytes, histiocytes, eosinophils, plasma cells	Lymphocytes, histiocytes
Fibrosis	Common	Rare
CD15	+	-
CD30	+	-
CD20	-/+	+
CD45	-	+
EMA	-	+
EBV (in RS cells)	+ (~50%)	-
Oct2	-/+	+
BOB.1	-/+	+
Background lymphocytes	T cells > B cells	B cells > T cells
CD57+ Tcells	-	+
Ig genes (single-cell PCR)	Rearranged, clonal, mutated, "crippled", no ongoing somatic hypermutation	Rearranged, clonal, mutated, productive, ongoing somatic hypermutation

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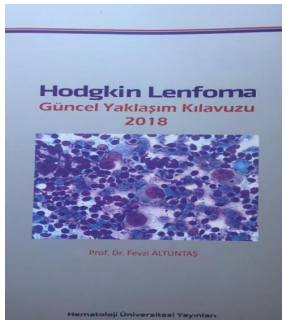
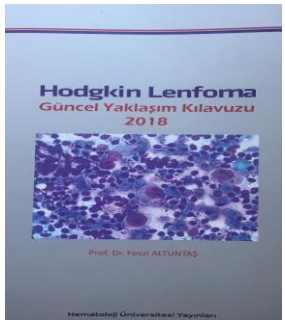


Hodgkin Lenfoma- Tedavi Seçenekleri

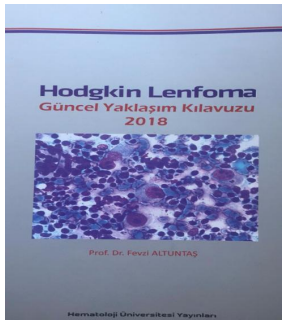
- Radyoterapi
- Kemoterapi
- Kemoterapi+Radyoterapi
  - Kemoterapi protokolü içinde
  - Kemoterapi bittikten sonra
- Kemik İliği Nakli
  - Otolog
  - Allojenik

- Güncel tedavi yaklaşımları ile Hodgkin Lenfomada kür oranı %80'lerin üzerindedir.
- ***Hodgkin Lenfomada tedavinin amacı; en düşük komplikasyon riski ile en yüksek kür oranı sağlamak olmalıdır.***



Hodgkin Lenfoma- Radyoterapi

- Radyoterapi bir çok kanser türünde olduğu gibi Hodgkin Lenfomada da tedavi seçeneklerinden bir tanesidir.
- Radyoterapinin istenmeyen etkisi kısa ve uzun sürede oluşan komplikasyonlarıdır.
- Radyoterapinin komplikasyonları uygulanan bölgeye, süre ve doza bağlı olarak değişmektedir.
- Radyoterapi ikincil kanserler, büyüme gelişme gerilikleri, troid fonksiyon bozuklukları, kardiyovasküler ve akciğer ile ilgili komplikasyonlara yol açabildiği için günümüzde kullanımı giderek azalmıştır.



Fevzi ALTUNTAŞ, Hodgkin Lenfoma Güncelleme 2018

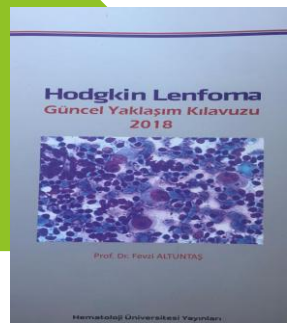
Hodgkin Lenfoma:
RADYOTERAPİ

- Radyoterapi bilindiği üzere lokal ve bölgesel bir tedavi yöntemidir.

Lokal kontrol, azalmış kemoterapi döngüleri, nüks esnasında azalmış dozlar

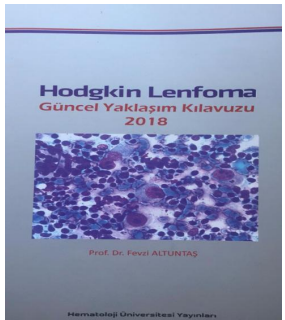
Geç yan etkiler

IFRT → ISRT → INRT



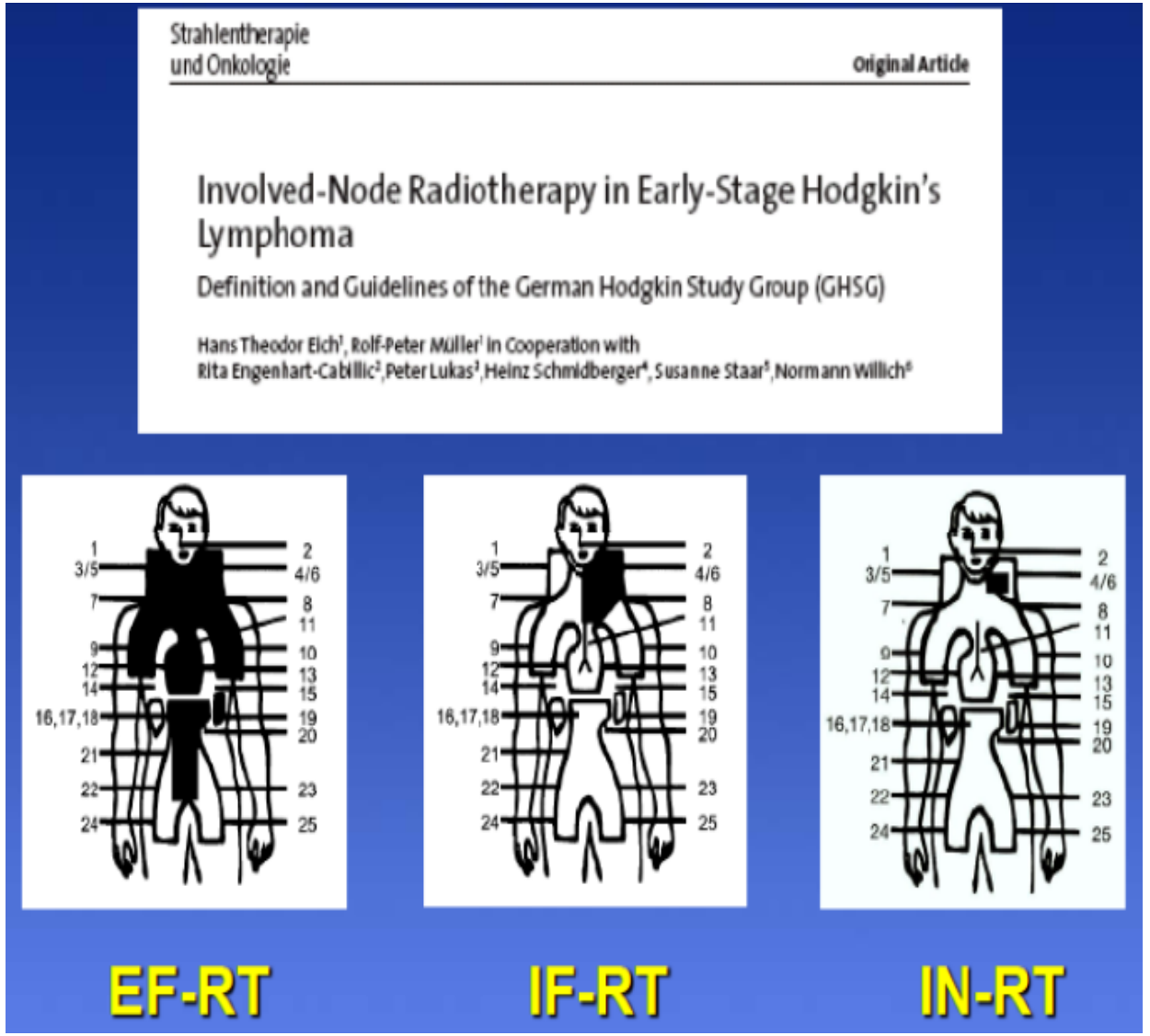
Hodgkin Lenfoma- RT bölge

- Tarihsel süreç içerisinde HL radyoterapi uygulamaları toksik etkisi ve uzun dönem komplikasyonlarını azaltmak için giderek küçülen hacimleri içeren tedaviler şeklinde gelişmiştir.
  - Total Lenfoid Işınlama (TLI)
  - Sub-Total Lenfoid Işınlama (STLI) (genişletilmiş Mantle, Mantle, Ters Y, para-aortik + dalak)
  - Tutulu alan (Involved Field; TART)
  - Tutulu yer (Involved Site; ISRT)
  - Tutulu lenf nodu (Involved Lymph Node; INRT)



Hodgkin Lenfoma- RT bölge büyüklüğü?

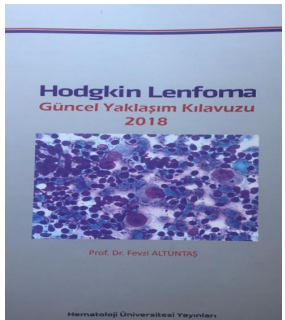
- Hodgkin Lenfomada radyoterapinin yeri kemoterapi sonrasında ISRT (tutulu yer) veya INRT (tutulu lenf nodu) ile sınırlandırma eğilimindedir.



Hodgkin Lenfoma- RT dozu?

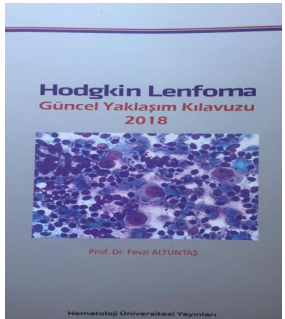
NCCN 2018 önerisi

- A. Klasik HL Radyoterapi dozu
  - Erken evre iyi risk grubunda 20 Gy
  - Erken evre kötü risk grubunda 30 Gy
  - Bulky hastalıkta 30-36 Gy
  - Kemoterapi sonrası PET Deauville puan 3-4 olanlarda 30-45 Gy önerilir.
- B. NLPHL Radyoterapi dozu
  - Sadece RT alanlarda 30 Gy olması önerilir.



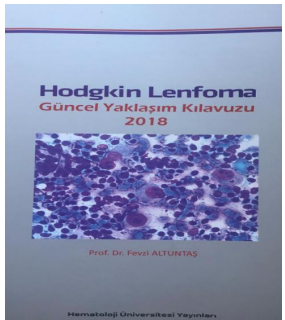
Hodgkin Lenfoma- RT süresi?

- RT günde 2 Gy, haftada 5 gün olacak şekilde 10-18 günde (2-4 hafta) tamamlanır.



Hodgkin Lenfoma- RT kür mümkün mü?

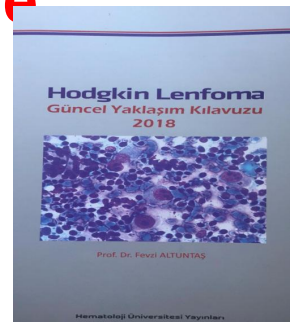
- Evre IA, IIA nodüler lenfosit predominat Hodgkin Lenfomada radyoterapi tek başına kür amaçlı olarak kullanılabilir.



Hodgkin Lenfoma:
RADYOTERAPİ- KOMPLİKASYON

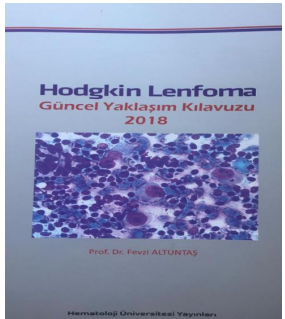
- Kalp hastalıkları
- Akciğer fonksiyon kaybı
- Sekonder malignite
- İnfertilite
- Hipotiroidi

- Tutulum olmadığı sürece tüm hastalarda **yüksek servikal lenf nodları ve kadınlarda aksilla her zaman RT alanının dışında tutulmalıdır.**



Hodgkin Lenfoma- Kemoterapi

- Erken ve ileri evre HL'da çeşitli kemoterapi protokolleri kullanılmaktadır.
- Kemoterapi erken evre HL'da genelde radyoterapi öncesinde radyoterapi ile birlikte kullanılmaktayken, ileri evre Hodgkin Lenfomalı hastalarda tek başına kemoterapi altın standarttır.



Hodgkin Lenfoma- KT protokoller

Chemotherapeutic regimens used for the treatment of Hodgkin lymphoma

Regimen	Dosage and schedule	Frequency
ABVD[1]		
Doxorubicin	25 mg/m^2 IV on days 1 and 15	Repeat cycle every 28 days
Bleomycin	10 units*/m^2 IV on days 1 and 15	
Vinblastine	6 mg/m^2 IV on days 1 and 15	
Dacarbazine	375 mg/m^2 IV on days 1 and 15	
A+AVD[2]		
Brentuximab vedotin	1.2 mg/kg IV on days 1 and 15	Repeat cycle every 28 days
Doxorubicin	25 mg/m^2 IV on days 1 and 15	
Vinblastine	6 mg/m^2 IV on days 1 and 15	
Dacarbazine	375 mg/m^2 IV on days 1 and 15	
Escalated BEACOPP[3,4]		
Bleomycin	10 units*/m^2 IV on day 8	Repeat cycle every 21 days
Etoposide	200 mg/m^2 IV on days 1 through 3¶km	
Doxorubicin	35 mg/m^2 IV on day 1¶	
Cyclophosphamide$^{\Delta}$	1250 mg/m^2 IV on day 1¶	
Vincristine	1.4 mg/m^2 (maximum 2 mg) IV on day 8	
Procarbazine	100 mg/m^2 oral on days 1 through 7	
Prednisone	40 mg/m^2 oral on days 1 through 14	
G-CSF	SQ starting on day 8	
STANFORD V[5] **(with radiation)**		
Doxorubicin	25 mg/m^2 IV on days 1 and 15	Repeat cycle every 28 days for a total of 3 cycles Radiotherapy to initial sites 5 cm or larger (dose: 36 Gy)
Vinblastine$^{\diamond}$	6 mg/m^2 IV on days 1 and 15	
Mechlorethamine	6 mg/m^2 IV on day 1	
Vincristine$^{\diamond}$	1.4 mg/m^2 (maximum 2 mg) IV on days 8 and 22	
Bleomycin	5 units*/m^2 IV on days 8 and 22	
Etoposide	60 mg/m^2 IV on days 15 and 16	
Prednisone	40 mg/m^2 oral every OTHER day x 9 weeks then taper	

IV: intravenous; SQ: subcutaneous; G-CSF: granulocyte colony-stimulating factor.
* 1 unit = 1 mg bleomycin.
¶ Note that these doses are for the Escalated BEACOPP regimen. The Baseline BEACOPP regimen differs from Escalated BEACOPP because the doses of three of the drugs are reduced:
- Etoposide 100 mg/m^2 (instead of 200 mg/m^2)
- Doxorubicin 25 mg/m^2 (instead of 35 mg/m^2)
- Cyclophosphamide 650 mg/m^2 (instead of 1250 mg/m^2)

Δ Mesna, total dose is the same as that of cyclophosphamide, administered: 20 percent IV at hour 0; 40 percent orally at hour 2; 40 percent orally at hour 5.
◇ Vinblastine dose reduced to 4 mg/m^2 and vincristine dose to 1 mg/m^2 (maximum 2 mg) during cycle 3 for patients 50 years of age or older.

References:

1. *Canellos GP, Anderson JR, Propert KJ, et al. Chemotherapy of advanced Hodgkin's disease with MOPP, ABVD, or MOPP alternating with ABVD. N Engl J Med 1992; 327:1478.*
2. *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; 378:331.*
3. *Dann EJ, Bar-Shalom R, Tamir A, et al. Risk-adapted BEACOPP regimen can reduce the cumulative dose of chemotherapy for standard and high-risk Hodgkin lymphoma with no impairment of outcome. Blood 2007; 109:905.*
4. *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; 28:4199.*
5. *Bartlett NL, Rosenberg SA, Hoppe RT, et al. Brief chemotherapy, Stanford V, and adjuvant radiotherapy for bulky or advanced-stage Hodgkin's disease: a preliminary report. J Clin Oncol 1995; 13:1080.*

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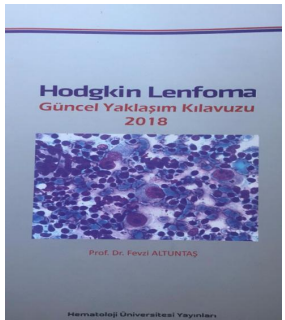


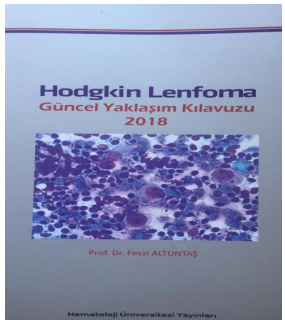
Hodgkin Lenfoma- KT+RT

Kemoterapi Protokolü İçinde

- Stanford V kemoterapi protokolü içinde standart olarak yeralır.

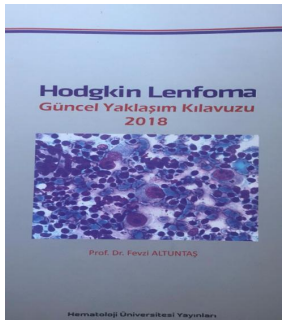
Kemoterapi Protokolü Ardından

- ABVD
- Doz arttırılmış BEACOPP gibi kemoterapi protokollerinden sonra uygulanabilir.



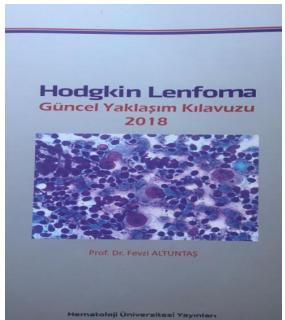
Hodgkin Lenfoma- KHN

- Hem otolog hem allojenik kök hücre nakli daha çok relaps/refrakter Hodgkin Lenfomalı hastalarda kullanılabilecek bir tedavi seçeneğidir.



Hodgkin Lenfoma- Tedavi neye göre?

- Hodgkin Lenfomada tedavi hastalığın evresi ve prognostik gruplara göre belirlenir.



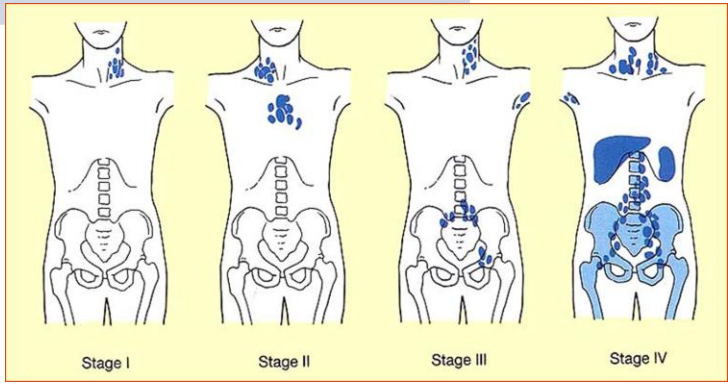
Evre?

Gözden Geçirilmiş ANN ARBOR EVRELENDİRME (Lugano sınıflaması)

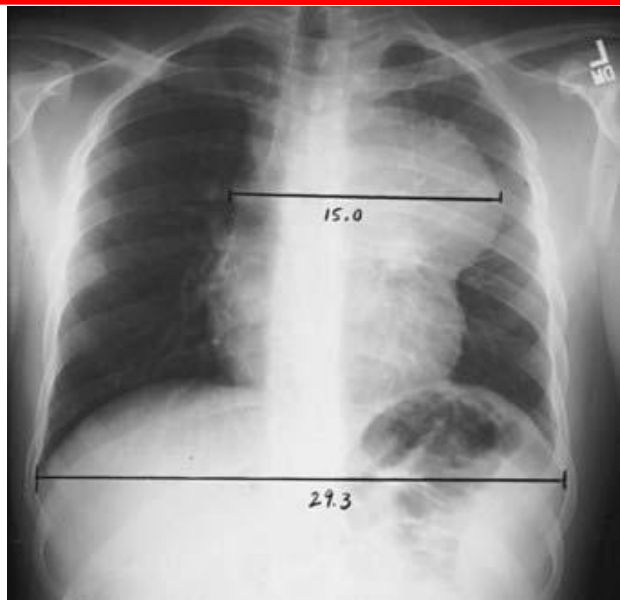
Evre	Tutulum	Extranodal (E) tutulum
Erken Evre		
I	Tek lenf bezi veya komşu lenf bezi grubu	Nodal tutulum olmadan tek ekstranodal lezyon
II	Diyaframın aynı tarafında 2 veya daha fazla tutulu lenf nodu grubu	Evre I veya II nodal yayılımlı sınırlı ekstranodal tutulum
II Kitlesel*	Yukarıdaki gibi kitlesel lezyonla evre II hastalık	Uygulanamaz
İleri Evre		
III	Diyaframın her iki tarafında nodal tutulum veya dalak tutulumu ile beraber diyafram ustu nodal tutulum	Uygulanamaz
IV	Komşu olmayan ekstra lenfatik tutulum	Uygulanamaz

*Tonsiller, Waldeyer halkası ve dalak NODAL doku olarak kabul edilir.

