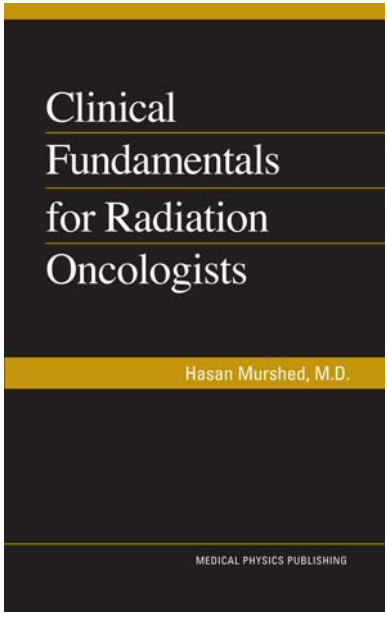
MEDICAL PHYSICS PUBLISHING



Here is a sample chapter from this book.

Chapter 8

LYMPHOMAS

HODGKIN'S LYMPHOMA

*Incidence is **7,400** with **1,400** deaths in 2005.*

Hodgkin's lymphoma peaks in early life and again after the fifth decade. Reed-Sternberg cells are mononuclear variants (large binucleate cells with central nucleoli and perinuclear clearing) and are a pathogonomic finding of Hodgkin's disease.

Work-up

Risk Factors

- Epstein-Barr virus

Symptoms and Signs

- fatigue and loss of energy
- systemic B symptoms
  - weight loss greater than 10% of body weight in the last 6 months
  - recurrent, unexplained fever over 101 °F and night sweats
- alcohol intolerance and pruritis
- respiratory problems secondary to mediastinal mass
- check for palpable lymph nodes (number, size, shape, consistency, mobility, location), palpable abdominal organs
- check for bony tenderness.

Investigations

- CBC with absolute lymphocyte count
- chemistry with liver/renal function, serum albumin, T4, TSH, ESR, LDH, bHCG (if child-bearing age)
- excisional biopsy of the lymph node
- chest x-ray and CT chest/abdomen/pelvis

- gallium scan
- PET and bone scan recommended if bony tenderness and bony only for clinical evidence of bone metastasis suspected or patient has elevated alkaline phosphatase
- bilateral bone marrow biopsy
- staging laparotomy is not recommended routinely.

Staging

Ann Arbor Staging System

Stage I	Limited to a single nodal region, or single extralymphatic site (IE).
Stage II	Two or more nodal regions on the same side of the diaphragm, or localized involvement of a single associated extralymphatic site and its regional nodes with or without involvement of other nodal regions on the same side of the diaphragm. (IIE), bilateral hilum is stage II.
Stage III	Nodal regions on both sides of the diaphragm (III), which may also be accompanied by localized involvement of an associated extralymphatic organ or site (IIIE), by involvement of the spleen (IIIS) or both (IIIE+S). Desser modification assigns subclass:
III1	Limited to spleen, splenic hilar lymph node, celiac lymph node, or porta hepatis lymph node (above renal hilar).
III2	Subdiaphragmatic involvement other than above (PA, iliac, mesenteric). (Below renal hilar).
Stage IV	Disseminated extralymphatic involvement with or without associated nodal involvement, or isolate extralymphatic involvement with distant (nonregional) nodal involvement.
A.	No symptoms.
B.	1. Unexplained weight loss of more than 10% body weight over 6 months prior to staging. 2. Unexplained, persistent, or recurrent fever (Pel-Ebstein pattern waxing and waning) with temperatures above 38 °C during the previous month. 3. Recurrent drenching night sweats.

The Cotswolds modification (1989) of the Ann Arbor classification is as follows:

E	Single extra nodal site contiguous or proximal to a known nodal site.
X	Bulky disease (≥10 cm max dimension nodal mass, mediastinal mass ≥1/3 the internal transverse diameter at T5/6 on PA CXR).
II1,2...	Subscript designating the number of sites involved in stage II disease.
CRu	Residual abnormalities after treatment that cannot be confirmed as benign or malignant (Complete response-unconfirmed).
S	Is eliminated as a subdesignation, and instead the definitions of stages are changed from "nodal regions" to "nodal region or lymphatic structure"; thus spleen is simply counted as another site.

Note: All ipsilateral neck nodes on one side are considered one involved-field (IF) site. Waldeyer's ring (tonsils, base of tongue, naropharynx) is a separate site; supraclavicular is a separate site from infraclavicular; axilla is a separate site from epitrochlear/brachial; hilar is separate from mediastinal; spleen, periaortic, iliac, and mesenteric are all separate sites. Inguinal and femoral are combined in one site, not separate.

Rye Classification

- nodular sclerosis
- mixed cellularity
- lymphocyte predominant (LP)
- lymphocyte depleted (LD)

Treatment

The treatment recommendations for Hodgkin's lymphoma (HL) are based on disease site(s), stage, histologic subtypes, and presence/absence of risk factors. Retrospective analyses have identified patient/disease characteristics that are prognostic and may assist in defining appropriate treatment regimens (age < 50, female sex, LP or LD subtype, absence of symptoms, neck mass disease, ESR ≤ 50).

Stage I/II

- The recommended treatment is combined modality therapy (CMT) with ABVD ×4–6 cycles, followed by involved-field RT for patients with initial bulky disease, B symptoms, and patients with nodular sclerosing, mixed cellularity, or lymphocyte depleted subtypes. RT dose if complete response to chemotherapy is 30.6 Gy to pre-chemo volume. If partial response, then 30.6 Gy to pre-chemo volume and 5.4 Gy boost to post-chemo volume.
- Patients carrying a very favorable prognosis may be treated with radiation alone (36 Gy), however this approach is controversial. If radiation is used alone, treatment portals need to be larger than involved-field radiation.

Stage III/IV

Recommendation is combination chemotherapy ABVD for advanced stage disease to complete response plus 2 cycles, usually ×6–8 cycles. The role of consolidated radiation for nonbulky stage III/IV Hodgkin's lymphoma is controversial. If there is initial bulky disease with complete response to chemotherapy, then RT to 30.6 Gy to pre-chemo volume followed by 5.4 Gy to the bulky site. If there is bulky disease with partial response, then biopsy is recommended. If biopsy is positive, then patients less than 60 years old should receive high dose chemotherapy followed by autologous peripheral stem-cell transplantation, or patient can receive RT to 30.6 Gy to pre-chemo volume followed by 5.4 to 9 Gy to post-chemo volume.

Bulky Mediastinal Disease

Recommendation is combined modality therapy with ABVD chemotherapy ×6 cycles and followed by modified mantle RT. Treat subclinical disease to 30.6 Gy followed by a boost to gross disease to 36–40 Gy. Consider MOPP/ABV hybrid chemotherapy.

Subdiaphragmatic Disease

For inguinal-femoral lymphoma disease with stage IA, recommend RT alone with inverted Y field. Other noninguinal/nonlymphocyte-predominant patients should get combined modality therapy with chemo ABVD ×6 cycles followed by involved-field radiation therapy to 30.6–36 Gy.

RT Technique

Pre-auricular Field

Borders: Superiorly at the top of the zygomatic arch, inferiorly below the mandible. Pre-auricular field is matched on the skin with the mantle field. Anteriorly posterior to 3rd molar and posteriorly to the external auditory canal.

Waldeyer's Field

Borders: Superiorly at the top of the zygomatic arch, inferiorly below the mandible, anteriorly at the mandibular symphysis and posteriorly beyond spinous process.

Mantle Field

Patient is supine, arms akimbo, neck extended. Patient is generally treated at 100 cm SSD. BBs are placed at neck, spinal cord, supraclavicular fossa, axilla, superior/middle/lower mediastinum points and any palpable lymph nodes are wired. Borders: Superiorly at the mandible/mastoid, inferiorly at T10 or T11 (one vertebral body above maximal diaphragm excursion to avoid matching through spleen if spleen and paraaortic lymph nodes are to be treated); laterally the fields are set clinically to include the axillae inferiorly to the 4th rib. The following blocks are used for the mantel field. See Figure 8–1.

- **PA C-spine** block placed for PA field after 30 Gy. If bulky cervical nodes approach the midline, then no PA C-spine block.
- **Mouth** block placed for AP/PA fields.
- **Humeral head** block for AP/PA fields. If arms above head, then no humeral block.
- **Larynx** block for AP field after 19.8 Gy.
- **Lung** blocks for AP/PA fields. (Do not block hilar.)
- **Left ventricle** block for AP field. If no pericardial or subcarinal disease is noted, then block the left ventricle from start of the treatment; if pericardium is being treated electively, then block after 14.4 Gy; if subcarina is being treated, then block at 30.6 Gy.