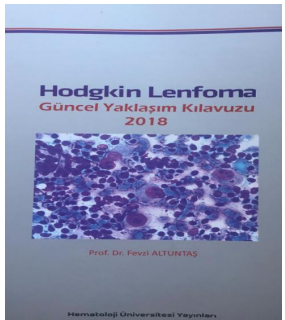
*Evre II BULKY hastalığın sınırlı veya ileri hastalık olarak muamele edilip edilmeyeceği, histoloji ve bir takım prognostik faktörler tarafından belirlenebilir.



Gözden Geçirilmiş ANN ARBOR EVRELENDİRME (Lugano sınıflaması)



- Lugano evreleme sisteminde PET-CT tercih edilen görüntüleme yöntemidir.
- Daha önce kullanılan Ann-Arbor evreleme sisteminden farklı olarak tonsiller, waldeyer halkası ve dalak nodal bölge olarak kabul edilir.
- Evre II kitlesel* hastalık sınırlı veya ileri evre hastalık olarak tedavi edilse de histoloji ve prognostik faktörlerin sayısına göre karar verilmelidir.
- Kitlesel* (bulky) hastalık:
  - Büyük çapı 10 cm'in üzerinde olan kitle
  - Ön/arka akciğer grafisinde torakal 5-6 intervertebral disk düzeyinde hesaplanan en uzun transvers transtorasik çapın 1/3'ünü aşan mediastinal kitle
- Karaciğerde ya da dalakta lezyon mevcut olması, bulky hastalık tanımlamasına dahil değildir.



Fevzi ALTUNTAŞ, Hodgkin Lenfoma Güncelleme 2018

Prognostik Gruplar?

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Unfavorable Risk Factors for Stage I-II Classic Hodgkin Lymphoma

Risk Factor	GHSG	EORTC	NCCN
Age		≥50	
Histology			
ESR and B symptoms	>50 if A; >30 if B	>50 if A; >30 if B	≥50 or any B symptoms
Mediastinal mass	MMR > .33	MTR > .35	MMR > .33
# Nodal sites	>2*	>3*	>3
E lesion	any		
Bulky			>10 cm

GHSG = German Hodgkin Study Group
EORTC = European Organization for the Research and Treatment of Cancer

MMR = Mediastinal mass ratio, maximum width of mass/maximum intrathoracic diameter
MTR = Mediastinal thoracic ratio, maximum width of mediastinal mass/intrathoracic diameter at T5-6

Definitions of Lymph Node Regions*

	Ann Arbor	EORTC	GHSG
R Cervical/SCL			
R ICL/Subpec			
R Axilla			
L Cervical/SCL			
L ICL/Subpec			
L Axilla			
Mediastinum			
R Hilum			
L Hilum			
Total	9	5	5

*Note that the EORTC includes the infraclavicular/subpectoral area with the axilla while the GHSG includes it with the cervical. Both EORTC and GHSG combine the mediastinum and bilateral hila as a single region.

International Prognostic Score (IPS) 1 point per factor (advanced disease)†

- **Albumin <4 g/dL**
- **Hemoglobin <10.5 g/dL**
- **Male**
- **Age ≥45 years**
- **Stage IV disease**
- **Leukocytosis (white blood cell count at least 15,000/mm³)**
- **Lymphocytopenia (lymphocyte count less than 8% of white blood cell count, and/or lymphocyte count less than 600/mm³)**

†From: 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;339:1506-1514. Copyright © 1998 Massachusetts Medical Society. Adapted with permission.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especiallyencouraged.

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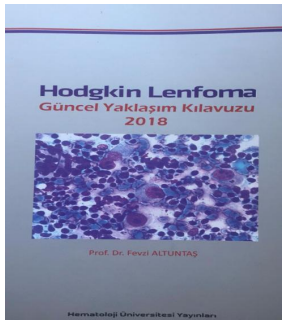
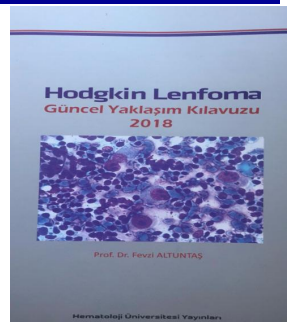


Prognostik Grupların Önemi?

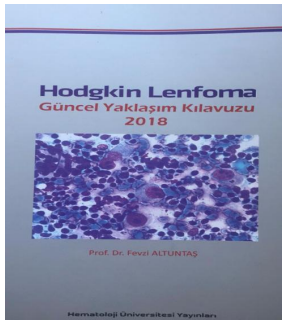
- Klasik Hodgkin lenfomalı hastalar evre ve içerdikleri risk gruplarına göre grup altında incelenebilir.
  1) Erken evre iyi prognostik grup, Evre I-II, risk faktörü yok
  2) Erken evre kötü prognostik grup , Evre I-II, risk faktörü var
     - Bulky
     - Non-Bulky
  3) İleri evre, Evre III-IV

Risk faktörleri:

*Büyük mediastinal kitle
*Ekstranodal tutulum
*Artmış Sedimentasyon (B semptomu varsa >30 mm, yoksa >50 mm)
*≥ 3 tutulmuş bölge



Tedaviye Hemen Başlayalım mı?



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NCCN Guidelines Version 3.2018
Hodgkin Lymphoma (Age ≥18 years)

NCCN Guidelines Index
Table of Contents
Discussion

DIAGNOSIS/WORKUP

- Excisional biopsy (recommended)
- Core needle biopsy may be adequate if diagnostic[a]
- Immunohisto-chemistry evaluation[b]

Essential:

- H&P including: B symptoms (unexplained fever >38°C; drenching night sweats; or weight loss >10% of body weight within 6 mo of diagnosis), alcohol intolerance, pruritus, fatigue, performance status, examination of lymphoid regions, spleen, liver
- CBC, differential, platelets
- Erythrocyte sedimentation rate (ESR)
- Comprehensive metabolic panel, lactate dehydrogenase (LDH), and liver function test (LFT)
- Pregnancy test for women of childbearing age
- Diagnostic CT[c] (contrast-enhanced)
- PET/CT scan[d] (skull base to mid-thigh)
- Counseling: Fertility, smoking cessation, psychosocial (See NCCN Guidelines for Supportive Care)

Useful in selected cases:

- Fertility preservation[e]
- Diagnostic neck CT with contrast, if neck is PET/CT+ or if neck RT contemplated
- Pulmonary function tests (PFTs incl. diffusing capacity [DLCO])[f] if ABVD or escalated BEACOPP are being used
- Pneumococcal, H-flu, meningococcal vaccines, if splenic RT contemplated
- HIV and hepatitis B/C testing (encouraged)
- Chest x-ray (encouraged, especially if large mediastinal mass)
- Adequate bone marrow biopsy if there are cytopenias and negative PET[g]
- Evaluation of ejection fraction if doxorubicin-based chemotherapy is indicated

- MRI or PET/MRI (skull base to mid-thigh) with contrast unless contraindicated

CLINICAL PRESENTATION

Classic Hodgkin lymphoma (CHL)[h] → See HODG-2

Nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL)[i] → See HODG-14

[a]Fine-needle aspiration (FNA) alone, in distinction from a core biopsy, is insufficient for diagnosis except in unusual circumstances when in combination with immunohistochemistry it is judged adequate by a hematopathologist or cytopathologist.

[b]Typical immunophenotype for CHL: CD15+, CD30+, PAX-5+ (weak); CD3-, CD20- (majority), CD45-, CD79a-. Typical immunophenotype for NLPHL: CD20+, CD45+, CD79a+, BCL6+, PAX-5+; CD3-, CD15-, CD30- (Swerdlow SH, Campo E, Harris NL, et al; WHO classification of tumours of haematopoietic and lymphoid tissues. Lyon, France: IARC; 2008). An expanded panel of markers may be required especially if equivocal diagnosis. See NCCN Guidelines for B-Cell Lymphomas.

[c]CT is considered diagnostic if it is IV contrast-enhanced. CT component of a conventional PET/CT is often not IV contrast-enhanced. Although the diagnostic CT will often be neck/chest/abdomen/pelvis, at minimum include the areas identified as abnormal on PET/CT.

[d]PET/CT should be done with patient on a flat table with arms up, if possible. In cases of PET positivity where sites of disease are inconsistent with usual presentation of Hodgkin lymphoma or if an unusual disease presentation (ie, HIV), additional clinical evaluation may be required to stage patient. See (ST-1).

[e]Fertility preservation options include: Semen cryopreservation, IVF, or ovarian tissue or oocyte cryopreservation and oophoropexy.

[f]In general a DLCO threshold of ≥60% is acceptable for use of bleomycin.

[g]In most instances, if the PET/CT displays a homogeneous pattern of marrow uptake (thought to be secondary to cytokine release) bone marrow involvement is not assumed; if there is multifocal (three or more) skeletal PET/CT lesions, marrow may be assumed to be involved. In general, bone marrow biopsies are no longer indicated.

[h]CHL includes nodular sclerosis (NSHL), mixed cellularity (MCHL), lymphocyte-depleted (LDHL), and lymphocyte-rich (LRHL) subtypes. If grey-zone, see NCCN Guidelines for B-Cell Lymphomas.

[i]NLPHL has a different natural history and response to therapy than CHL, especially stages I-II. For that reason, separate guidelines are presented for NLPHL. Patients who present with bulky disease, subdiaphragmatic disease, or splenic involvement have a high risk for initial or later transformation to large cell lymphoma.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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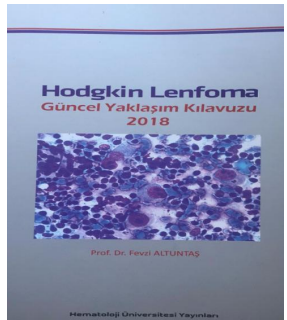


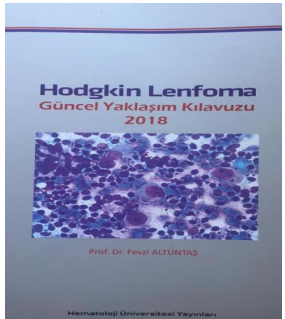
Hodgkin Lenfoma

Table 1. Diagnostic work-up in HL

Diagnosis	Lymph node biopsy (or a biopsy from another organ with suspected affection)
Staging and risk stratification	Medical history and physical examination X-ray of the chest Contrast-enhanced CT scan of the neck, chest and abdomen PET Full blood cell count and blood chemistry, ESR HBV, HCV and HIV screening
Pretreatment examinations	ECG Echocardiography Pulmonary function test Reproductive counselling (in patients of reproductive age) Serum pregnancy test (in female patients of reproductive age) Consultation of an ear, nose and throat specialist including a fibreoptic nasolaryngoscopy (if PET–CT scan is not available at initial staging)

CT, computed tomography; ECG, electrocardiography; ESR, erythrocyte sedimentation rate; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HL, Hodgkin lymphoma; PET, positron emission tomography.

Hodgkin's Lymphoma: ESMO Clinical Practice Guidelines, 2018

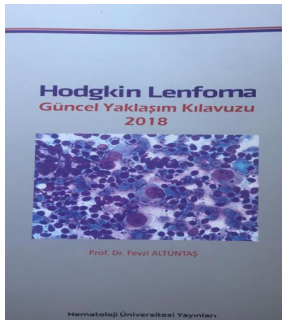


Hodgkin Lenfoma- Tedavi

- Klasik Hodgkin lenfomalı hastalar evre ve içerdikleri risk gruplarına göre 3 grup altında incelenebilir.
  1) Erken evre iyi prognostik grup: Evre I-II, risk faktörü yok
  2) Erken evre kötü prognostik grup: Evre I-II, risk faktörü var
     - Bulky
     - Non-Bulky
  3) İleri evre: Evre III-IV

Risk faktörleri:

*Büyük mediastinal kitle
*Ekstranodal tutulum
*Artmış Sedimentasyon (B semptomu varsa >30 mm, yoksa >50 mm)
*≥ 3 tutulmuş bölge



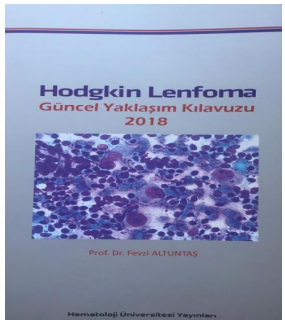
Hodgkin Lenfoma

Table 2. Definition of HL risk groups according to the EORTC/LYSA and the GHSG

	EORTC/LYSA	GHSG
Treatment group		
Limited stages	CS I–II without risk factors (supradiaphragmatic)	CS I–II without risk factors
Intermediate stages	CS I–II with ≥ 1 risk factors (supradiaphragmatic)	CS I, CS IIA with ≥ 1 risk factors CS IIB with risk factors C and/or D, but not A/B
Advanced stages	CS III–IV	CS IIB with risk factors A and/or B CS III/IV
Risk factors		
	A: Large mediastinal mass[a] B: Age ≥ 50 years C: Elevated ESR[b] D: ≥ 4 nodal areas[c]	A: Large mediastinal mass[a] B: Extranodal disease C: Elevated ESR[b] D: ≥ 3 nodal areas[c]

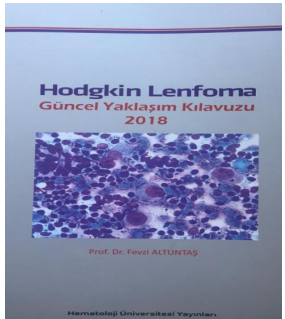
[a]Large mediastinal mass: mediastinum-to-thorax ratio ≥ 0.35 (EORTC/LYSA); mediastinal mass larger than one-third of the maximum thoracic width (GHSG).
[b]Elevated ESR: > 50 mm/h without B symptoms, > 30 mm/h with B symptoms (B symptoms: fever, night sweat, unexplained weight loss >10% over 6 months).
[c]Nodal areas: involvement of ≥ 4 out of 5 supradiaphragmatic nodal areas (EORTC/LYSA); involvement of ≥ 3 out of 11 nodal areas on both sides of the diaphragm (GHSG).
CS, clinical stage; EORTC, European Organisation for Research and Treatment of Cancer; ESR, erythrocyte sedimentation rate; GHSG, German Hodgkin Study Group; HL, Hodgkin lymphoma; LYSA, Lymphoma Study Association.

Hodgkin's Lymphoma: ESMO Clinical Practice Guidelines, 2018

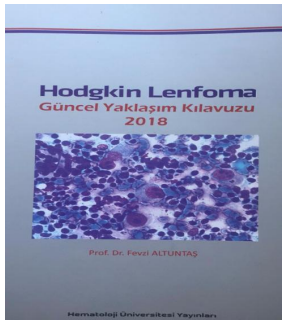


Hodgkin Lenfoma- Tedavide yeni bir rol

- 1) PET tabanlı olmayan Tedaviler
- 2) PET tabanlı tedaviler



Erken evre iyi prognostik grup-Tedavi



Hodgkin Lenfoma

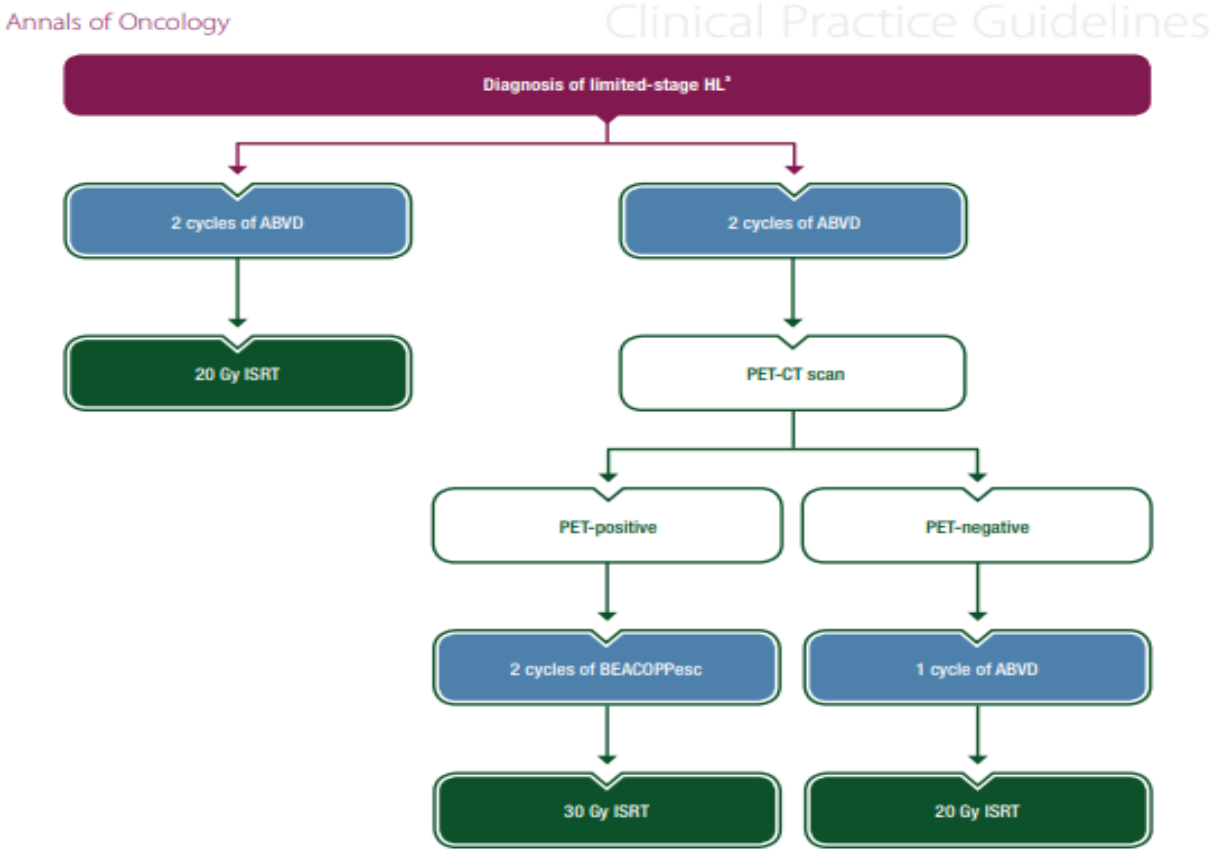
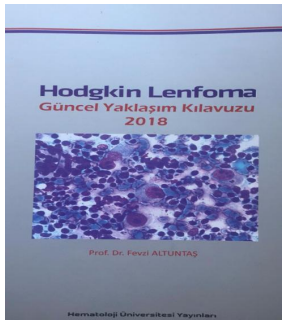


Figure 1. Therapeutic algorithm for newly diagnosed, limited-stage HL in patients ≤ 60 years.
*Except for stage IA NLPHL without risk factors (treated with ISRT alone).
The figure includes one approach not guided by interim PET based on the GHSG HD10 study (left) and one PET-guided approach based on the EORTC/LYSA/FIL H10 study (right).
ABVD, doxorubicin/bleomycin/vinblastine/dacarbazine; BEACOPPesc, bleomycin/etoposide/doxorubicin/cyclophosphamide/vincristine/procarbazine/prednisone in escalated dose; CT, computed tomography; EORTC, European Organisation for Research and Treatment of Cancer; FIL, Fondazione Italiana Linfomi; GHSG, German Hodgkin Study Group; HL, Hodgkin lymphoma; ISRT, involved-site radiotherapy; LYSA, Lymphoma Study Association; NLPHL, nodular lymphocyte-predominant Hodgkin lymphoma; PET, positron emission tomography.

Hodgkin's Lymphoma: ESMO Clinical Practice Guidelines, 2018



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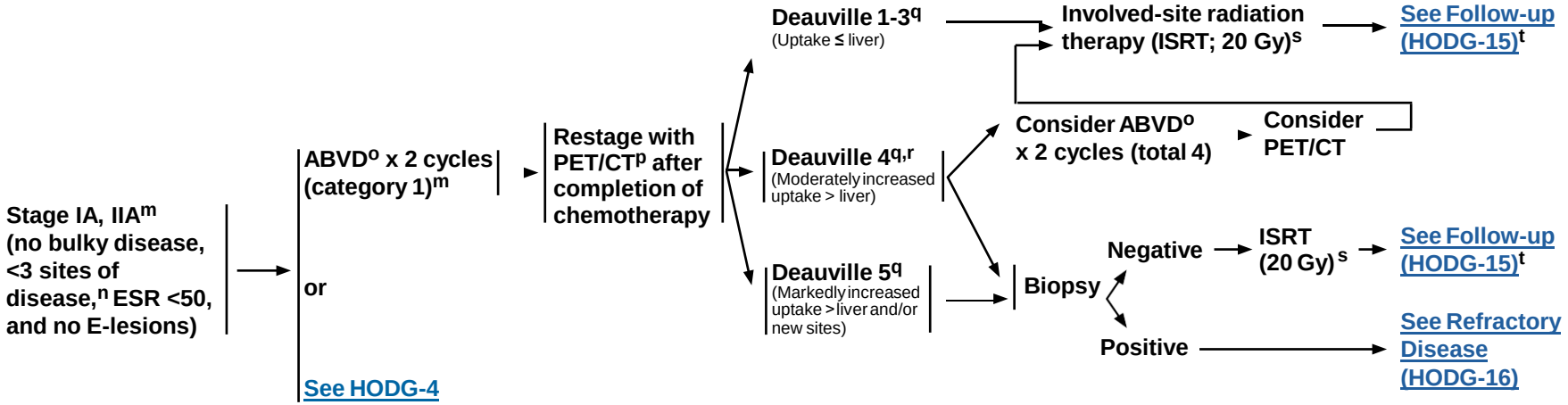
NCCN Guidelines Version 3.2018
Hodgkin Lymphoma (Age ≥18 years)

CLINICAL PRESENTATION:
Classic Hodgkin Lymphoma[h]
Stage IA, IIA Favorable

PRIMARY TREATMENT[l]
(Modified from GHSG HD10[m] Trial)



[h]CHL includes nodular sclerosis (NSHL), mixed cellularity (MCHL), lymphocyte-depleted (LDHL), and lymphocyte-rich (LRHL) subtypes. If grey-zone, see NCCN Guidelines for B-Cell Lymphomas.