PA Field

Patient is supine; generally treated at 100 cm SSD with AP/PA fields. Borders: Superior is at T10 or T11; inferior border is at L4/L5, laterals

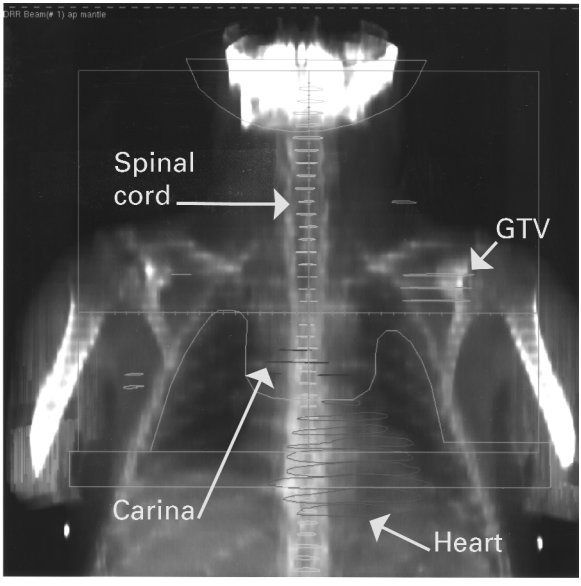


Figure 8–1. AP DRR of mantle field, Hodgkin's disease, showing a mouth block and lung and left ventricle block. Superior border at the mandible/mastoid; inferior border at T10/T11.

2 cm from vertebral body edge. PA field is matched at mid plane with a 3-mm safety margin extra to the skin gap. The field is extended laterally to encompass the entire spleen, if present.

Note: PA field is often treated one month after the mantle field treatment is completed, to avoid excessive toxicity.

Pelvic Field/Inverted Field

Patient is supine, and AP/PA fields are used. Borders: Superior is at L4/L5; inferiorly at 2.5 cm below ischial tuberosity; laterally to encompass inguinal lymph nodes; need a midline block to avoid unnecessary radiation to bladder/bowel and to encompass iliac nodes. Pelvic field is matched at mid plane to PA field.

Outcome

Stage	Therapy	Disease-free Survival @ 5 years (%)	Overall Survival @ 5 years (%)
IA	RT	85	95
IIA	RT	75	90
IB/IIB	Chemo+RT	85	90
III	Chemo+RT	80	80
III/IV	Chemo alone	—	50

(Modified from Table 8.1, p. 194, "Lymphoma and Hematologic Malignancies" by Benjamin Movsas, M.D., and Lawrence Coia, M.D., in *Introduction to Clinical Radiation Oncology,* 3rd edition, L. R. Coia and D. J. Moylan, © 1996 Lawrence R. Coia and David J. Moylan, with permission from Medical Physics Publishing.)

Late Complications of RT

- herpes zoster
- hypothyroidism
- pulmonary pneumonitis and chronic fibrosis
- acute and chronic pericarditis, cardiomyopathy, myocardial infarction, early coronary artery disease
- change in bowel habit with diarrhea, bowel, or rectal damage
- infertility for males and females with pelvic radiation
- radiation-induced malignancies.

NON-HODGKIN'S LYMPHOMA

*Incidence is **54,900** with **26,100** deaths in 2005.*

More patients with non-Hodgkin's lymphoma (NHL) present quite differently from the Hodgkin's patients. Fewer patients present with B symptoms as opposed to Hodgkin's disease. In addition, the common Ann Arbor staging system does not quite predict the clinical presentation of

non-Hodgkin's disease. As such, non-Hodgkin's lymphomas are divided into low, intermediate, and high grades that more appropriately reflect the clinical behaviors of the disease. Each grade has three or four subtypes with distinctly different behaviors.

Work-up

Risk Factors

- immunodeficiency (HIV) virus infection or immunosuppression secondary to organ transplant
- Epstein-Barr virus infection
- H pylori bacterial infection
- alkalyting agents and prior radiation exposure.

Symptoms and Signs

- B symptoms
  –weight loss more than 10% of body weight
  –recurrent unexplained fever over 101 °F
  –recurrent night sweats
- check for palpable lymph node (number, size, location, shape, texture, mobility) and palpable abdominal organs
- pleural effusion and pericardial rub
- site-specific findings, such as thyroid mass for thyroid lymphoma or bony tenderness for
- palpable viscera
- bony tenderness.

Investigations

- CBC, absolute lyphocyte count, chemistry with liver/renal, serum albumin, T4, TSH, ESR, LDH, bHCG (if child bearing age), HIV
- examination of pharynx and oral cavity to evaluate Waldeyer's ring
- biopsy of peripheral lymph node/excisional biopsy
- bilateral bone marrow biopsy/aspiration
- CSF cytology in patients with high-grade lymphoma, primary CNS lymphoma, and testicular lymphoma
- CT neck/chest/abdomen/pelvis
- PET is preferred as opposed to gallium scan
- upper endoscopy for mucosa-associated lymphoid tissue (MALT).

Staging/Grading

The standard staging system is the Ann Arbor system as for Hodgkin's disease. The following is the Working Formulation and REAL classification for non-Hodgkins's disease.

Working Formulation	REAL
Low Grade:	**B-cell neoplasms**
A. Small lymphocytic	Lymphoplasmacytic-immunocytoma, MALT
B. Follicular, predominantly small cleaved cell	Follicular center, gr 1, mantle, MALT
C. Follicular mixed, small cleaved and large cell	Follicular center, gr 2, marginal zone/MALT
D. Gastrointestinal MALT	
E. Mantle zone (has short overall survival)	
F. CTCL (omitted in WC, present in NCI)	
Intermediate Grade:	
D. Follicular predominantly large cell	Follicular center, gr 3/diffuse small cell, mantle, MALT
E. Diffuse small cleaved cell (indolent by natural history)	Follicular center, gr 3/diffuse small cell, mantle, MALT
F. Diffuse mixed small and large cell	Large B cell, follicular center diffuse small, mantle, MALT
G. Diffuse large cell	Diffuse large B cell lymphoma
High Grade:	
H. Large cell immunoblastic (intermediate in NCI)	Diffuse large B cell lymphoma

(continued)

Working Formulation	REAL
I. Lymphoblastic	Presursor B lymphoblastic
J. Small noncleaved cell (Burkitt's/nonBurkitt's)	Burkitt's/Burkitt-like diffuse large B cell
I. Adult T cell leukemia-lymphoma (in NCI)	

CTCL: Cutaneous T cell lymphoma; MALT: mucosa-associated lymphoid tissue; NCI: National Cancer Institute; REAL: Revised European/American Lymphoma (classification); WC: Working classification.

Treatment

Low Grade, Stage I/II

- Recommended treatment is involved-field RT. The RT dose for nonbulky disease that regresses promptly is 30.6 Gy, with doses of 36–40 Gy for bulky or slowly regressing disease.
- Alternatively, observation until disease progression, or single-agent/combination chemotherapy may also be used to treat low-grade early-stage disease.

Low Grade, Stage III/IV

Recommended treatment is watch and wait. Symptomatic patients require chemotherapy CHOP [cyclophosphamide, hydroxydaunomycin (doxorubicin), Oncovin (vincristine), and prednisone] ×6–8 cycles. RT is reserved for palliative control of local symptoms; the recommended dose is 30.6–36 Gy.

Intermediate Grade, Stage I/II

- Traditionally, treatment for intermediate grade, early-stage NHL was CHOP[1] ×8. However, randomized data support treatment consisting

[1]CHOP: [**C**yclophosphamide/adriamycin (doxorubicin/**H**ydroxydoxorubicin)/vincristine (**O**ncovin)/ **P**rednisone].

of CHOP ×3 followed by involved-field RT (30 Gy for complete responders, 36–40 Gy for partial responders or bulky disease).
- The anti CD-20 monoclonal antibody rituximab (R) has demonstrated a clinical benefit for patients with B cell NHL and is routinely given with CHOP and as maintenance therapy.
- There are no randomized trials evaluating the use of RT in R-CHOP regimen, hence the role of RT has become somewhat controversial. Many treatment centers still advocate the routine use of involved-field RT to improve local control and disease-free survival, especially in the presence of bulky disease, while others reserve RT for treatment failures.

Intermediate Grade, Stage III/IV

Recommended treatment is combination chemotherapy ×6–8 cycles +/− rituximab. There is no clear role for consolidation with RT. However, 30–40 Gy may be used to improve local control in partial responders and those patients with initial bulky disease.

High Grade

High-grade non-Hodgkin's lymphoma occurs mostly in children and is often treated with similar regimens for acute lymphoblastic leukemia.

Primary CNS Lymphoma

Treatment of primary CNS lymphoma with combination chemotherapy and whole brain RT (WBRT) (45 Gy) improves tumor response rates and survival compared with WBRT alone, but is also associated with significant neurotoxicity, especially when radiation is followed by methotrexate. Methotrexate-based chemotherapy without WBRT regimens results in similar tumor response rates and survival compared to chemo+RT, and is associated with lower toxicity; however, no randomized trials have been performed.

Outcome

Low-grade stage I, II disease-free survival is 40%, overall survival is 40%; III, IV overall survival is 40%. High-grade stage I, II disease-free survival is 75%, overall survival is 85%; III, IV overall survival is 55%.