[l]Individualized treatment may be necessary for older patients and patients with concomitant disease. See Management of Classic Hodgkin Lymphoma in Older Adults (HODG-F).

[m]The GHSG HD10 trial did not use PET after ABVD x 2 cycles to define eligibility for ISRT. GHSG HD10 study: Engert A, et al. N Engl J Med 2010;363:640-652.

[n]See Definitions of Lymph Node Regions (HODG-A).

[o]See Principles of Systemic Therapy (HODG-B).

[p]An integrated PET/CT or a PET with a diagnostic CT is recommended.

[q]See PET 5-Point Scale (Deauville Criteria) (HODG-D).

[r]Deauville 4 is often difficult to assess and treatment decisions will require clinical judgment (See Discussion).

[s]ISRT fields are generally smaller than IFRT fields. See Principles of Radiation Therapy (HODG-C).

[t]Complete response should be documented including reversion of PET to "negative" within 3 months following completion of therapy.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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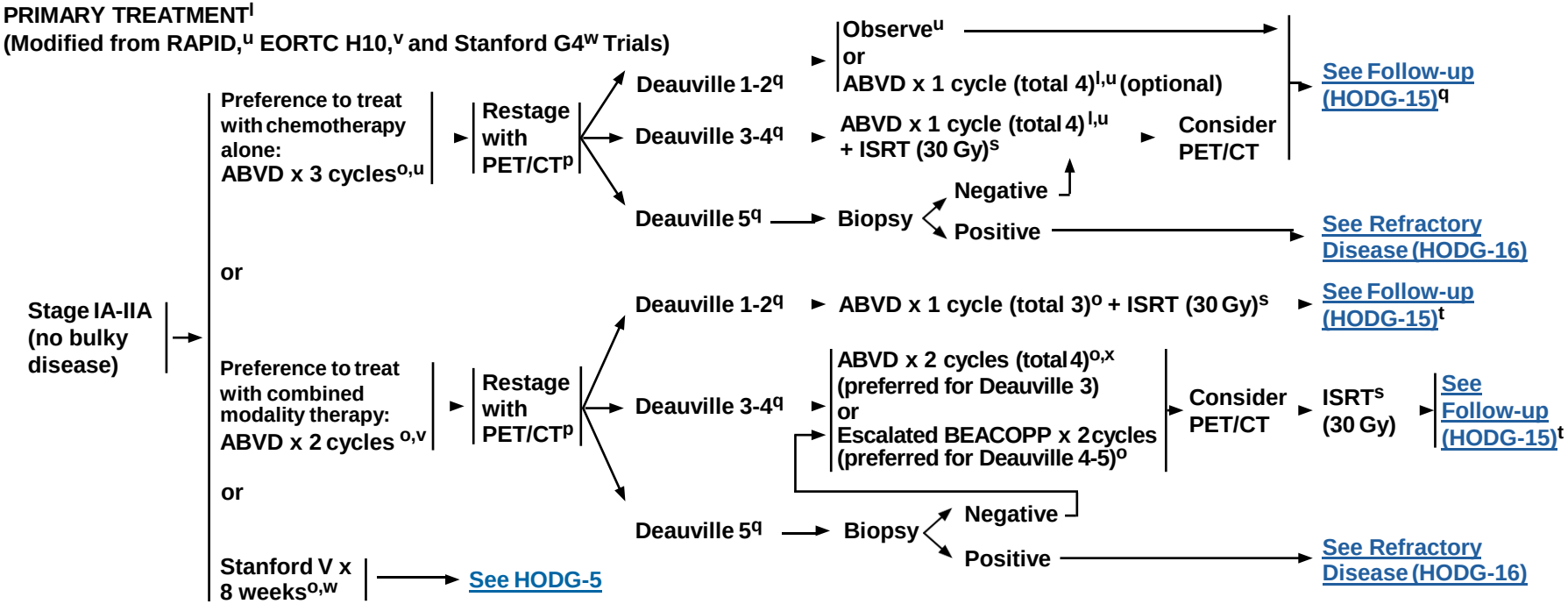
CLINICAL PRESENTATION:
Classic Hodgkin Lymphoma[h]
Stage IA, IIA Favorable
PRIMARY TREATMENT[l]
(Modified from RAPID,[u] EORTC H10,[v] and Stanford G4[w] Trials)



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[l]Individualized treatment may be necessary for older patients and patients with concomitant disease. See Management of Classic Hodgkin Lymphoma in Older Adults (HODG-F).
[o]See Principles of Systemic Therapy (HODG-B).
[p]An integrated PET/CT or a PET with a diagnostic CT is recommended.
[q]See PET 5-Point Scale (Deauville Criteria) (HODG-D).
[s]ISRT fields are generally smaller than IFRT fields. See Principles of Radiation Therapy (HODG-C).
[t]Complete response should be documented including reversion of PET to "negative" within 3 months following completion of therapy.
[u]RAPID Trial: Radford J et al. N Engl J Med 2015;372:1598-1607.
[v]EORTC/LYSA/FIL H10 Trial: Raemaekers JM, et al. J Clin Oncol 2014;32:1188-1194.
[w]Stanford G4 Trial: Advani RH, et al. Ann Oncol 2013;24:1044-1048.
[x]Consider PFTs after 4 cycles of ABVD.

Note: All recommendations are category 2A unless otherwise indicated.
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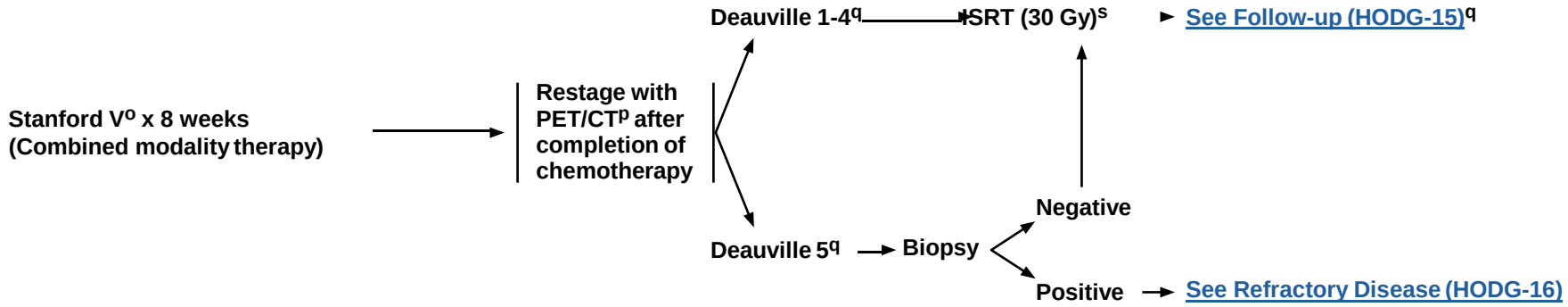
CLINICAL PRESENTATION:
Classic Hodgkin Lymphoma[h]
Stage IA, IIA Favorable
(Continued from HODG-4)

PRIMARY TREATMENT[l]
(Modified from Stanford G4 Trial[w])



[h]CHL includes nodular sclerosis (NSHL), mixed cellularity (MCHL), lymphocyte-depleted (LDHL), and lymphocyte-rich (LRHL) subtypes. If grey-zone, see NCCN Guidelines for B-Cell Lymphomas.

[l]Individualized treatment may be necessary for older patients and patients with concomitant disease. See Management of Classic Hodgkin Lymphoma in Older Adults (HODG-F).

[o]See Principles of Systemic Therapy (HODG-B).

[p]An integrated PET/CT or a PET with a diagnostic CT is recommended.

[q]See PET 5-Point Scale (Deauville Criteria) (HODG-D).

[s]ISRT fields are generally smaller than IFRT fields. See Principles of Radiation Therapy (HODG-C).

[t]Complete response should be documented including reversion of PET to "negative" within 3 months following completion of therapy.

[w]Stanford G4 Trial: Advani RH, et al. Ann Oncol 2013;24:1044-1048.

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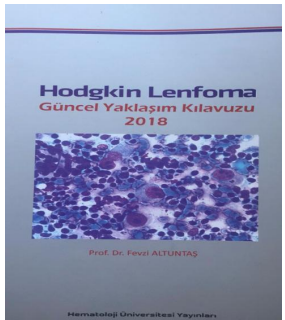
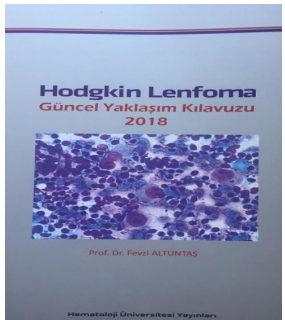


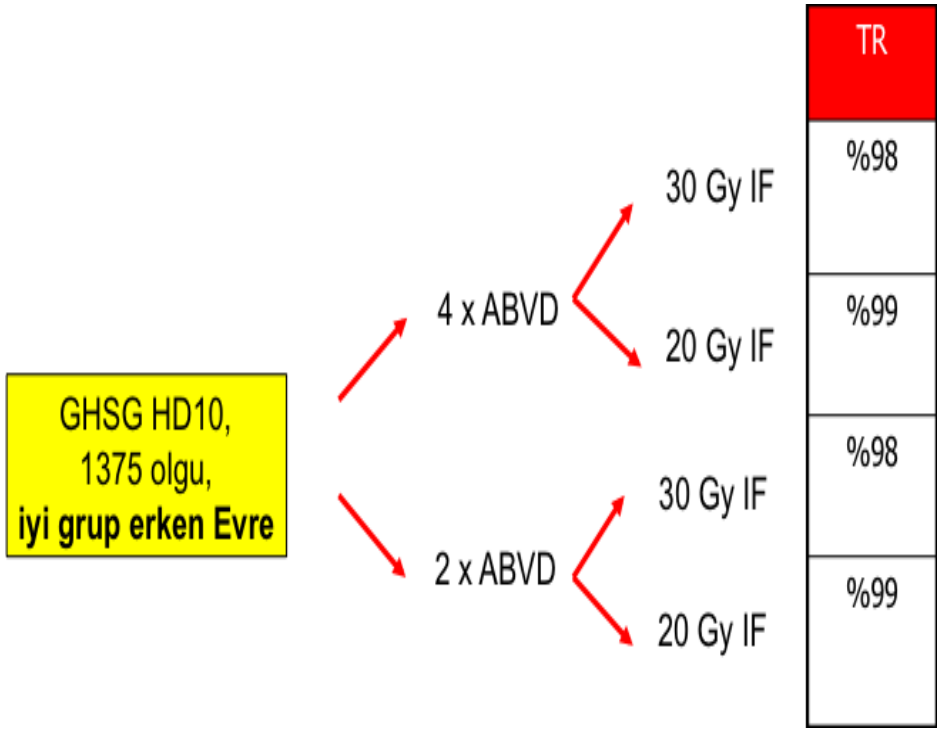
Tedavi seçenekleri arasındaki farklar?

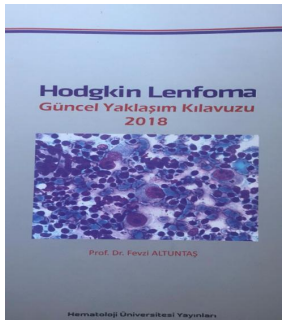
- Tedavi kür sayısı ve radyoterapi dozu arttığı süre içinde tedavi toksisitesi artmakta.
  - 2 kür ABVD+20 Gy (INRT ve TART) radyoterapi en az toksik iken,
  - 3-4 kür ABVD+ 30 Gy radyoterapi (INRT veya ISRT) relaps oranı düşük fakat toksitesi fazla
  - Radyoterapinin uzun dönem komplikasyonlarının daha sıkıntılı olabileceği (akciğer, meme ca gibi) hasta grubunda 4-6 kür ABVD en uygun tedavi seçeneği gibi durmakta.
  - Stanfort V programı 8 haftalık+ 30 Gy TART tedavi süresinin kısa olması avantajı iken radyoterapiyi standart olarak protokol içinde barındırması ve radyoterapinin uzun dönem komplikasyonları dezavantajıdır.



Erken Evre İyi Prognostik Grupta Altın Standart?

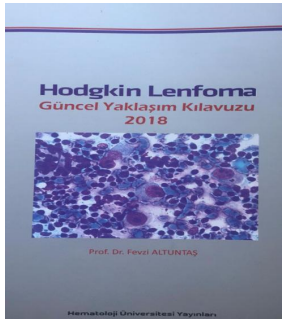
- GHSG HD10 ve EORTC/GELA H9F çalışmasında, 2 kür ABVD + tutulmuş alan RT (TART) protokolünün sonuçlarının oldukça iyi bulunması erken evre iyi prognostik grupta kısa süreli kemoterapi + TART'ın standart tedavi olmasını sağlamıştır.
- NCCN bunu ISRT (tutulu yer radyoterapisi) şeklinde önermektedir.





Radyoterapi ne zaman?

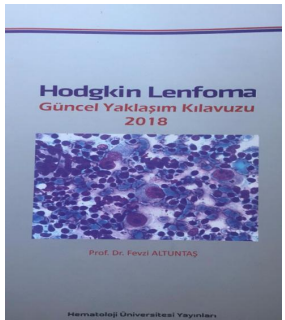
- Erken evre HL'da RT kemoterapi bitimi sonrası 3 hafta içinde başlanmalıdır.



NCCN PET önerisi

- Ara değerlendirme PET/BT;
  - Tek başına ABVD alanlarda 2 siklus sonra,
  - Kombine ABVD ve RT alanlarda 2-4 siklus sonrası,
  - Sekiz haftalık Stanford V kemoterapisi alanlarda KT tamamlandıktan sonra TART öncesi önerilmektedir.

Erken evre kötü prognostik grup-Tedavi



Hodgkin Lenfoma

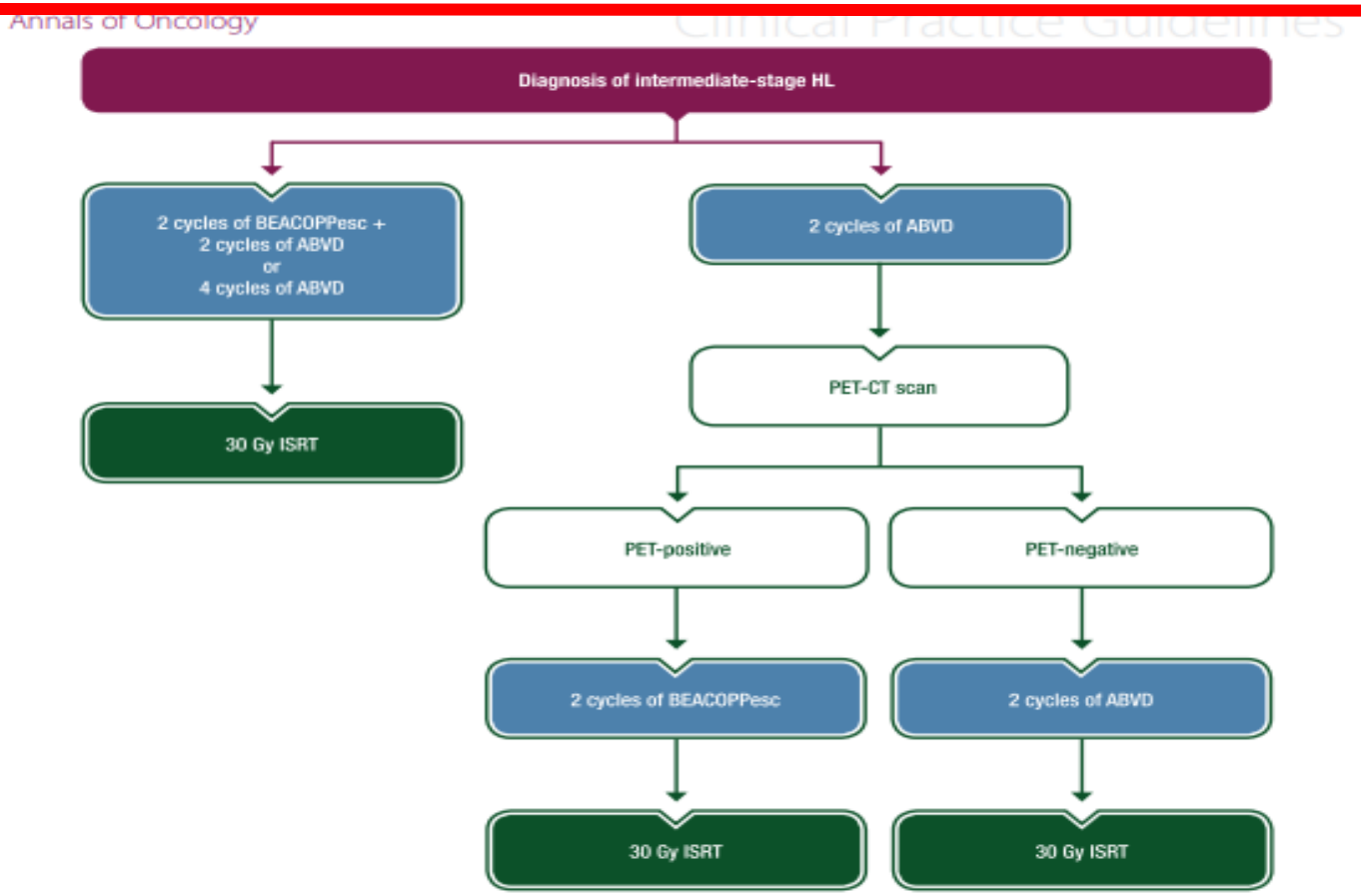
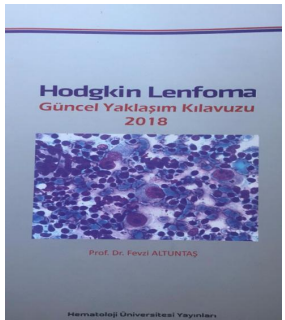


Figure 2. Therapeutic algorithm for newly diagnosed, intermediate-stage HL in patients ≤ 60 years.
The figure includes one approach not guided by interim PET, based on the GHSG HD14 study (left) and one PET-guided approach based on the EORTC/LYSA/FIL H10 study (right).
ABVD, doxorubicin/bleomycin/vinblastine/dacarbazine; BEACOPPesc, bleomycin/etoposide/doxorubicin/cyclophosphamide/vincristine/procarbazine/prednisone in escalated dose; CT, computed tomography; EORTC, European Organisation for Research and Treatment of Cancer; FIL, Fondazione Italiana Linfomi; GHSG, German Hodgkin Study Group; HL, Hodgkin lymphoma; ISRT, involved-site radiotherapy; LYSA, Lymphoma Study Association; PET, positron emission tomography.