Complications

Complications are mainly treatment site–specific and can be:

- pulmonary pneumonitis and chronic fibrosis
- acute and chronic pericarditis, cardiomyopathy, myocardial infarction
- change in bowel habit with diarrhea, bowel, or rectal damage
- infertility for males and females
- radiation-induced malignancies.

ANNOTATED BIBLIOGRAPHY

EARLY-STAGE HODGKIN'S DISEASE

Carde et al. (1988). "Clinical stages I and II Hodgkins disease: a specially tailored therapy according to prognostic factors." *J Clin Oncol* 6(2):239–252 (EORTC H5F&H5U).

This study followed 494 patients with clinical stage I/II (CS I/II), prognostic assessment on age, histology (NS/LP—nodular sclerosis/lymphocyte predominant), ESR, mediastinal involvement in stage II. Patients were grouped as favorable F (age 40 or under, NS/LP, ESR 70 or less, up to three sites but had no mediastinal disease with stage II), unfavorable U (all other). All favorable (F) patients had a staging laparotomy (Sx), randomized to:

F: *Sxlap+splenectomy, if negative, then mantle vs. mantle+PA RT. Mantle and PA both got 40 Gy, did not cover splenic hilum in LAP patients.*

U: *Clinically U or lap positive, then TNI (STNI+inverted Y or oophoropexy) vs. sandwich chemorads (×3 MOPP-mantle-×3 MOPP) TNI to 40 Gy, mantle with MOPP 35 Gy.*

Results at 9 years in favorable group F DES 70% in both RT arms, proving if laparotomy negative, there is no need for para-aortic RT. Overall survival of 90% was equal between both RT arms. In unfavorable group U, disease-free survival favored combined modality therapy CMT) 66% vs. 83%, and overall survival 73% vs. 88% but not significant, and no difference in patients under 40 years old. Abdominal failure was 11% in laparotomy negative group.

Gospodarowicz et al. (1992). "Analysis of supradiaphragmatic clinical stage I and II Hodgkin's disease treated with radiation alone." *Int J Radiat Oncol Biol Phys* 22(5):859–865.

This study followed 250 patients with Hodgkin's lymphoma, CS supradiaphragmatic disease, treated with RT alone on the absence of adverse prognostic factors (age over 50 years, B symptoms, unfavorable histology MC/LD, large multiple myeloma). RT technique included involved-field RT in selected patients (those with upper neck involvement), mantle+PA RT. Results at 8 years showed the following:

Local Control	***Recurrence-free Survival***	***Cancer-specific Survival***	***Overall Survival***
95%	*72%*	*90%*	*83%*

A dose of 35 Gy was found to be sufficient for the clinical disease. Careful selection of clinically staged supradiaphragmatic stage I, II Hodgkin's disease patients can yield excellent results without requiring that staging laparotomy be routinely performed or the use of systemic chemotherapy as initial treatment. (They recommended mantle alone because of their previous studies that suggested a lower relapse rate.)

Carde et al. (1993). "Clinical staging versus laparotomy and combined modality with MOPP versus ABVD in early-stage Hodgkin's disease: the H6 twin randomized trials from the European Organization for Research and Treatment of Cancer Lymphoma cooperative Group." *J Clin Oncol* 11(11):2258–2272 (EORTC H6F&U).

This study followed 578 patients with CS I/II. Patients were stratified by a combination of B symptoms, number of nodal areas involved, bulk of mediastinal involvement, and erythrocyte sedimentation rate (ESR). Patients were grouped as favorable F (no B symptoms with ESR less than 50, yes B symptoms with ESR less than 30, nodal areas less than 3 sites, nonbulky mediastinum), unfavorable U (all other), randomized to:

F *Staging lap+splenectomy vs. clinical staging. If laparotomy negative and if NS/LP histology, then patients received mantle alone to 40 Gy. If mixed cellularity/lymphocyte depleted histology, then patients received STNI+splenic RT 40 Gy. The CS patients received STNI+splenic RT. If laparotomy positive, patients were transferred to unfavorable U group.*

U *No lap, all CS patients ×3 MOPP-mantle RT-×3 MOPP vs. ×3 ABVD-mantle RT-×3 ABVD.*
Mantle RT 35 Gy, MOPP (mechlorethamine 6 mg/m², vincristine 1.4 mg/m² up to 2 mg on day 1, 8 procarbazine 100 mg/m²,

prednisone 40 mg/m^2 on days 1–14 every 28-day cycle), ABVD (doxorubicin 25 mg/m^2, bleomycin 10 mg/m^2, vinblastin 6 mg/m^2, dacarbazine 250 mg/m^2 on days 1,15 every 28-day cycle).