Hodgkin's Lymphoma: ESMO Clinical Practice Guidelines, 2018

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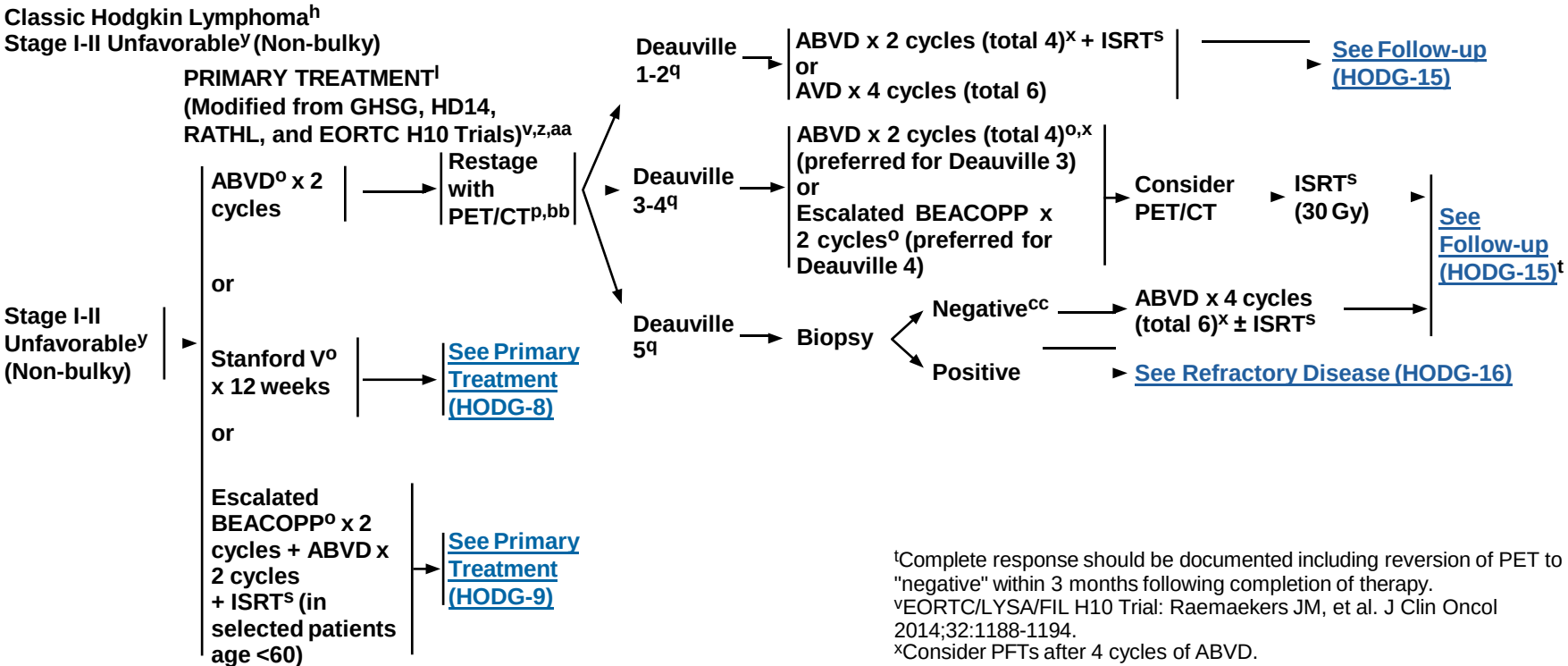
NCCN Guidelines Version 3.2018
Hodgkin Lymphoma (Age ≥18 years)



[h]CHL includes nodular sclerosis (NSHL), mixed cellularity (MCHL), lymphocyte-depleted (LDHL), and lymphocyte-rich (LRHL) subtypes. If grey-zone, see NCCN Guidelines for B-Cell Lymphomas.

[l]Individualized treatment may be necessary for older patients and patients with concomitant disease. See Management of Classic Hodgkin Lymphoma in Older Adults (HODG-F).

[o]See Principles of Systemic Therapy (HODG-B).

[p]An integrated PET/CT or a PET with a diagnostic CT is recommended.

[q]See PET 5-Point Scale (Deauville Criteria) (HODG-D).

[s]ISRT fields are generally smaller than IFRT fields. See Principles of Radiation Therapy (HODG-C).

[t]Complete response should be documented including reversion of PET to "negative" within 3 months following completion of therapy.

[v]EORTC/LYSA/FIL H10 Trial: Raemaekers JM, et al. J Clin Oncol 2014;32:1188-1194.

[x]Consider PFTs after 4 cycles of ABVD.

[y]For this algorithm, NCCN unfavorable factors include B symptoms, ESR ≥50, and >3 sites of disease.

[z]GHSG trial HD14: von Tresckow B, et al. J Clin Oncol 2012;30:907-913.

[aa]RATHL study: Johnson PW, et al. N Engl J Med 2016;374:2419-2429.

[bb]The value of interim PET imaging is unclear for many clinical scenarios. All measures of response should be considered in the context of management decisions.

[cc]Use clinical judgment to determine if tissue specimen is adequate for accurate biopsy results. Confirm clinically that patient is not progressing symptomatically.

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Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especiallyencouraged.

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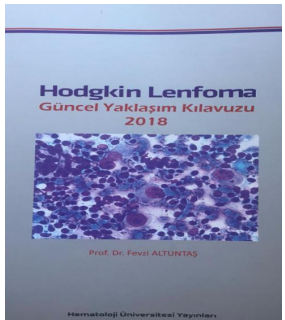

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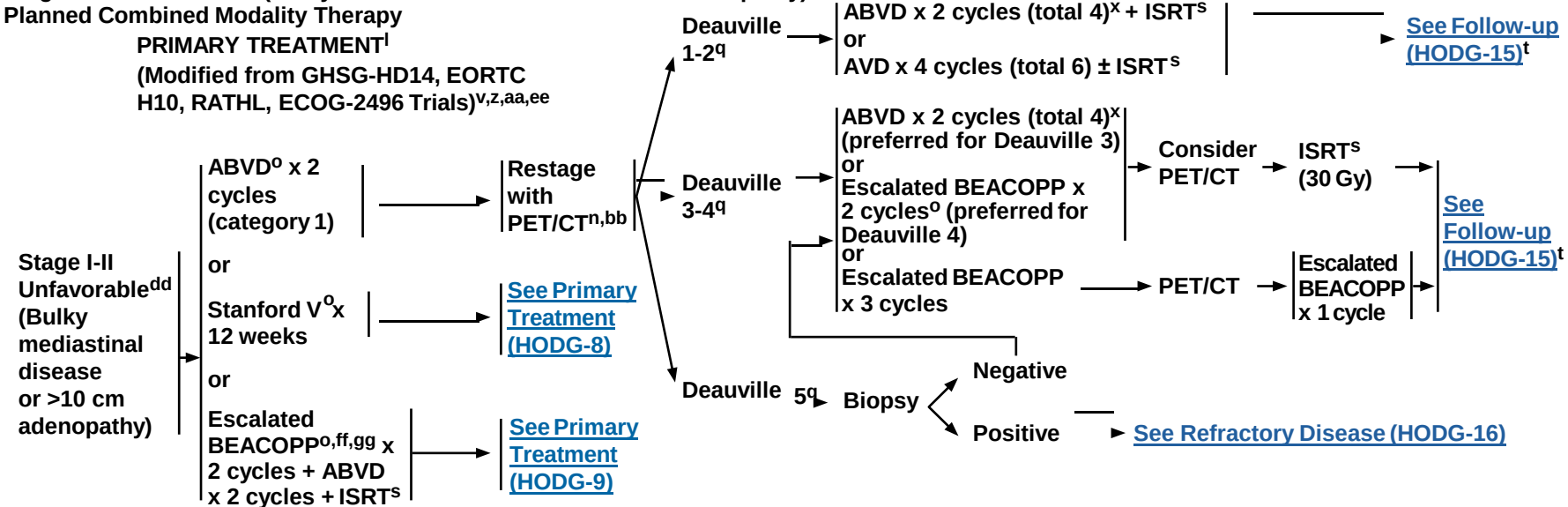
NCCN Guidelines Version 3.2018
Hodgkin Lymphoma (Age ≥18 years)

CLINICAL PRESENTATION:
Classic Hodgkin Lymphoma[h]
Stage I-II Unfavorable[dd] (Bulky mediastinal disease or >10 cm adenopathy)
Planned Combined Modality Therapy

PRIMARY TREATMENT[l]
(Modified from GHSG-HD14, EORTC H10, RATHL, ECOG-2496 Trials)[v,z,aa,ee]



[h]CHL includes nodular sclerosis (NSHL), mixed cellularity (MCHL), lymphocyte-depleted (LDHL), and lymphocyte-rich (LRHL) subtypes. If grey-zone, see NCCN Guidelines for B-Cell Lymphomas.
[l]Individualized treatment may be necessary for older patients and patients with concomitant disease. See Management of Classic Hodgkin Lymphoma in Older Adults (HODG-F).
[o]See Principles of Systemic Therapy (HODG-B).
[p]An integrated PET/CT or a PET with a diagnostic CT is recommended.
[q]See PET 5-Point Scale (Deauville Criteria) (HODG-D).
[s]ISRT fields are generally smaller than IFRT fields. See Principles of Radiation Therapy (HODG-C).
[t]Complete response should be documented including reversion of PET to "negative" within 3 months following completion of therapy.
[v]EORTC/LYSA/FIL H10 Trial: Raemaekers JM, et al. J Clin Oncol 2014;32:1188-1194.
[x]Consider PFTs after 4 cycles of ABVD.
[z]GHSG trial HD14: von Tresckow B, et al. J Clin Oncol 2012;30:907-913.
[aa]RATHL study: Johnson PW, et al. N Engl J Med 2016;374:2419-2429.
[bb]The value of interim PET imaging is unclear for many clinical scenarios. All measures of response should be considered in the context of management decisions.
[dd]NCCN Unfavorable Factors include bulky mediastinal or >10 cm disease, B symptoms, ESR ≥50, and >3 sites of disease (see HODG-A).
[ee]ECOG-2496: Gordon LI, et al. J Clin Oncol 2013;31:684-691.
[ff]Used with caution in patients >60 years old.
[gg]In the GHSG HD14 trial (von Tresckow B, et al. J Clin Oncol 2012;30:907-913) patients with B symptoms in combination with bulky or extranodal disease were excluded and treated according to the algorithm for stage III-IV disease (HODG-12).

Note: All recommendations are category 2A unless otherwise indicated.
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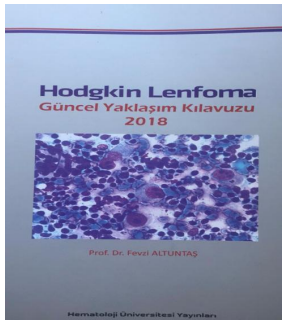

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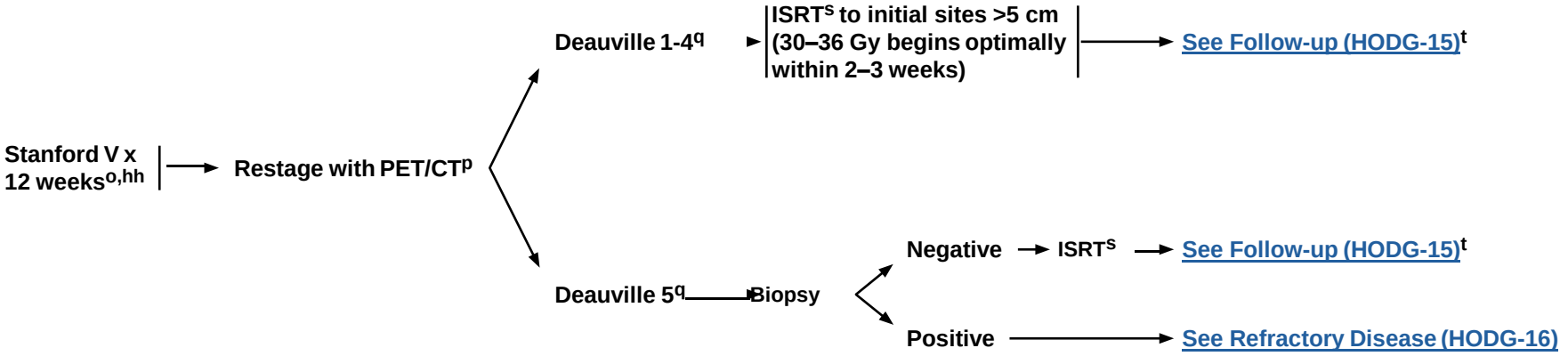
CLINICAL PRESENTATION:
Classic Hodgkin Lymphoma[h]
Stage I-II Unfavorable[dd] (Bulky or non-bulky)

PRIMARY TREATMENT[l] (continued from HODG-7)
(Modified from ECOG-2496 Trial)[ee]



[h]CHL includes nodular sclerosis (NSHL), mixed cellularity (MCHL), lymphocyte-depleted (LDHL), and lymphocyte-rich (LRHL) subtypes. If grey-zone, see NCCN Guidelines for B-Cell Lymphomas.
[l]Individualized treatment may be necessary for older patients and patients with concomitant disease. See Management of Classic Hodgkin Lymphoma in Older Adults (HODG-F).
[o]See Principles of Systemic Therapy (HODG-B).
[p]An integrated PET/CT or a PET with a diagnostic CT is recommended.
[q]See PET 5-Point Scale (Deauville Criteria) (HODG-D).
[s]ISRT fields are generally smaller than IFRT fields. See Principles of Radiation Therapy (HODG-C).
[t]Complete response should be documented including reversion of PET to "negative" within 3 months following completion of therapy.
[dd]NCCN Unfavorable Factors include bulky mediastinal or >10 cm disease, B symptoms, ESR ≥50, and >3 sites of disease (see HODG-A).
[ee]ECOG-2496: Gordon LI, et al. J Clin Oncol 2013;31:684-691.
[hh]The Stanford V regimen is used in this fashion for patients with bulky mediastinal disease or >10 cm disease and/or B symptoms. Patients with elevated ESR, and/or >3 sites in absence of bulky disease are treated according to the Stanford V algorithm on HODG-5.

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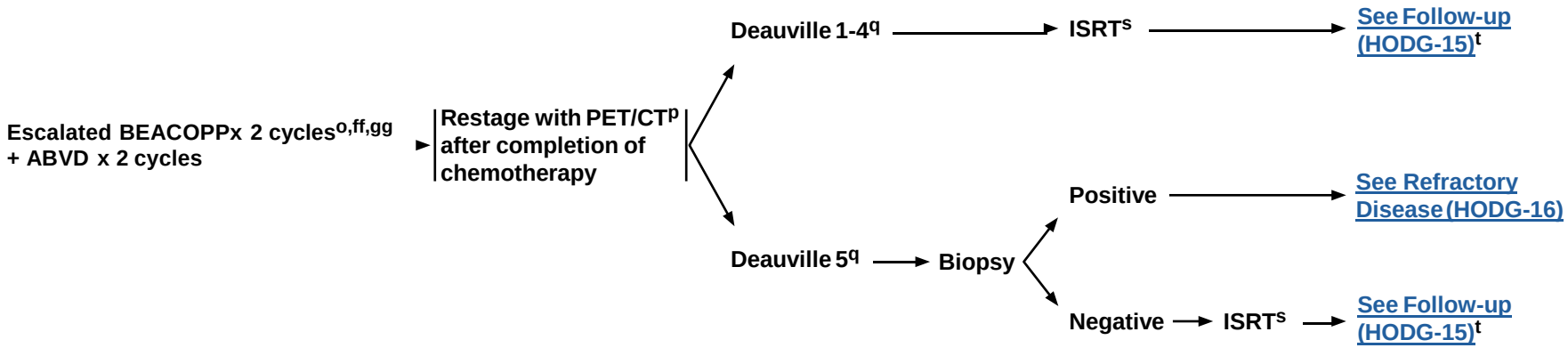
CLINICAL PRESENTATION:
Classic Hodgkin Lymphoma[h]
Stage I-II Unfavorable[dd] (Bulky or Non-bulky)
PRIMARY TREATMENT[l]
(continued from HODG-7)
(Modified from GHSG HD14 Trial)[gg]



[h]CHL includes nodular sclerosis (NSHL), mixed cellularity (MCHL), lymphocyte-depleted (LDHL), and lymphocyte-rich (LRHL) subtypes. If grey-zone, see NCCN Guidelines for B-Cell Lymphomas.
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[o]See Principles of Systemic Therapy (HODG-B).
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[q]See PET 5-Point Scale (Deauville Criteria) (HODG-D).
[s]ISRT fields are generally smaller than IFRT fields. See Principles of Radiation Therapy (HODG-C).
[t]Complete response should be documented including reversion of PET to "negative" within 3 months following completion of therapy.
[dd]NCCN Unfavorable Factors include bulky mediastinal or >10 cm disease, B symptoms, ESR ≥50, and >3 sites of disease (see HODG-A).
[ff]Used with caution in patients >60 years old.
[gg]In the GHSG HD14 trial (von Tresckow B, et al. J Clin Oncol 2012;30:907-913), patients with bulky disease in combination with B symptoms or extranodal disease were excluded and treated according to the algorithm for stage III-IV disease (HODG-12). PET/CT was not utilized in the GHSG HD14.

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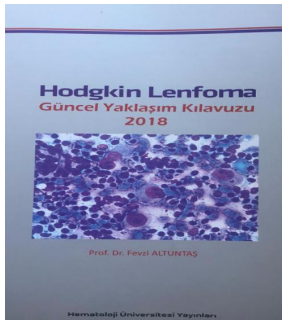
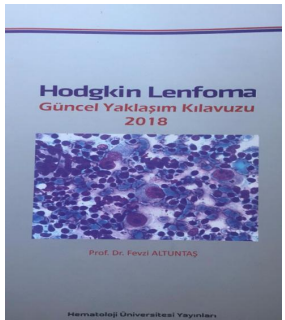


Erken Evre Kötü Prognostik Grupta Altın Standart?

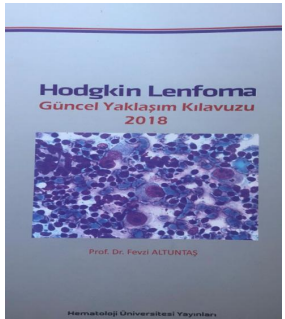
- Özellikle 60 yaş altı hastalarda 4 siklus ABVD + TART tedavisinin erken evre kötü prognostik grup için standart tedavi olmasına rağmen
- NCCN'de olduğu gibi 2 kür ABVD sonrası PET ile ara değerlendirme yapılması (ABVD'den 12-13 gün sonra veya bir sonraki KT'den hemen önce) ve
- Deauville skoru 1-3 olan hastalarda tedaviye aynen devam edilmesi,
- Deauville skoru 4-5 olanlarda yüksek doz BEACOPP'a geçilmesi giderek uygulama alanı bulmaktadır.
- Fakat PET bazlı tedavinin takip süresinin henüz kısa olduğu da unutulmamalıdır.



Fevzi ALTUNTAŞ, Hodgkin Lenfoma Güncelleme 2018

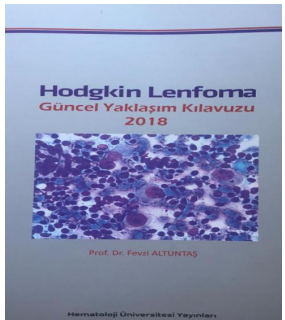
Erken Evre Kötü Prognostik Grupta Diğer seçenekler

- Genel sağkalım avantajı göstermemesine karşın, 2 kür doz arttırılmış BEACOPP+2 kür ABVD takiben 30 Gy RT alternatif bir tedavidir.
- Özellikle Alman grupları **arasında yaygın kullanım alanı bulmasına rağmen ağır yan etki profili, ikincil malignite ve azospermi riski** nedeniyle diğer gruplar arasında fazla destek görmemiştir.



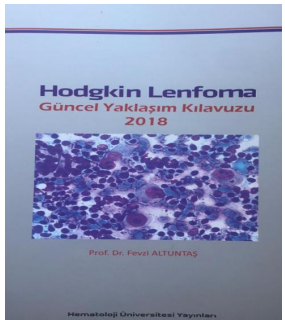
Erken Evre Kötü Prognostik Grupta
Diğer seçenekler

- Meme, tiroid gibi sekonder malignite riski yüksek olan RT uygulanacak hastalara 6 kür ABVD bir diğer alternatif olabilir.

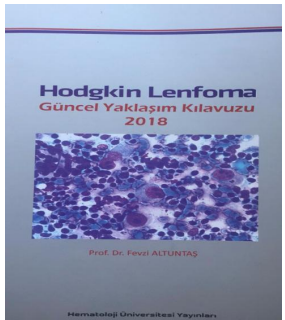


İleri Evre Hastalıkta Tedavi
İleri Hastalık?

- Evre III-IV ve bazı otörler evre II+bulky hastalığı bu grupta değerlendirmektedir.

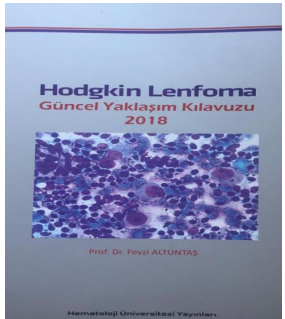


İleri Evre Hastalıkta Tedavi



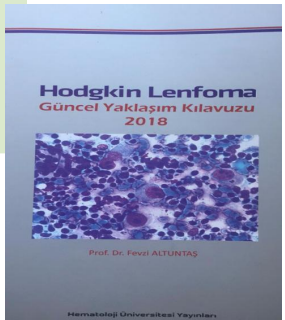
İleri Evre Hastalıkta Tedavi

- ABVD, Stanford V ve arttırılmış doz BEACOPP evre III-IV hastalığın tedavisinde önerilen primer tedavilerdir.



İleri Hastalıkta Tedavi Seçenekleri?

ABVD	Escalated BEACOPP	Stanford V
-Standart rejim	• ABVD ile karşılaştırıldığında • OS farksız, • PFS üstün (Özellikle IPS'si yüksek olanlarda). • Sepsis, ikincil malignite, sterilite oranları yüksek. • Yaşlılarda uygunsuz. • Otolog KHN öncesinde kurtarma tedavisi olarak kullanılabilir.	• ABVD'ye karşı bir avantajı yok. • Hatta daha toksik • Diğerlerine göre daha kısa uygulanabilirlik süresi (12 vs 24 to 32) ve pulmoner toksite daha az. • Standart olarak RT'nin içinde olması dezavantajı



Hodgkin Lenfoma

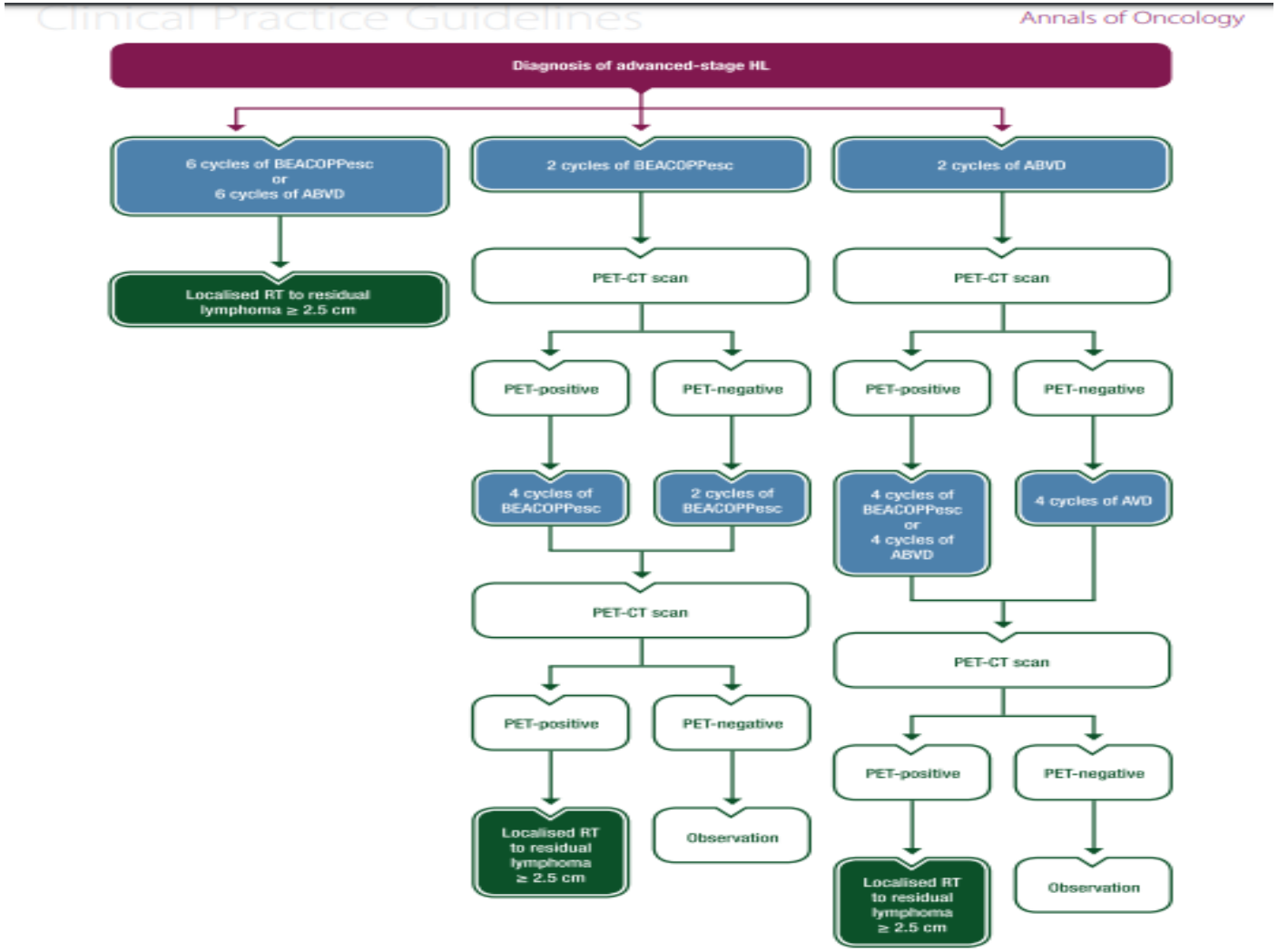
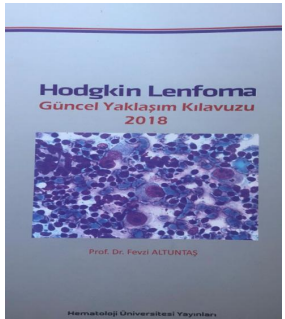


Figure 3. Therapeutic algorithm for newly diagnosed, advanced-stage HL in patients ≤ 60 years.
The figure includes one approach not guided by interim PET (left) and two PET-guided approaches based on the GHSG HD18 study (middle) and the RATHL study (right).
[illegible] vinblastine/dacarbazine; BEACOPPesc, bleomycin/etoposide/doxo- [illegible] dose; CT, computed tomography; GHSG, German Hodgkin Study Group; HL, Hodgkin lymphoma; PET, positron emission tomography; RT, radiotherapy.

Hodgkin's Lymphoma: ESMO Clinical Practice Guidelines, 2018



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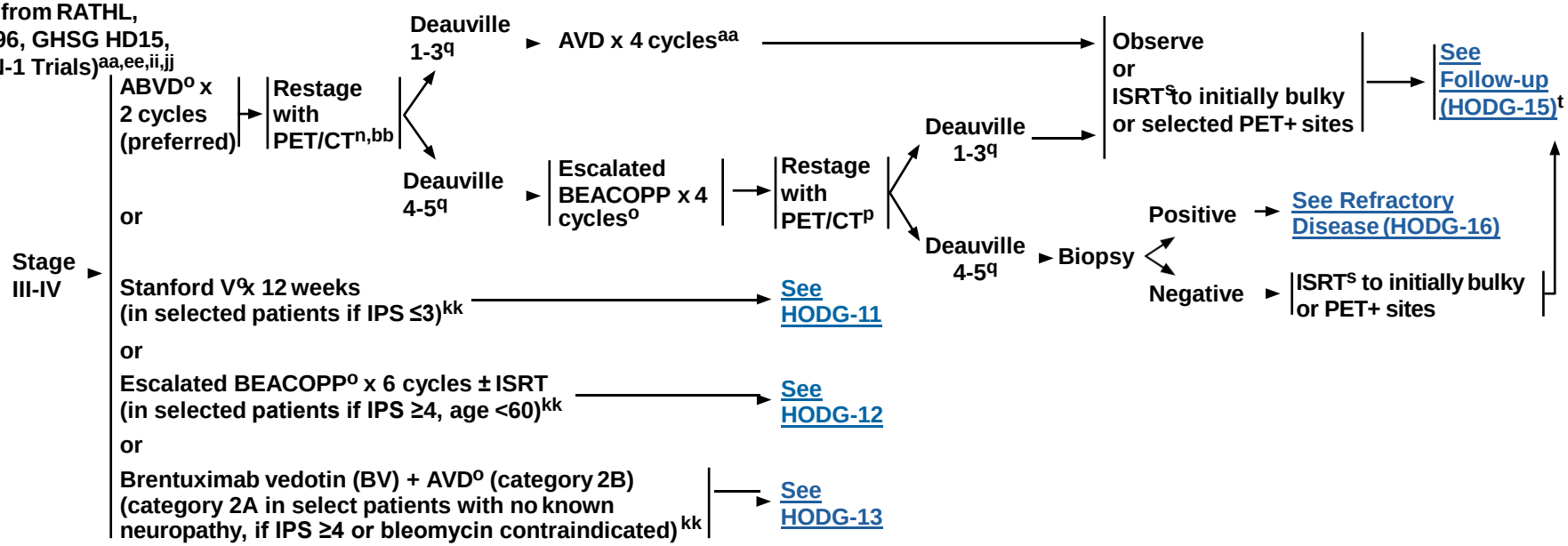
CLINICAL PRESENTATION:
Classic Hodgkin Lymphoma[h]
Stage III-IV

PRIMARY TREATMENT[l]
(Modified from RATHL, ECOG-2496, GHSG HD15, ECHELON-1 Trials)[aa,ee,ii,jj]



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[q]See PET 5-Point Scale (Deauville Criteria) (HODG-D).
[s]ISRT fields are generally smaller than IFRT fields. See Principles of Radiation Therapy (HODG-C).
[t]Complete response should be documented including reversion of PET to "negative" within 3 months following completion of therapy.

[aa]RATHL study: Johnson PW, et al. N Engl J Med 2016;374:2419-2429.
[bb]The value of interim PET imaging is unclear for many clinical scenarios. All measures of response should be considered in the context of management decisions.
[ee]ECOG-2496: Gordon LI, et al. J Clin Oncol 2013;31:684-691.
[ii]HD15 trial: Engert A, et al. Lancet 2012; 379(9828):1791-1799.
[jj]ECHELON-1: Connors JM, et al. NEJM 2018; 374(4):331-344.
[kk]See International Prognostic Score (IPS) (HODG-A).

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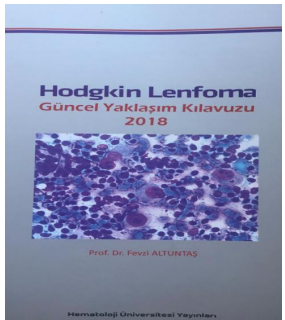

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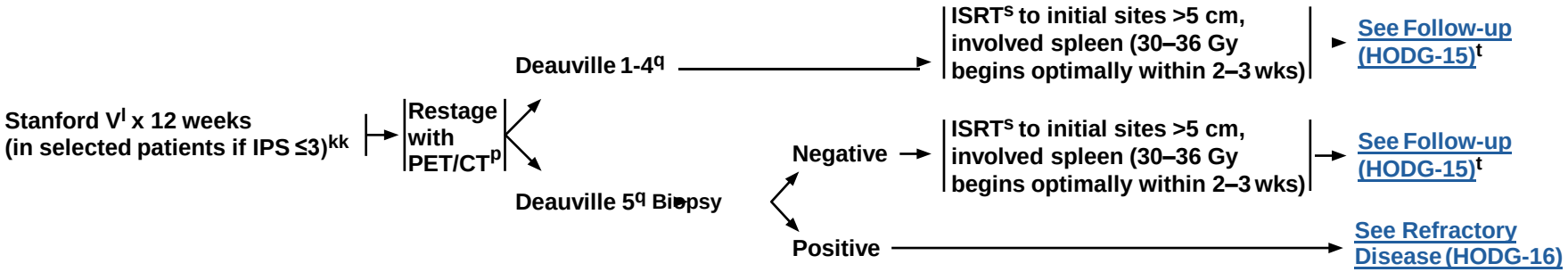
CLINICAL PRESENTATION:
Classic Hodgkin Lymphoma[h]
Stage III-IV

PRIMARY TREATMENT[l] (continued from HODG-10)
(Modified from ECOG-2496 Trial)[ee]



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[o]See Principles of Systemic Therapy (HODG-B).

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[q]See PET 5-Point Scale (Deauville Criteria) (HODG-D).

[s]ISRT fields are generally smaller than IFRT fields. See Principles of Radiation Therapy (HODG-C).

[t]Complete response should be documented including reversion of PET to "negative" within 3 months following completion of therapy.

[ee]ECOG-2496: Gordon LI, et al. J Clin Oncol 2013;31:684-691.

[kk]See International Prognostic Score (IPS) (HODG-A).

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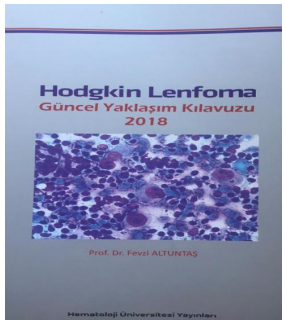

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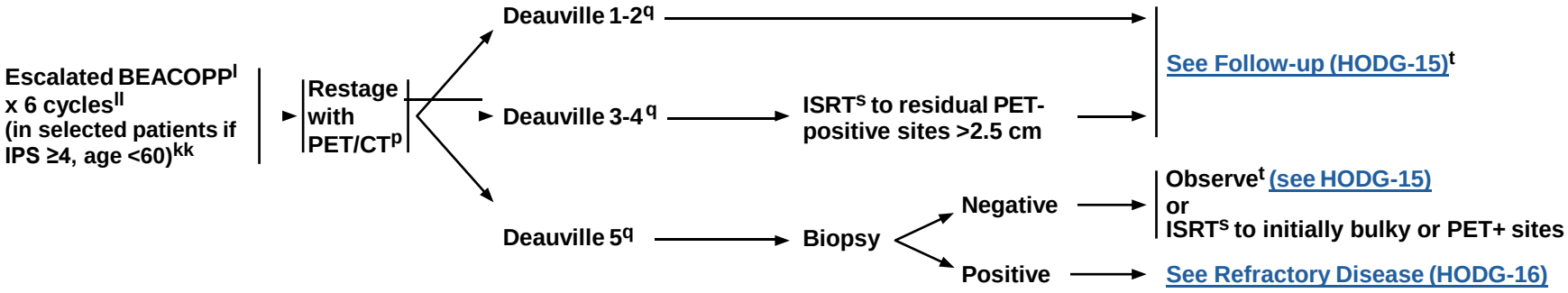
CLINICAL PRESENTATION:
Classic Hodgkin Lymphoma[h]
Stage III-IV

PRIMARY TREATMENT[l] (continued from HODG-10)
(Modified from HD15 Trial)[ii]



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[q]See PET 5-Point Scale (Deauville Criteria) (HODG-D).
[s]ISRT fields are generally smaller than IFRT fields. See Principles of Radiation Therapy (HODG-C).
[t]Complete response should be documented including reversion of PET to "negative" within 3 months following completion of therapy.
[hh]HD15 trial: Engert A, et al. Lancet 2012; 379(9828):1791-1799.
[ii]See International Prognostic Score (IPS) (HODG-A).
[ll]Interim restaging with PET/CT may be considered after 2 cycles of escalated BEACOPP with a possible de-escalation of therapy (4 cycles of ABVD) in patients with a negative interim PET/CT. (Avigdor A, et al. Ann Oncol 2010;21:126-132.)

Note: All recommendations are category 2A unless otherwise indicated.
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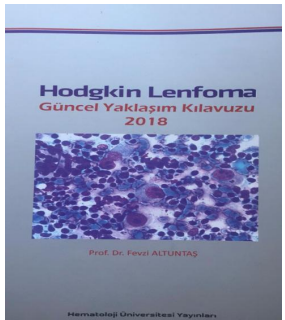

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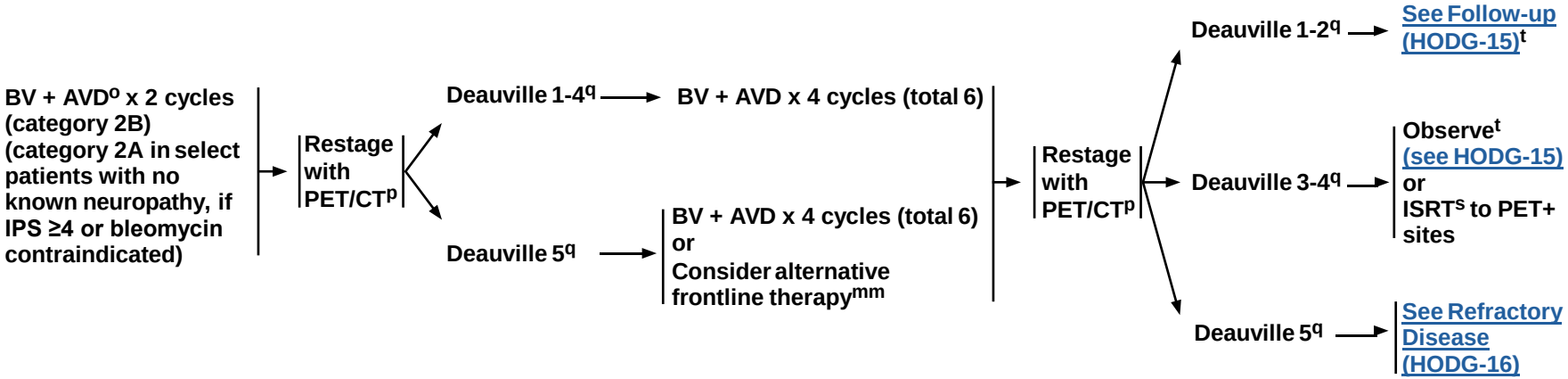
CLINICAL PRESENTATION:
Classic Hodgkin Lymphoma[h]
Stage III-IV

PRIMARY TREATMENT[l] (continued from HODG-10)
(Modified from ECHELON-1 Trial)[jj]



[h]CHL includes nodular sclerosis (NSHL), mixed cellularity (MCHL), lymphocyte-depleted (LDHL), and lymphocyte-rich (LRHL) subtypes. If grey-zone, see NCCN Guidelines for B-Cell Lymphomas.
[l]Individualized treatment may be necessary for older patients and patients with concomitant disease. See Management of Classic Hodgkin Lymphoma for Older Adults (HODG-F).

[o]See Principles of Systemic Therapy (HODG-B).
[p]An integrated PET/CT or a PET with a diagnostic CT is recommended.
[q]See PET 5-Point Scale (Deauville Criteria) (HODG-D).
[t]Complete response should be documented including reversion of PET to "negative" within 3 months following completion of therapy.
[jj]ECHELON-1: Connors JM, et al. NEJM 2018; 374(4):331-344.
[kk]See International Prognostic Score (IPS) (HODG-A).
[mm]Options may include escalated BEACOPP (category 2B) or therapy for refractory disease (see HODG-16).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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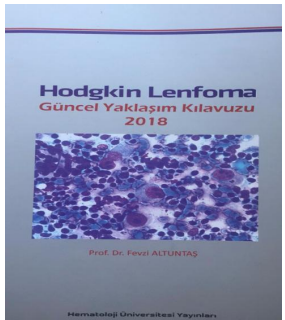
İleri Evre Hastalıkta Altın Standart Tedavi?

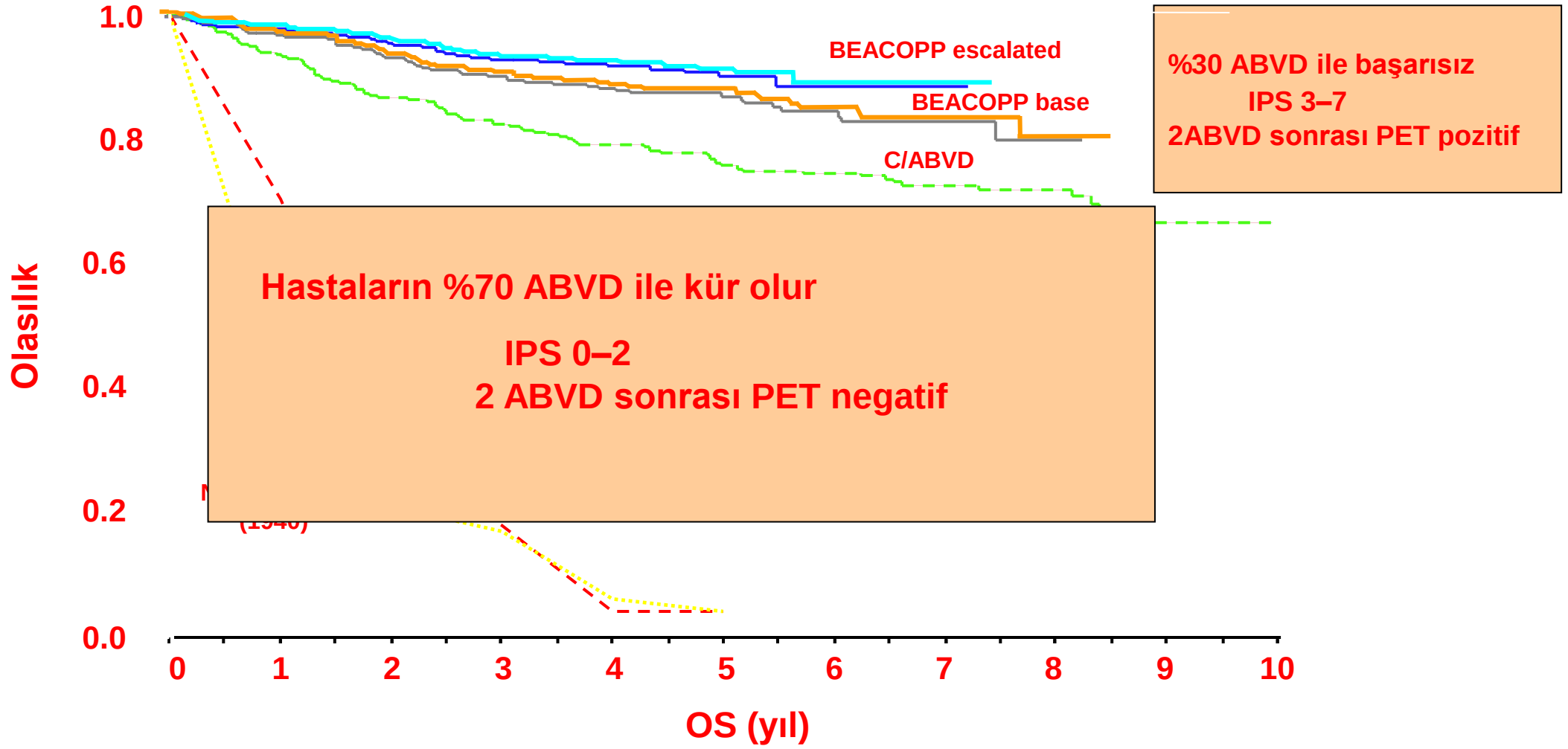
- İleri Evre HL'da altın standart tedavi yoktur.
- ABVD Altın standart mı?
  - Hayır! Değil!
  - En azından tüm risk grupları için DEĞİL!
- IPS < 4 hastalarda ABVD ile başlamak,
- 60 yaş altında ve IPS>3 üstünde olanlarda ise doz arttırılmış BEACOPP başlamak daha genel anlayış gibi gözükmektedir.