Results at 6 years in the favorable group F showed disease-free survival of 89% vs. 78% were better in laparotomy vs. clinical staging arms; however overall survival of 93% vs. 89% was similar in both laparotomy and clinical arms (this was because of salvage). In the unfavorable group U, the ABVD arm had superior results with disease-free survival 76% vs. 88% significant, but overall survival 85% vs. 91% not significant. Pulmonary function tests (PFTs) were worse in the ABVD arm but recovered in the second year of follow-up. There were no changes in left ventricular ejection fraction (LVEF) or cardiac symptoms in either arm. Gonadal toxicity was less in the ABVD arm.

Conclusions: Staging laparotomy before STNI may be deleted in favorable F patients at no cost to disease-free survival/overall survival. In unfavorable U patients ABVD achieved better results than MOPP, at lower hematologic and gonadal toxicity.

Noordijk et al. (1994). "Preliminary results of the EORTC-GPMC controlled clinical trial H7 in early-stage Hodgkin's disease. EORTC Lymphoma Cooperative Group. Groupe Pierre-et-Marie-Curie." *Ann Oncol 5 Suppl* 2:107–112 (EORTC H7).

This study followed 770 patients, stage I/II. Patients were enrolled as very favorable VF (stage IA, female, under 40 years, NS/LP, ESR less than 50, no mediastinal mass), favorable F (all other), unfavorable UF (over 50 years, more than 3 nodal sites, ESR greater than 50 if A or greater than 30 if B, yes mediastinal mass). Patients were randomized to:

VF	*None, all received mantle RT alone.* *Mantle RT 40 Gy for involved areas, 36 Gy to uninvolved areas.*
F	*STNI vs. ×6 EBVP+involved-field RT.* *STNI received spleen/PA to 36 Gy, involved-field RT following chemotherapy 36–40 Gy.*
U	*×6 EBVP+involved-field RT vs. ×6 MOPP/ABV+involved-field RT.*

Results at 6 years were as follows:

	Disease-free Survival	*Overall Survival*
VF, mantle	*68*	*97*
F (STNI)	*81*	*96*
F (EBVP+IF RT)	*92*	*98*
U (EBVP+IF RT)	*69*	*82 (closed due to poor results)*
U (M/A+IF RT)	*88*	*89*

VF with M only resulted in greater failures than anticipated; as such EORTC recommends EBVP+IF RT. In the favorable group, STNI and chemo+involved-field RT had the same overall survival. The unfavorable group, due to an increased number of relapses in the EBVP arm, was stopped even though overall survival was the same. Further study H8 has been designed using the MOPP/ABV scheme for unfavorable patients.

Specht et al. (1998). "Influence of more extensive radiotherapy and adjuvant chemotherapy on long-term outcome of early-stage Hodgkin's disease: a meta-analysis of 23 randomized trials involving 3,888 patients. International Hodgkin's Disease Collaborative Group." *J Clin Oncol* 16(3):830–843.

In this study 1974 patients with Hodgkin's lymphoma in eight randomized trials of more vs. less extensive radiotherapy and 1688 patients in 13 trials of RT versus RT+CT alone were analyzed to assess the effect of long-term outcome of early stage Hodgkin's lymphoma. Results at 10 years showed the following:

	Local Failure (%)	*Overall Survival (%)*
Less RT	*43*	*77*
More RT	*31 ss*	*77*
RT alone	*33*	*77*
RT+CT	*16 ss*	*79*

More extensive RT fields or the addition of chemotherapy to RT in the initial treatment of early stage Hodgkin's lymphoma had a large effect on disease control, but only a small effect on overall survival. Recurrences could be prevented by more extensive RT or by additional chemotherapy.

ADVANCED-STAGE HODGKIN'S DISEASE

Fabian et al. (1994). "Low-dose involved field radiation after chemotherapy in advanced Hodgkin disease. A Southwest Oncology Group randomized study." *Ann Intern Med* 120(11):903–912 (SWOG).