Rejimler	RT %	Yanıt %	EFS/FFP/FFTF			OS	
			%	yıl		%	yıl
ABVD	0	82	61	5	FFP	73	5
MOPP/ABVD	0	83	65	5	FFP	75	5
MOPP/ABV	67	95	82	5	EFS	84	5
ChlVPP/EVA	58	65	82	5	FFP	95	5
COPP/ABVD	64	85	69	5	FFTF	83	5
BEACOPP baseline	71	88	76	5	FFTF	88	5
Stanford V	86	99	89	5	FFP	93	5
BEACOPP escalated	71	96	87	5	FFTF	91	5
BEACOPP-14	60	94	90	3	FFTF	97	3
4 ABVD + BEAM	ns	90	75	4	FFP	88	4
MEC	44	92	87	3	FFS	96	3



Fevzi ALTUNTAŞ, Hodgkin Lenfoma Güncelleme 2018

İleri Evre HL:
İyi ve Kötü risk grupları nasıl tespit ederiz?

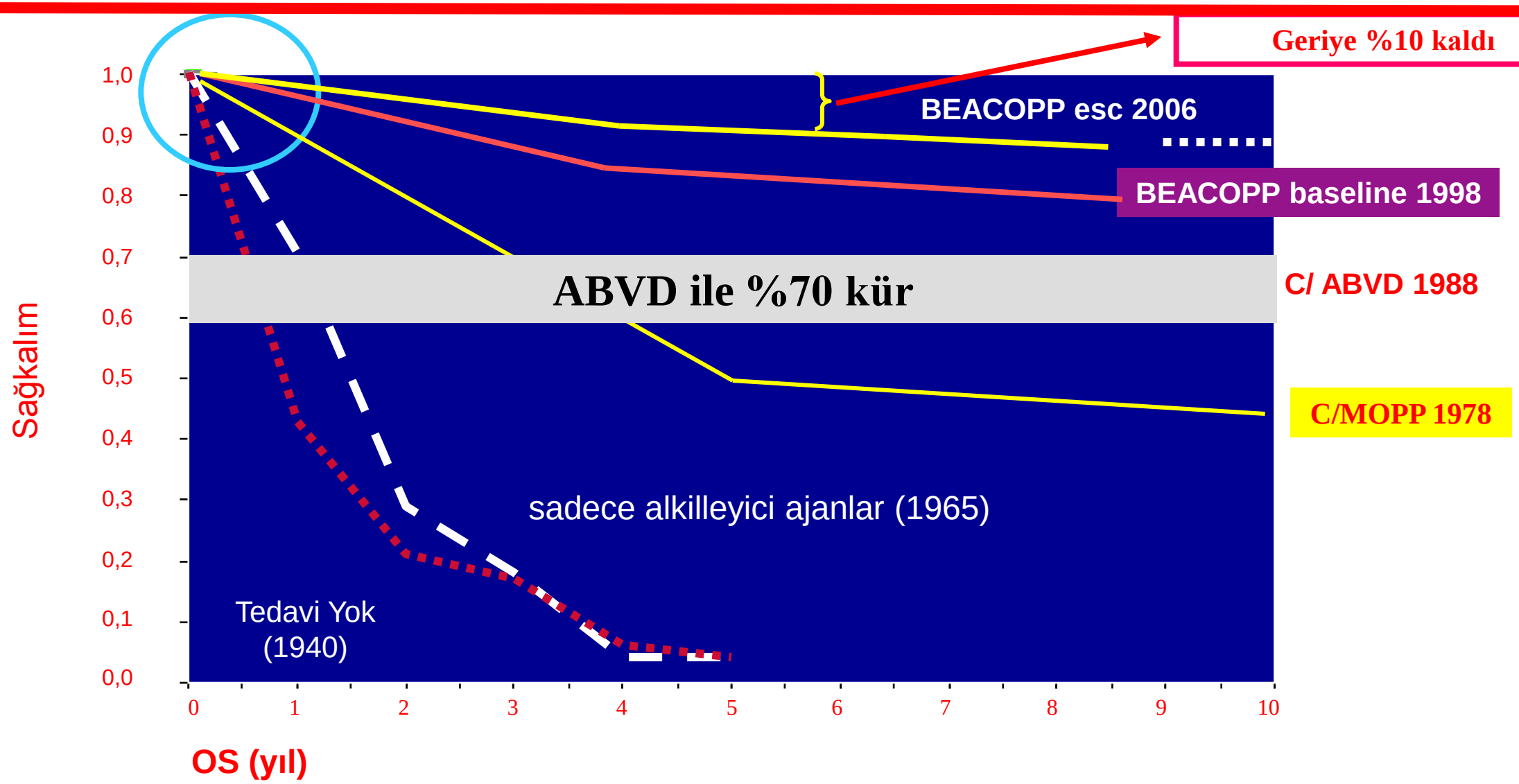


%30 ABVD ile başarısız
IPS 3–7
2ABVD sonrası PET pozitif

Hastaların %70 ABVD ile kür olur

IPS 0–2
2 ABVD sonrası PET negatif

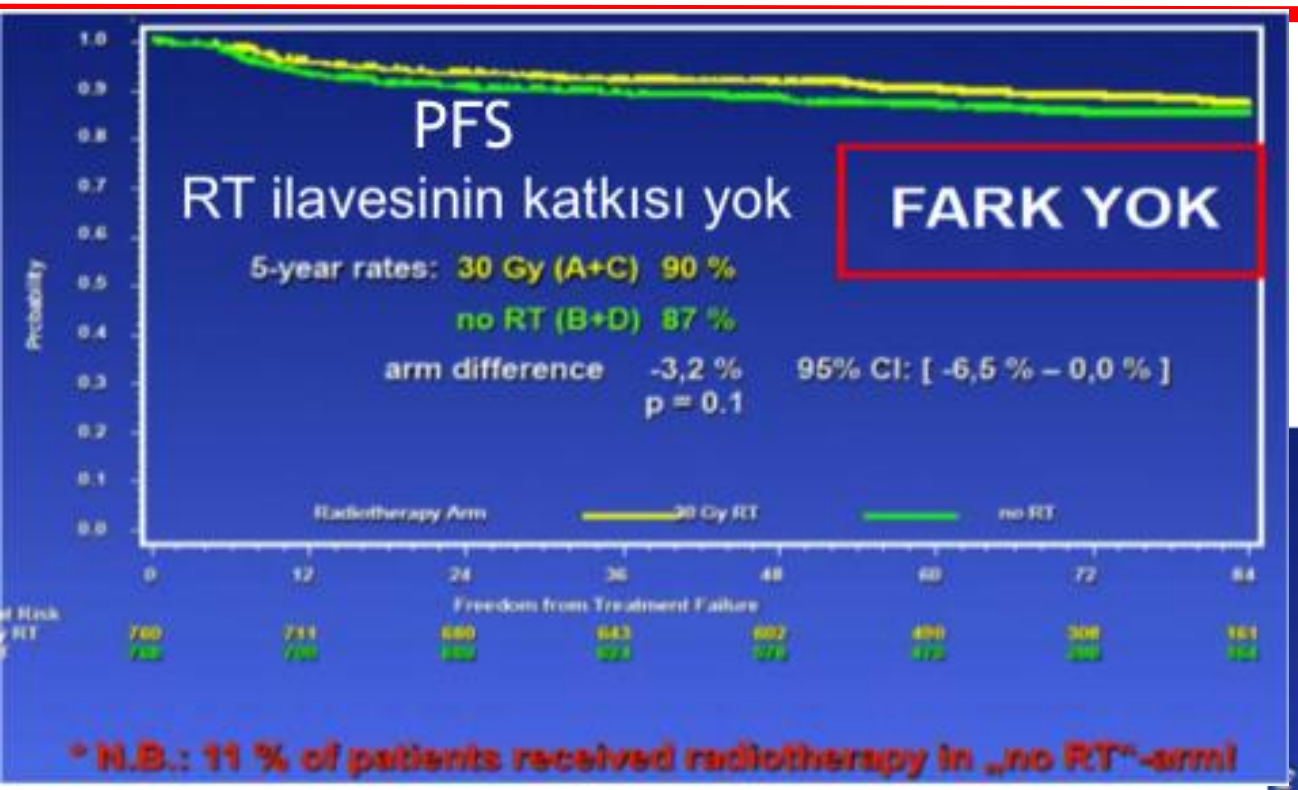
İleri Evre Hodgkin Lenfoma:
Tedavi- GELİŞMELER- GHSG

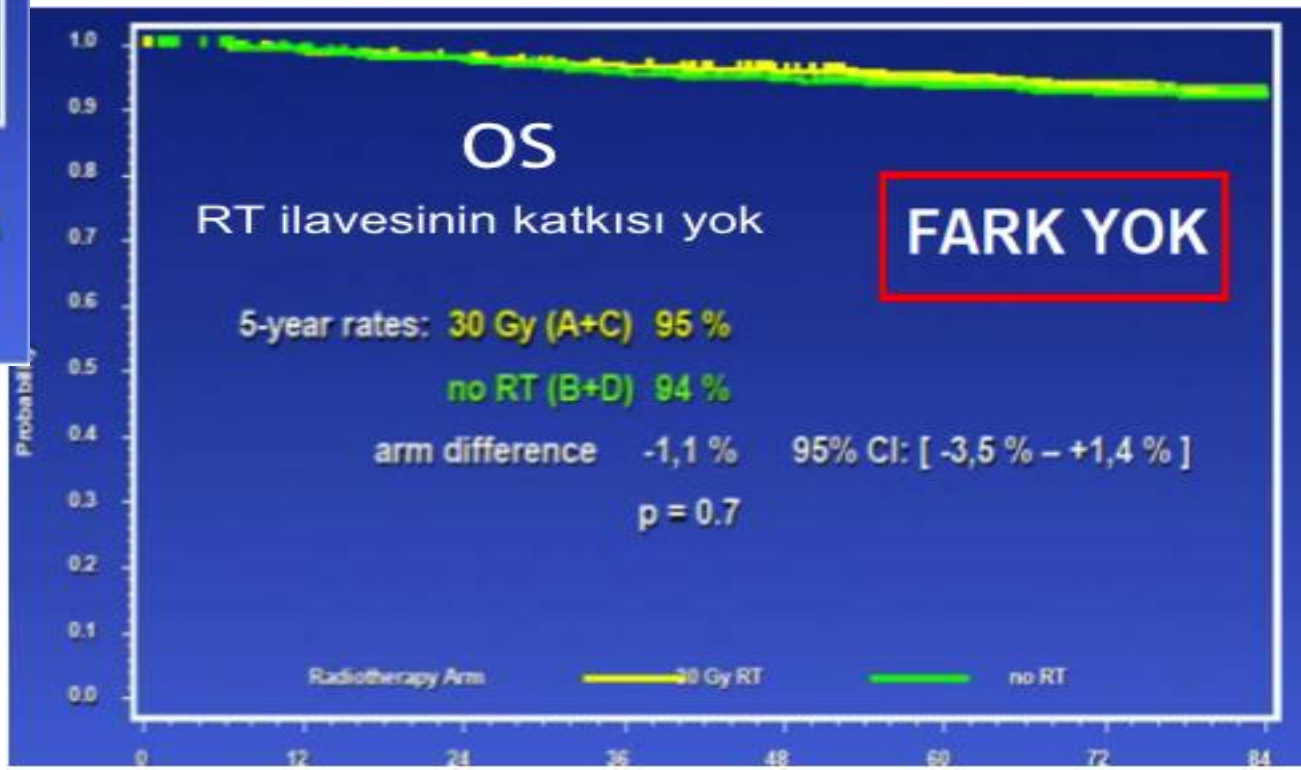


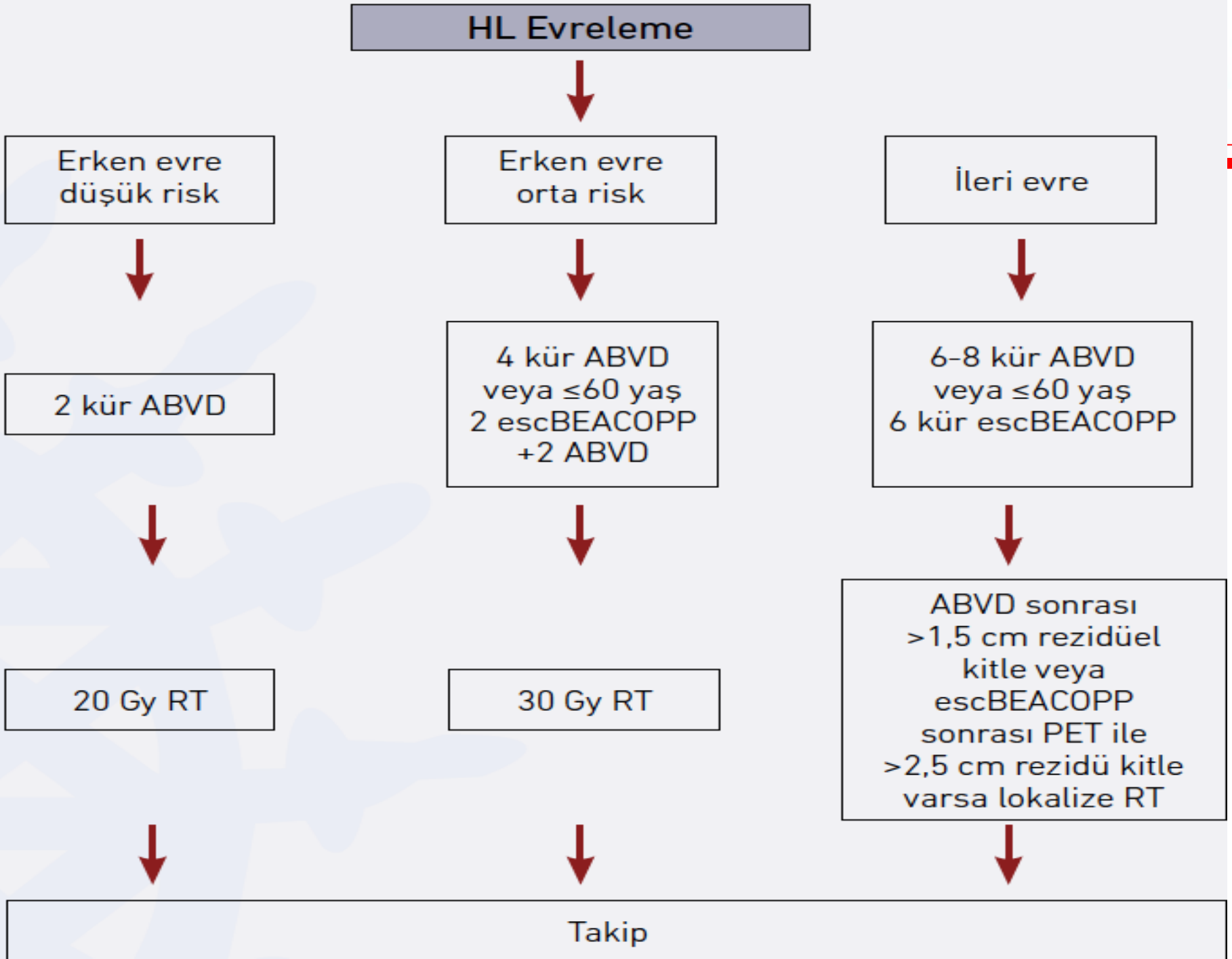
İleri Evre Hodgkin Lenfoma Tedavisi:

HD12 Çalışması-RT rolü- Sağkalım

HD12

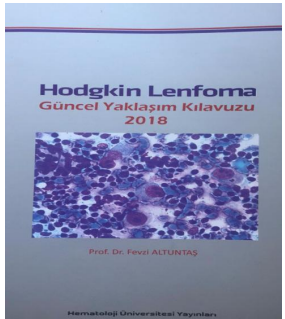





HL Evreleme
Erken evre düşük risk
Erken evre orta risk
İleri evre
2 kür ABVD
4 kür ABVD veya ≤60 yaş 2 escBEACOPP +2 ABVD
6-8 kür ABVD veya ≤60 yaş 6 kür escBEACOPP
20 Gy RT
30 Gy RT
ABVD sonrası >1,5 cm rezidüel kitle veya escBEACOPP sonrası PET ile >2,5 cm rezidü kitle varsa lokalize RT
Takip

Nodüler Lenfosit Predominant Hodgkin Lenfomada Tedavi

- Nodüler Lenfosit Predominant Hodgkin Lenfoma (NLPHL),
- indolen seyirli, nadir olarak geç nüksler görülebilen ve WHO sınıflamasında, klinik ve biyolojik özellikleri, doğal seyri ve tedaviye yanıttaki farklılıklar nedeniyle klasik HL'dan ayrı olarak tanımlanan bir lenfoma tipidir.



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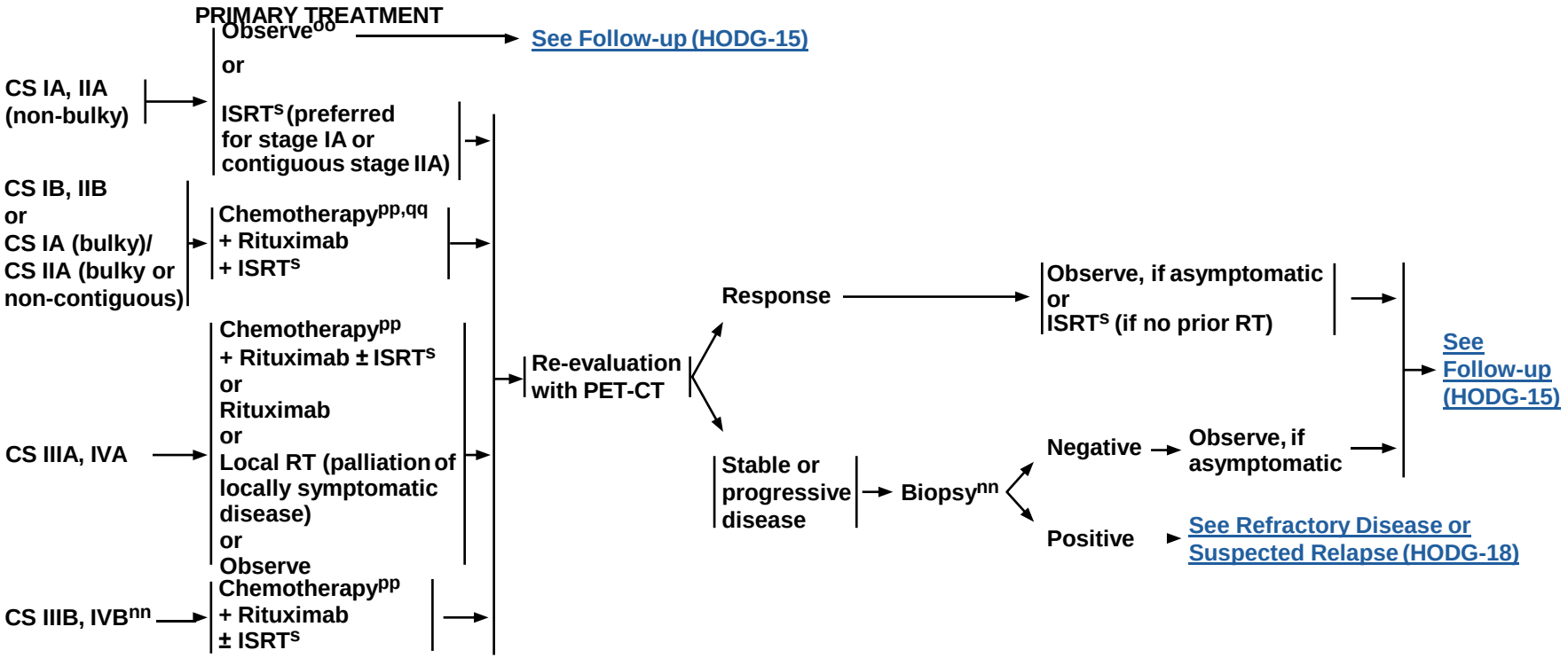
NCCN Guidelines Version 3.2018
Hodgkin Lymphoma (Age ≥18 years)

CLINICAL PRESENTATION:
Nodular Lymphocyte-Predominant Hodgkin Lymphoma[i]



[i]NLPHL has a different natural history and response to therapy than CHL, especially stages I-II. For that reason, separate guidelines are presented for NLPHL. Patients who present with bulky disease, subdiaphragmatic disease, or splenic involvement have a high risk for initial or later transformation to large cell lymphoma.

[s]ISRT fields are generally smaller than IFRT fields. See Principles of Radiation Therapy (HODG-C).

[nn]Consider biopsy of persistent or new subdiaphragmatic sites to rule out transformation.

[oo]Observation may be an option for stage IA patients with a completely excised solitary lymph node.

[pp]See Principles of Systemic Therapy (HODG-B 2 of 2).

[qq]Generally a brief course of chemotherapy (3–4 months) would be given with radiation therapy.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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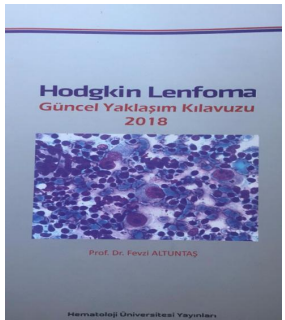
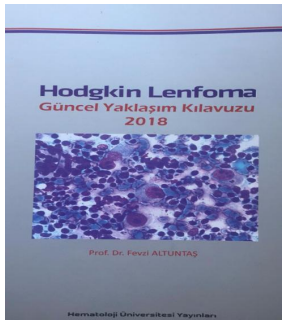
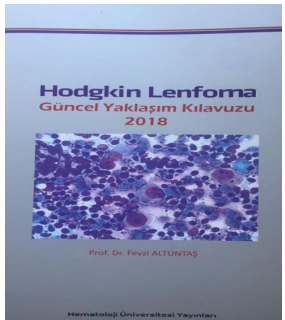


PROGNOZ

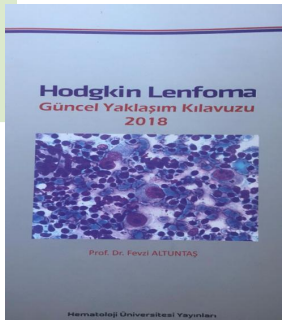

Hodgkin Lenfoma
Güncel Yaklaşım Kılavuzu
2018
Prof. Dr. Fevzi ALTUNTAŞ

YANIT DEĞERLENDİRME



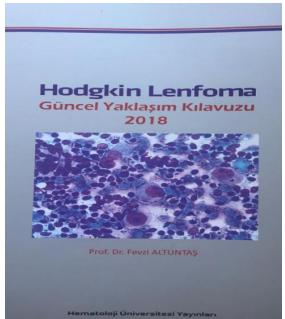
FDG-PET DEĞERLENDİRME

2007 rehberleri	Lugano sınıflaması
• Görsel yorumlamaya dayalı ve tedavi sonlanımına yönelik PET görüntüleme • Karşılaştırma için mediastinal kan havuzu kullanılır	• 5-puanlı skalayı (Mediastinal kan havuzu ve karaciğer) kullanır. • Erken tedavi yanıtını değerlendirmek için ara PET-BT • Remisyon durumunu tespit için tedavi sonu PET-BT



FDG-PET ZAMANLAMASI?

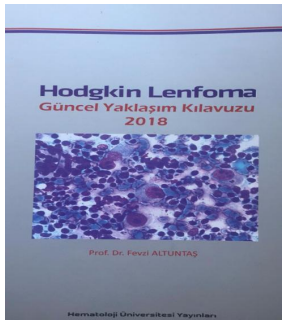
- Ara incelemede, son kemoterapi uygulamasından mümkün olduğunca uzun süre sonra
- Tedavinin sonunda, ideal olarak kemoterapiden 6-8 hafta sonra (ancak en az 3 hafta)
- Tedavi sonu yanıt değerlendirmesi kemoterapi sonrası RT öncesinde yapılmalıdır.
- Radyoterapiden ≥3 ay sonra



PET-BT-Yanıt Değerlendirmesi

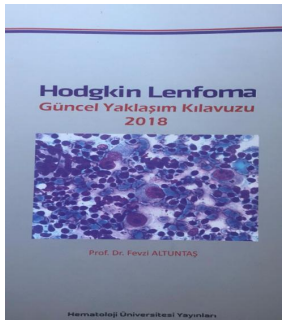
- Deauville ölçeğine göre 5-puan ölçeği (5-PS) kullanılarak yanıt değerlendirmesi yapılır.

Score	PET/CT scan result
1	No uptake
2	Uptake ≤ mediastinum
3	Uptake > mediastinum but ≤ liver
4	Uptake moderately higher than liver
5	Uptake markedly higher than liver and/or new lesions
X	New areas of uptake unlikely to be related to lymphoma



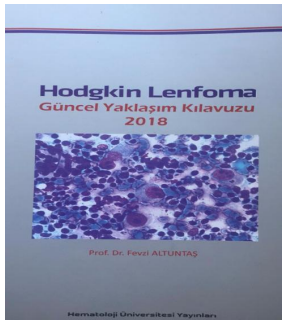
5 Puanlı skora göre Yanıt

- Puan 1, 2 negatif yanıt (Komplet Metabolik Yanıt (CMR)) olarak değerlendirilir.
- Puan 3’ de değerlendirme zamanına, klinik içeriğe ve tedaviye bağlıdır.
- Puan 4-5 pozitif olan olgularda biyopsi yapılmalıdır.
  - Biyopsi sonucu negatif olması halinde hastaya 3 ay sonra PET ile tekrar değerlendirme yapılmalı ve PET’in negatifleştiği görülmelidir.



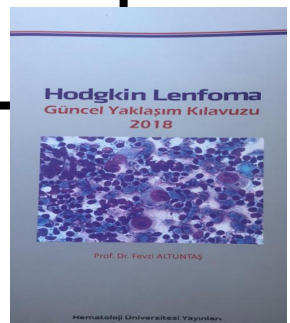
Rezidü Kitle?

- PET CT'de rezidü kitle kuşkusu var ise metabolik olarak aktif dokunun biyopsisi önerilmektedir.

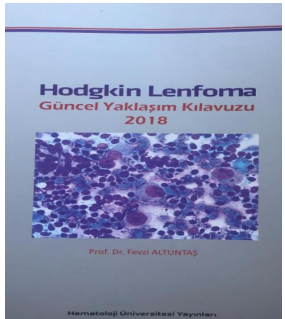


YANIT DEĞERLENDİRME-BT

Tam yanıt (TR)	Tümör kitlesinde % 100 küçülme
Kanıtlanmamış tam yanıt (CRu)	Klinik ve görüntüleme yöntemleriyle tümöre ait bulgular yok
Kısmi yanıt (PR)	Tümör kitlesinde % 50’den fazla küçülme
Sabit hastalık	Tümör kitlesinde % 50’nin altında kalan küçülme ve % 25’in altında kalan büyüme
İlerleyici hastalık	Tümör kitlesinde % 25’den fazla artış veya yeni lezyon ortaya çıkması



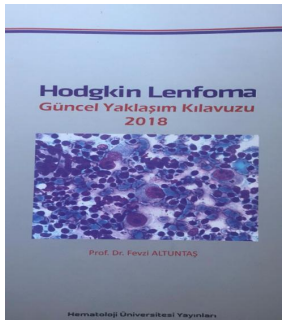
KOMPLİKASYONLAR



KOMPLİKASYONLAR

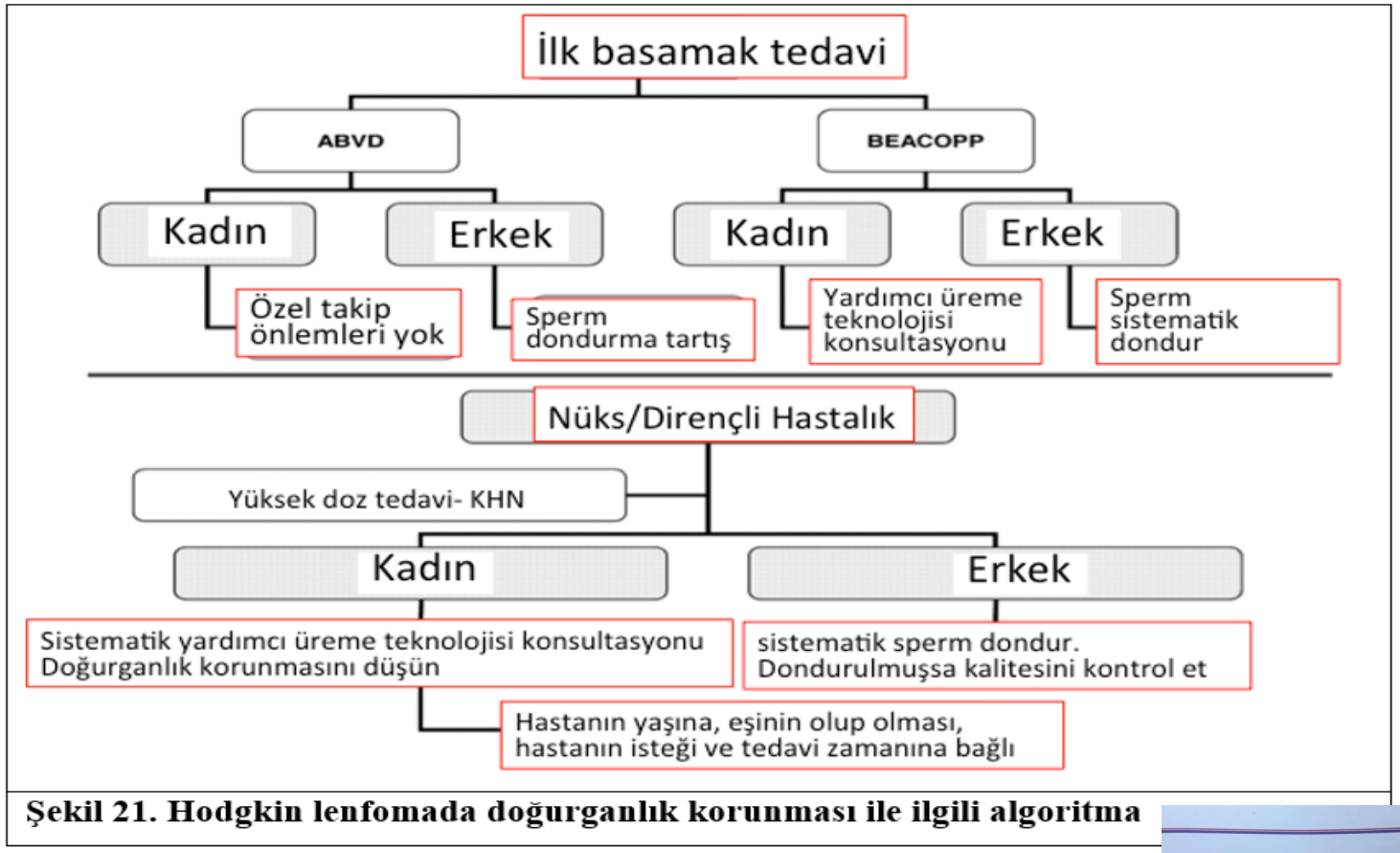
Hastanın aldığı radyoterapinin doz, süre, yoğunluğa ve kemoterapi protokolünün içerdiği ilaçlara bağlı olarak değişebilmektedir.

- 1) İnfertilite
- 2) İkincil malignite
  - Deri, AML, akciğer kanseri, MDS, NHL, tiroid, meme kanseri ...
- 3) Troid hastalığı
- 4) Kardiyovasküler sistem hastalıkları
- 5) Myelosupresyon
- 6) Pulmoner Toksisite
- 7) Boyun kas zayıflığı

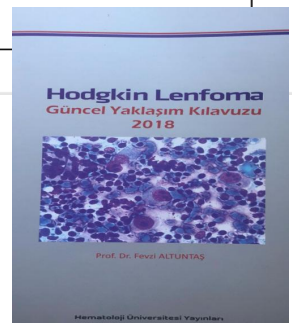


Komplikasyonlar- İnfertilite

- Riskli grup;
  - Pelvik RT
  - Alkilleyici ajanlara maruziyet (MOPP>ABVD)
  - Agresif kurtarma terapisi

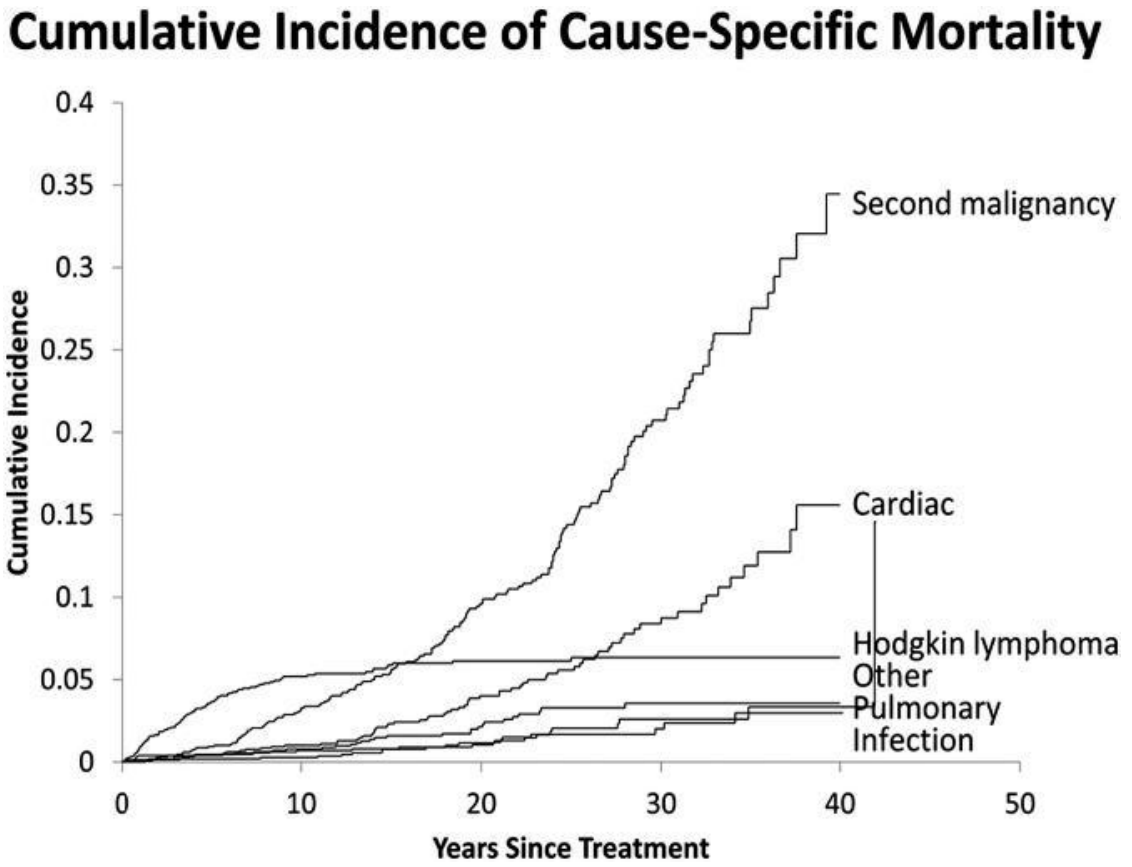


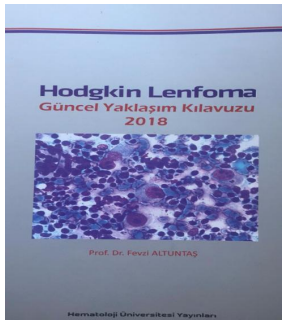
Şekil 21. Hodgkin lenfomada doğurganlık korunması ile ilgili algoritma



Komplikasyonlar- İkinci malignite

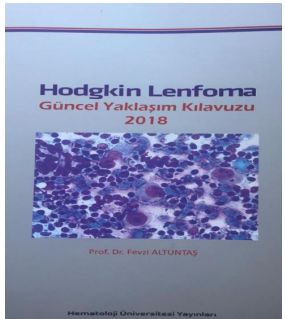
- RT sekonder kanser riskini artırır.
- Solid tümörler en sık görülen ikincil kanserlerdir.
- Çoğunlukla tedavi bittikten 10 yıl sonra görülmeye başlamaktadır.
- Risk açısından **RT>KT+RT>KT** şeklinde sıralanır.
- Mümkün olan en sınırlı alan ve dozda uygulanmalıdır.
- GART uygulananlarda daha fazla kanser gelişme risk belirtilmiştir.
- En sık akciğer, meme kanseri, gastrointestinal sistem kanserleri görülür.





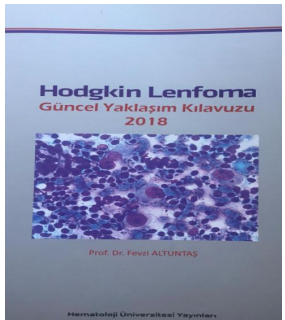
Komplikasyonlar- Troid Hastalığı

- Boyun ve üst mediastene RT alanların %50'inde tiroid fonksiyon bozuklukları bildirilmiştir.
- Hipotroid en sık görülen troid hastalığı komplikasyonudur.



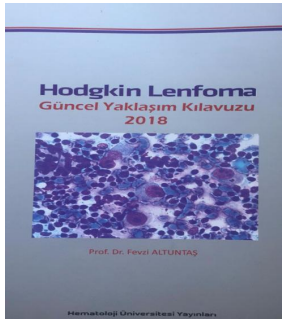
Komplikasyonlar- Kardiyovasküler hastalıklar

- Mediasten ışınlanması (mantle RT) ve antrasiklin bazlı kemoterapiler alanlar kalp hastalığı gelişimi yönünden en yüksek risk grubundaki hastalardır.
- RT ile ilişkili kardiyotoksisite sıklıkla tedavi tamamlanmasından 5-10 yıl sonra görülmeye başlar.



Komplikasyonlar- Myelosüpresyon

- Primer tedavi sonrası myelosüpresyonun uzun süre devam etmesi beklenmez.
- Myelosupresyonun daha uzun sürdüğü OKHN/AKHN yapılan hastalar enfeksiyon yönünden risk altında olabilir.



Komplikasyonlar- Pulmoner toksisite

- ABVD'ye bağlı pulmoner toksisite %1.5-2 civarındadır.
- ABVD ile birlikte kullanılan büyüme faktör kullanımının akciğer toksisitesi görülme sıklığını arttırdığını göstermiştir. Rutin önermemektedir.
- Bilinen en sık risk faktörleri;
  - İleri yaş
  - Kümülatif bleomisin dozu (<400 mg)
  - Akciğer ışınlanması
  - Önceden akciğer hastalığı öyküsü
  - GCSF kullanımı

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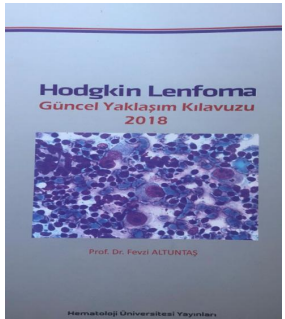
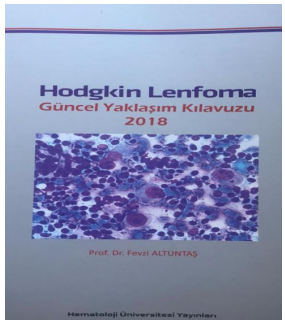


TAKİP


Hodgkin Lenfoma
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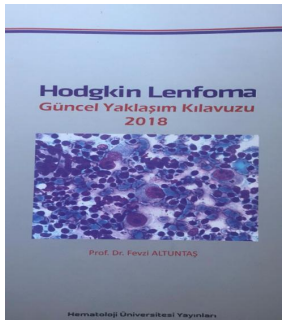
2018
Prof. Dr. Fevzi ALTUNTAŞ

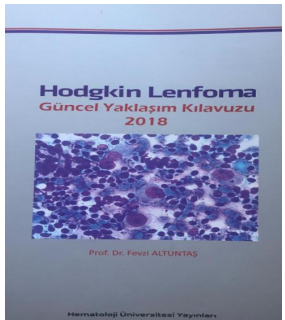
Takip-Nüks açısından

- Hodgkin Lenfoma gibi kürabl lenfomalarda takip sıklığı düşük nüks ihtimali nedeni ile zamanla azalır.
- İlk 2 yılda 3 ayda bir, daha sonraki 3 yılda 6 ayda bir, daha sonra ise yıllık aralıklarla takip yapılmalıdır.
- Klinik, hikaye ve muayene takibin temel taşlarıdır.
- Her klinik kontrolde tam kan sayımı, biyokimya (alkalin fosfataz, AST, ALT, albumin, BUN ve kreatinin dahil olmak üzere KCFT) ve tanıda yüksekse ESH bakılmalıdır.
- Hastanın her kontrolde BT veya PET/BT ile taranması önerilmez.