In this study 278 patients with clinical/pathologic stage III, IV Hodgkin's lymphoma who achieved complete response after 6 cycles of MOP-BAP were randomly assigned to observation vs. low-dose RT. RT was given 1000–1500 cGy to involved organ and 2000 cGy to lymph node areas. Results at 5 years showed the following:

	Disease-free Survival (nodular sclerosis) (%)	***Disease-free Survival (multiple myeloma) (%)***	***Disease-free Survival (all patients) (%)***	***Overall Survival (subgroup/ all patients) (%)***
Observation	*60*	*57*	*No*	*86*
Low-dose RT	*82 ss*	*75 ss*	*difference*	*86*

Low-dose involved-field RT after MOP-BAP chemotherapy in patients with stage III, IV HL did not prolong disease-free survival or overall survival in randomized patients. However, disease-free survival was prolonged in several subgroups of patients, most prominently in those with nodular sclerosis histology.

Hughes-Davies et al. (1997). "Stage IA-IIB Hodgkin's disease: management and outcome of extensive thoracic involvement." *Int J Radiat Oncol Biol Phys* 39(2):361–369.

In this study 172 patients with Hodgkin's disease clinical stage IA-IIB and massive mediastinal mass treated in three groups lap+RT vs. lap+chemo+RT vs. chemo+RT (94% to mantle only) were retrospectively analyzed. RT was given 180–200 cGy to 36 Gy with areas of initial involvement boosted to 40–45 Gy; if large numbers of nodal sites above diaphragm mantle treated to 40–45 Gy, patients received whole lung or whole heart treated 150 cGy to 16.5 Gy (the whole heart rarely <20 Gy). Chemotherapy was given MOPP, ChiVPP, later with ABVD ×6 cycles. Patients did not undergo laparotomy, and all chemo was given before RT. Results at 10 years were as follows:

	Local Control (above diaphragm) (%)	*Local Control (below diaphragm) (%)*	*Local Control (total) (%)*	*Disease-free Survival (%)*	*Overall Survival (%)*	*Pneu-monitis (%)*	*2nd Cancer (%)*
Lap+RT (Lap±)	*57*	*--*	*55*	*54*	*84*	*11*	*2*
Chemo+RT	*93*	*96*	*89*	*88*	*89 ns*	*17*	*21*

The introduction of chemo+RT has been associated with improvement of disease-free survival; no benefit of overall survival. The high risk of second cancer in the chemo+RT group suggests careful long-term surveillance is required.

Loeffler et al. (1998). "Meta-analysis of chemotherapy versus combined modality treatment trials in Hodgkin's disease. International Database on Hodgkin's Disease Overview Study Group." *J Clin Oncol* 16(3):818–829.

In this study 1740 patients with advanced stage Hodgkin's lymphoma from 14 trials compared adjuvant RT to programs with either more cycles of chemotherapy or additional chemotherapy combinations. Results at 10 years showed the following:

	Local Control	*Overall Survival*		*Local Control*	*Overall Survival*
No RT		*No*	***CT alone***	*No*	*8% more*
RT	*11% less ss*	*difference*	***CT+RT***	*difference*	

Combined modality treatment in patients with advanced stage Hodgkin's lymphoma overall has a significantly inferior long-term survival outcome than CT alone, if CT is given over an appropriate number of cycle. The role of RT in this setting is limited to specific indications.

Aleman et al. (2003). "Involved-field radiotherapy for advanced Hodgkin's lymphoma." *N Engl J Med* 348(24):2396–2406 (EORTC 20884).

In this study 736 patients enrolled with Hodgkin's disease stage III/IV complete response after MOPP/ABV chemotherapy were randomized to observation vs. involved-field RT. RT was given 150–200 cGy/fraction to 16–24 Gy to all initially involved extranodal areas and 24 Gy to all nodal areas. Patients with partial response after ×6 MOPP/ABV were treated with involved-field RT to all initially involved lymph nodes and all initially involved organs. RT was given to 18–24

Gy to extranodal sites and 30 Gy to nodal sites +/– boost 4–10 Gy when necessary. At median follow-up of 6 years the results showed that:

	Relapse-free Survival (%)	***Event-free Survival (%)***	***Overall Survival (%)***
NoRT	*85*	*82*	*89*
CR-IFRT	*87*	*79*	*85*
PR-IFRT	*--*	*80*	*87*

Involved-field RT does not improve the treatment results in patients with stage III/IV Hodgkin's disease who reach complete response after standard chemotherapy MOPP/ABV. However, in partial response after ×6 cycles chemotherapy, additional involved-field RT induces similar event-free survival and overall survival as those of complete response patients.

NON-HODGKIN'S LYMPHOMA

Horning SJ, Rosenberg SA. (1984). "The natural history of initially untreated low-grade non-Hodgkin's lymphomas." *N Engl J Med* 311(23): 1471–1475 (Stanford).

In this study 83 patients with non-Hodgkin's lymphoma low-grade (all histology) stage III, IV, initially managed without therapy were followed. Results at 10 years showed the following:

Treatment for:	***Progression (%)***	***Regression (%)***	***Transform (%)***	***Overall Survival (%)***
	61	*12*	*19*	*73*

Median time for treatment was 72 months for small lymphocytic, 48 months for follicular predominantly small, but 16.5 months for follicular mixed. This suggested that follicular mixed may require up-front treatment. Spontaneous regressions were also seen in 30%.

Gospodarowicz M, Sutcliffe S, Brierley J. "Involved Field Radiotherapy in Clinical Stage I-II Low Grade Lymphoma" in Proceedings of the 05th International Conference on Malignant Lymphoma, Lugano, Switzerland, 1993 (Princess Margaret Hospital, Toronto).

In this study 283 patients with low-grade stage I and II, non-Hodgkin's lymphoma were treated at Princess Margaret Hospital with involved-field RT. Results showed the following:

	Disease-free Survival (%)	*Overall Survival (%)*	*Cause-Specific Survival (%)*
10 years	*52*	*65*	*77*
15 years	*47*	*57*	*71*
20 years	*47*	*44*	*61*

A plateau in relapse rates can be seen after 10 years. But due to prolonged survival after failure, a plateau in cause-specific survival is not expected.

Mac Manus MP, Hoppe RT. (1996). "Is radiotherapy curative for stage I and II low-grade follicular lymphoma? Results of a long-term follow-up study of patients treated at Stanford University." *J Clin Oncol* 14(4): 1282–1290.

In this study 177 patients with non-Hodgkin's lymphoma low-grade (follicular small cleaved, follicular mixed) stage I, II were treated with RT all; only 9 patients received adjuvant chemotherapy and were analyzed retrospectively. RT was given to involved field (IF), extended field (EF), total nodal irradiation (TNI) 000 cGy to 35–50 Gy. Chemotherapy was given with C-MOPP. Results at 20 years were as follows:

Median Survival	*10-yr Disease-free Survival (%)*	*20-yr Disease-free Survival (%)*	*10-yr Overall Survival (%)*	*20-yr Overall Survival (%)*
14 yrs	*44*	*37*	*64*	*35*

RT remains the treatment of choice for low-grade early stage follicular non-Hodgkin's lymphoma. Patients who have remained disease free at 10 years are unlikely to relapse. Field size did not make any difference in overall survival.

These studies indicate that about 40%–50% of patients with low-grade early-stage disease may be cured if they are young and have small-volume stage I disease. There is controversy regarding appropriate fields. Those treated with less than total nodal irradiation (TNI) often relapse in nodal sites outside the field, prompting some to recommend TNI. This is supported by the retrospective Stanford data that found that freedom from relapse was higher in patients treated with TNI versus IF or EF (67% vs. 36% at 10 years), but there was no overall survival difference (75% vs. 65% at 10 years).

Miller et al. (1998). "Chemotherapy alone compared with chemotherapy plus radiotherapy for localized intermediate- and high-grade non-Hodgkin's lymphoma." *N Engl J Med* 339(1):21–26 (SWOG 8737).

In this study 401 patients with intermediate-/high-grade stage I, II nonbulky non-Hodgkin's lymphoma were randomized between CHOP ×8 versus CHOP ×3+IF (involved-field) RT. RT was given 40 Gy with boost to 50 Gy for residual disease. Results at 5 years showed the following:

	Disease-free Survival (%)	***Overall Survival (%)***	***Toxicity (%)***
CHOP ×8	*64*	*72*	*40*
CHOP ×3+IF RT	*77 ss*	*82 ss*	*31*

No difference in disease-free survival was due to excess cardiac death in CHOP alone, but improved overall survival. Patients with stage I, age under 60 years, normal KPS, had 97% 4-year overall survival.

Horning et al. (2004). "Chemotherapy with or without radiotherapy in limited-stage diffuse aggressive non-Hodgkin's lymphoma: Eastern Cooperative Oncology Group study 1484." *J Clin Oncol* 22(15): 3032–3038 (ECOG 1484).

In this study 345 patients with intermediate-grade bulky or extranodal stage I and nonbulky stage II non-Hodgkin's lymphoma were randomized to CHOP ×8 versus CHOP ×8+30 Gy involved-field RT (40 Gy to partial responders). Results at 6 years showed the following:

	Disease-free Survival (%)	***Overall Survival (%)***	
CHOP ×8	*58*	*70*	
CHOP ×8+RT	*73*	*84*	*Chemo+RT improved disease-free survival/overall survival.*

NOTES