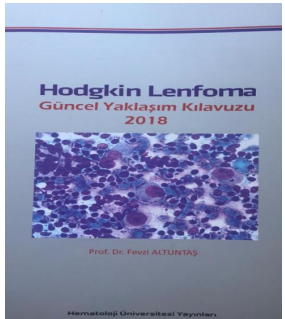
Takip-Troid Fonksiyonları

- Tiroid muayenesi fizik muayenenin parçası olmalı ve tiroid fonksiyon testlerinin en az 6 ay-yılda bir kez yapılması önerilmektedir.



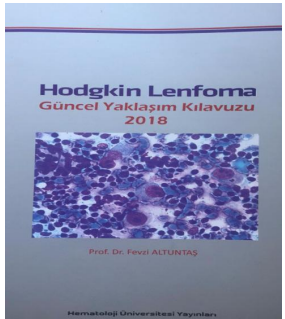
Takip-Enfeksiyon Açısından

- Hastaya splenik alana radyoterapi uygulanmışsa, 5 yılda bir pnömokok, meningokok ve hemofilus influenza aşısı ve tüm hastalara yıllık influenza aşısı (özellikle hasta bleomisin veya göğüs radyoterapisi ile tedavi edilirse) yapılmalıdır.



Takip-Meme kanseri

- Özellikle göğüs ve aksiller bölgeye radyoterapi alan hastalarda tedavi bitiminden 8-10 yıl sonra ve/veya 40 yaşından sonra (hangisi önce gelirse) yıllık mamografi ile taranması önerilmektedir.
- Amerika kanser derneği 10-35 yaş arasında göğüs bölgesine radyoterapi almış hastalarda mammografi yanına yıllık meme MR'ıda tarama yöntemine eklenmesini önermektedir.



Cumulative absolute risk for developing breast cancer in young women treated for Hodgkin lymphoma after 30 years of follow-up

Age at Dx	Mediastinal RT (Gy)	Absolute risk of breast CA after 30 years of follow-up	
		Alk agents used	Alk agents not used
15	0	0.8	1.7
	20 - <40	4.1	8.5
	≥40	5.0	10.3
20	0	1.6	3.4
	20 -<40	7.9	16.0
	≥40	9.5	19.1
25	0	2.6	5.5
	20 -<40	12.5	24.6
	≥40	15.0	29.0
30	0	4.0	8.2
	20 -<40	18.1	34.1
	≥40	21.6	39.6

This table shows the estimated absolute risk of developing breast cancer (percent) after 30 years of follow-up in young women treated for Hodgkin lymphoma as a function of age at diagnosis (dx), amount of mediastinal irradiation (Gy), and whether or not alkylating (alk) agents were employed in the treatment program.

Data from: Travis LB, Hill D, Dores GM, et al. Cumulative absolute breast cancer risk for young women treated for Hodgkin lymphoma. J Natl Cancer Inst 2005; 97:1428.

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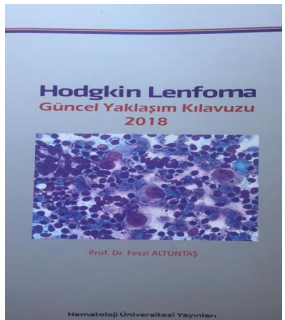
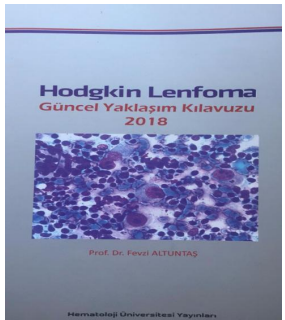


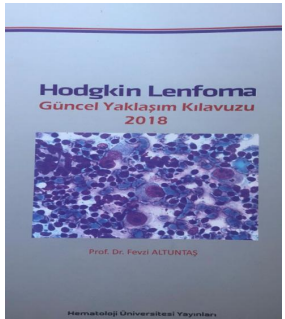
Takip-Koroner Arter Hastalığı

- Özellikle mediastinal bölgeye RT alan hastalar KAH, kalp kapak hastalığı, kardiyomiyopati, KKY, iletim bozukluğu, karotid hastalığı ve kardiyovasküler risk faktörleri açısından yıllık hikaye ve fizik Muayene yapılmalıdır.
- Her 1-2 yılda bir lipid paneli istenmelidir.
- Taramalar kardiyovasküler hastalık tanısını düşündürüyorsa, uygun görüntüleme çalışmaları yapılmalıdır.
- Tedavi tamamlandıktan 10 yıl sonra 10 yıllık aralıklar ile stres testi, ekokardiyografi ve boyuna radyoterapi öyküsü var ise boyun karotis ultrasonografisi yapılması gerekmektedir.



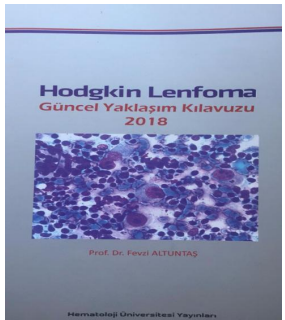
Takip-Serviks kanseri

- Serviks kanseri için yıllık servikal smear örneklemesi alınabilir.



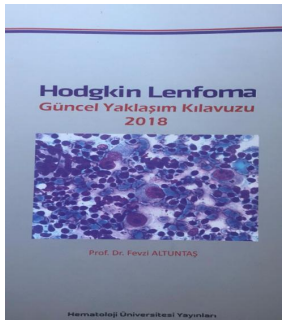
Takip-Akciğer kanseri

- Akciğer kanseri gelişmesi açısından riski olan (göğüse RT alan, alkilleyici ajan KT uygulanan ve sigara içme öyküsü) hastalara tarama akciğer görüntülemesi (düşük doz akciğer BT) önerilmektedir. Fakat ne sıklıkta tekrarlanacağı konusunda fikir birliği yoktur. Akciğer kanseri doğrudan radyasyon dozu ile ilişkili olduğundan her aşamada radyasyona maruziyeti azaltmak önemlidir.



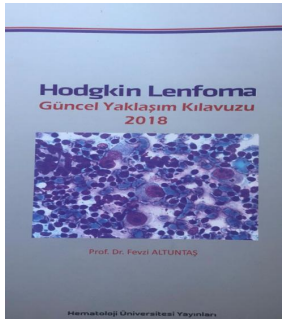
Takip-Gastrointestinal kanser

- Gastrointestinal kanserlerden özellikle özafagus, mide, pankreas, kolon kanseri gelişebilir.
- Sıklıkla radyasyon dozu ve uygulanan kemoterapi protokolü ile ilişkilidir.
- Pelvik RT alanlar (>30 Gy) kolonoskopi ile 35 yaşından başlayarak veya RT sonrası 10 yıl sonra (hangisi önce gelirse) her 5 yılda bir tekrarlanan kolon kanseri tarama programına alınmalıdır.



Takip-Deri Kanseri

- Özellikle radyasyoterapi uygulanan bölgeye yıllık cilt kanseri muayenesi yapılmalıdır.



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NCCN Guidelines Version 3.2018
Hodgkin Lymphoma (Age ≥18 years)

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FOLLOW-UP AFTER COMPLETION OF TREATMENT AND MONITORING FOR LATE EFFECTS

- CR should be documented including reversion of PET to "negative" within 3 months following completion of therapy.
- It is recommended that the patient be provided with a treatment summary at the completion of his/her therapy, including details of radiation therapy, organs at risk (OARs), and cumulative anthracycline dosage given.
- Follow-up with an oncologist is recommended, especially during the first 5 years after treatment to detect recurrence, and then annually due to the risk of late complications including second cancers and cardiovascular disease.[rr,ss] Late relapse or transformation to large cell lymphoma may occur in NLPHL.
- The frequency and types of tests may vary depending on clinical circumstances: age and stage at diagnosis, social habits, treatment modality, etc. There are few data to support specific recommendations; these represent the range of practice at NCCN Member Institutions.

Follow-up After Completion of Treatment up to 5 Years

- Interim H&P: Every 3–6 mo for 1–2 y, then every 6–12 mo until year 3, then annually
- Annual influenza vaccine
- Laboratory studies:
  - CBC, platelets, ESR (if elevated at time of initial diagnosis), chemistry profile as clinically indicated.
  - Thyroid-stimulating hormone (TSH) at least annually if RT to neck.
- Acceptable to obtain a neck/chest/abdomen/pelvis CT scan with contrast, at 6, 12, and 24 mo following completion of therapy, or as clinically indicated. PET/CT only if last PET was Deauville 4-5, to confirm complete response.
- Counseling: Reproduction, health habits, psychosocial, cardiovascular, breast self-exam, skin cancer risk, end-of-treatment discussion.
- Surveillance PET should not be done routinely due to risk for false positives. Management decisions should not be based on PET scan alone; clinical or pathologic correlation is needed.

Suspected Relapse CHL (HODG-17) or NLPHL (HODG-18)

Follow-up and Monitoring After 5 Years[pp,qq]

- Interim H&P: Annually
  - Annual blood pressure, aggressive management of cardiovascular risk factors
  - Pneumococcal, meningococcal, and H-flu revaccination after 5–7 y, if patient treated with splenic RT or previous splenectomy (according to CDC recommendations)
  - Annual influenza vaccine
- Cardiovascular symptoms may emerge at a young age.
  - Consider stress test/echocardiogram at 10-y intervals after treatment is completed.
  - Consider carotid ultrasound at 10-y intervals if neck irradiation.
- Laboratory studies:
  - CBC, platelets, chemistry profile annually
  - TSH at least annually if RT to neck
  - Biannual lipids
  - Annual fasting glucose
- Annual breast screening: Initiate 8–10 y post-therapy, or at age 40, whichever comes first, if chest or axillary radiation. The NCCN Hodgkin Lymphoma Guidelines Panel recommends breast MRI in addition to mammography for women who received irradiation to the chest between ages 10–30 y, which is consistent with the American Cancer Society (ACS) Guidelines. Consider referral to a breast specialist.
- Perform other routine surveillance tests for cervical, colorectal, endometrial, lung, and prostate cancer as per the ACS Cancer Screening Guidelines.
- Counseling: Reproduction, health habits, psychosocial, cardiovascular, breast self-exam, and skin cancer risk.
- Treatment summary and consideration of transfer to PCP.
- Consider a referral to a survivorship clinic.

[rr]Mauch P, Ng A, Aleman B, et al. Report from the Rockefeller Foundation-sponsored International Workshop on reducing mortality and improving quality of life in long-term survivors of Hodgkin's disease: July 9-16, 2003, Bellagio, Italy. Eur J Haematol 2005;75(s66).
[ss]Appropriate medical management should be instituted for any abnormalities.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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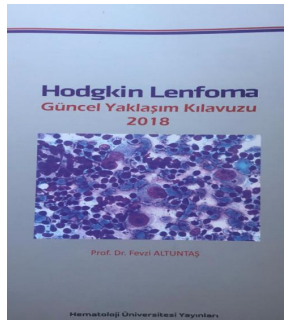
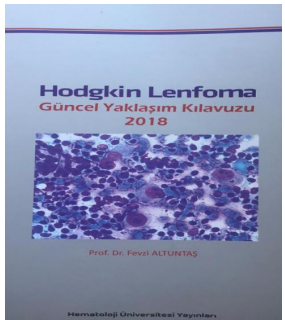


Eve Götürelecek Mesajlar

- Hodgkin lenfomada tek amacın kür olmadığı
- PET tabanlı tedavilerin kullanılabilirliğinin giderek arttığını
- Seçilecek tedavi protokolü tamamen hastaya göre belirlenmesi
- Deaville yanıt kriterleri hakkında Nükleer Tıp uzmanlarının yeterince bilgilendirilmesi
- Uzun dönem komplikasyonları iyi bilmek ve hastalık takibinde oluşabilecek komplikasyonlara karşı önlem almak

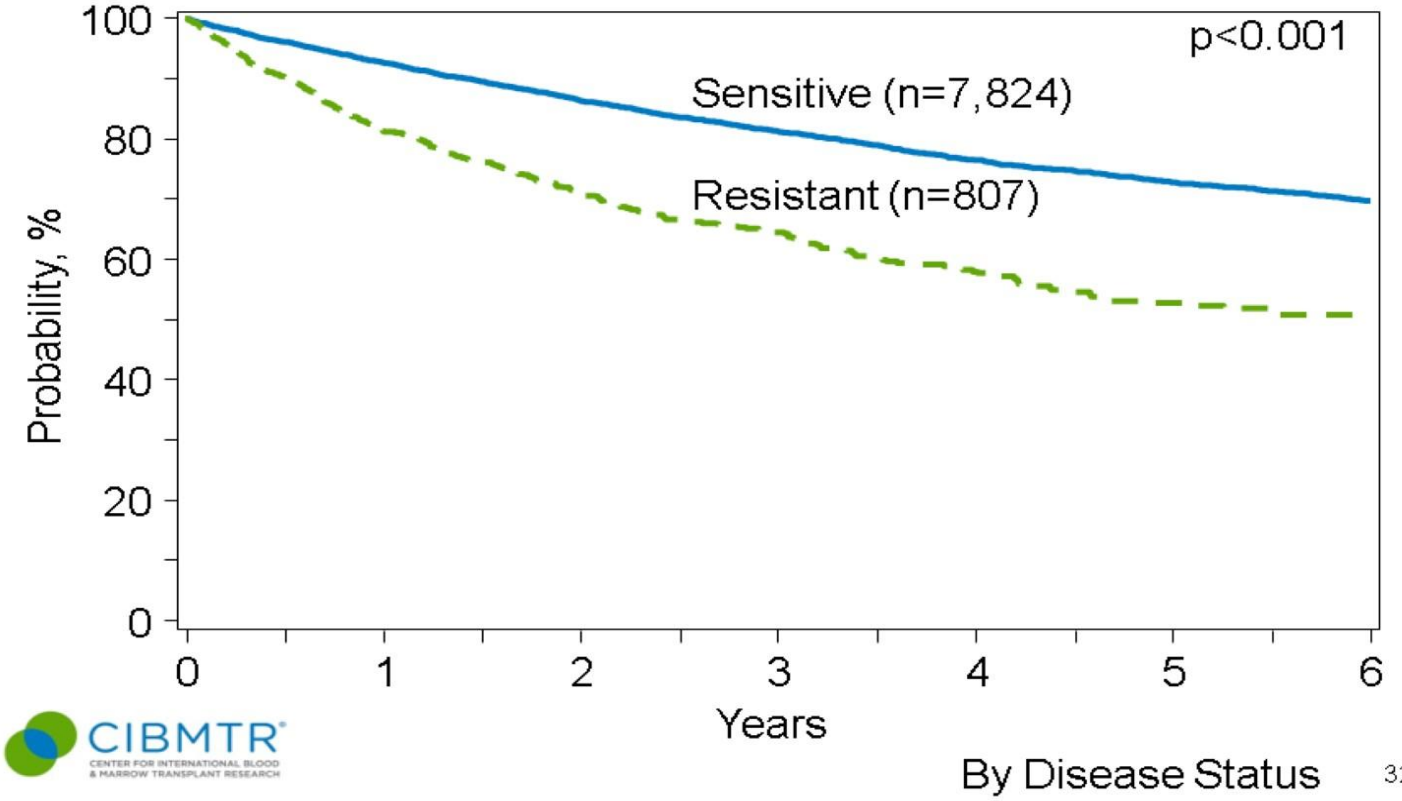


Nüks/Dirençli HL: Kurtarma Tedavi Seçimi- Rejimler

Author, year	Chemotherapy	Number of subjects	Age range (years)	ORR (%)	CR (%)	Toxic deaths (%)
Schmitz 2002[11]	Dexa-BEAM	144	16–55	81	27	5
Martin 2001[12]	Mini-BEAM	55	15–60	84	51	2
Aparicio 1999[13]	ESHAP	22	>18	73	41	5
Moskowitz 2001[14]	ICE	65	12–59	88	26	0
Josting 2002[15]	DHAP	102	21–64	89	21	0
Schellong 2005[16]	IEP-ABVD	176	4–24	85	NR	0
Baetz 2003[17]	GDP	23	19–57	69	17	0
Bonfante 2001[18]	VI	47	20–NR	83	45	0
Proctor 2003[19]	IVE	51	16–53	84	60	0
Santoro 2007[20]	IGEV	91	17–59	81	28	0
Ferme 2002[21]	MINE	157	15–65	75	NR	5
Cole 2009[22]	GV	30	11–29	76	20	0
Shafey 2012[23]	DICEP	73	19–55	86	18	1

▶ Kurtarma tedavisine yanıt %50-89

Survival after Autologous Transplants for Hodgkin Lymphoma, 2003-2013



Transplantation for Hodgkin Lenfoma Lymphoma (HL) is indicated in patients who have failed initial chemotherapy or radiation therapy. Survival after HCT for HL depends on disease response to previous salvage therapy. Among the 8,631 patients receiving autotransplants for HL between 2003 and 2013, the 3-year probabilities of survival were 81% ± 1% and 64% ± 2% for patients with chemosensitive and with chemoresistant disease, respectively.

OKHN sonrası Nüks:
Tedavi seçenekleri

1. Tek ajan kemoterapi
2. Kombine kemoterapi
3. Radyoterapi
4. İmmünokonjugat brentixumab*
5. CPI (Nivolumab, pembrolizumab)*
6. Lenalidomid
7. mTOR inh (Everolimus)
8. HDAC inhibitörleri
9. AKHN
10. Gözlem

*En ümit verici biyolojik ajanlar

Nüks/Dirençli HL Tedavisi: REHBERLER

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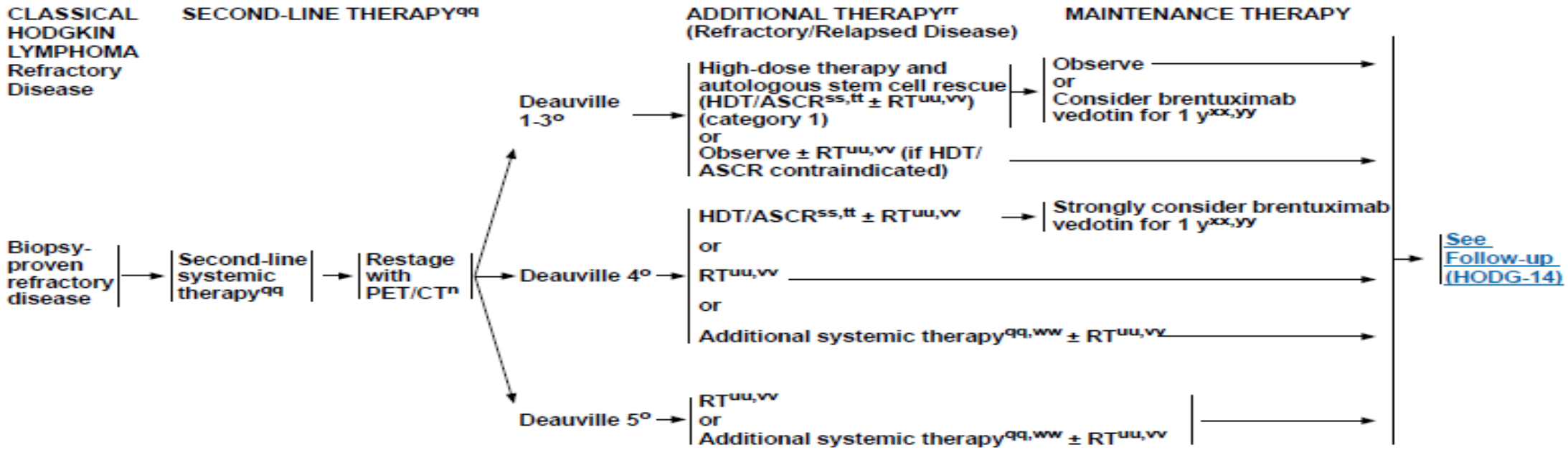

[n]An integrated PET/CT or a PET with a diagnostic CT is recommended.
[o]See PET 5-Point Scale (Deauville Criteria) (HODG-D).
[qq]See Principles of Systemic Therapy for Relapsed or Refractory Disease (HODG-E).
[rr]There are no data to support a superior outcome with any of the treatment modalities. Individualized treatment is recommended.
[ss]Radiation therapy recommended when sites have not been previously irradiated. In a radiation-naive patient, TLI may be an appropriate component of HDT.
[tt]Allotransplant is an option in select patients as a category 3 recommendation.
[uu]Conventional-dose chemotherapy may precede high-dose therapy. Timing of RT may vary.
[vv]See Principles of Radiation Therapy (HODG-C).
[ww]Additional systemic therapy options include second-line therapy options that were not previously used (See HODG-E).
[xx]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;385:1853-1862.
[yy]The value of brentuximab maintenance for a patient who previously received brentuximab vedotin is not known. It does not provide a survival benefit.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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faltuntas@hotmail.com

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