# Radiation Therapy for Extranodal Lymphomas


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**Outline**

1. Definition.
2. Incidence
3. Diagnosis
4. Stage
5. Treatment/Sites
6. Outcome
7. Toxicity
8. Future directions
9. Conclusion.

# Extra nodal lymphomas: ENLs

ENLs: Lymphoma arising in an extranodal organ/site

- Common with NHL, 25-40% (1/3rd )of NHL cases.

- Any organ or site can be involved.

**Common sites:**

GI(stomach, Intestine)- 30-40% of ENLs and 4-20% of NHLs,

In Western countries, the most common localization is GI, Stomach (approximately 50-60%), followed by the small (30%) and large intestine (around 10%),

2nd common site -Head and Neck, the Ann Arbor staging system considers tonsils and the Waldeyer's ring as lymphatic localizations, there is controversy about their designation as ENLs, CNS, Testicular and Cutaneous lymphomas,

- ENLs arise from B-cell or T /NK cell.

Primary extranodal presentation is variable across the different B-cell histologic subtypes, encompassing the majority of Burkitt's lymphomas (BL), up to 50% of DLBCL and less than 10% of follicular lymphomas (FL).

The distribution of histologic types may be site specific: Testis or central nervous system (CNS)- nearly all cases are DLBCL.

GI tract- a wide spectrum of lymphoma types. comprising DLBCL, MZL of mucosa-associated lymphoid tissue (MALT), BL, mantle cell lymphoma (MCL), and FL.

T cell: NK/T cell nasal, Cutaneous T cell lymphomas.

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# Penile Ulcer as the Unusual Initial Presentation of Nasal NK/T Cell Lymphoma

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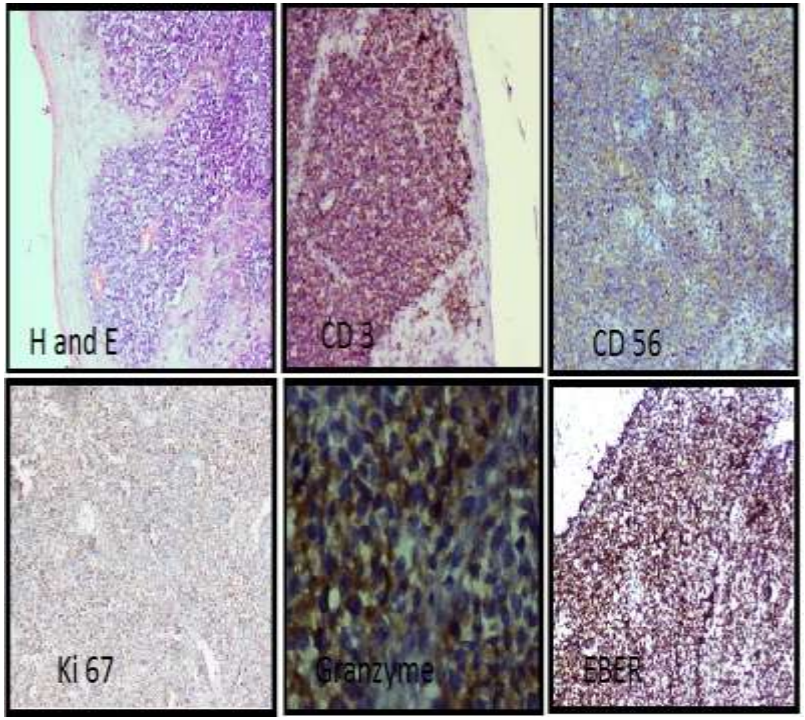
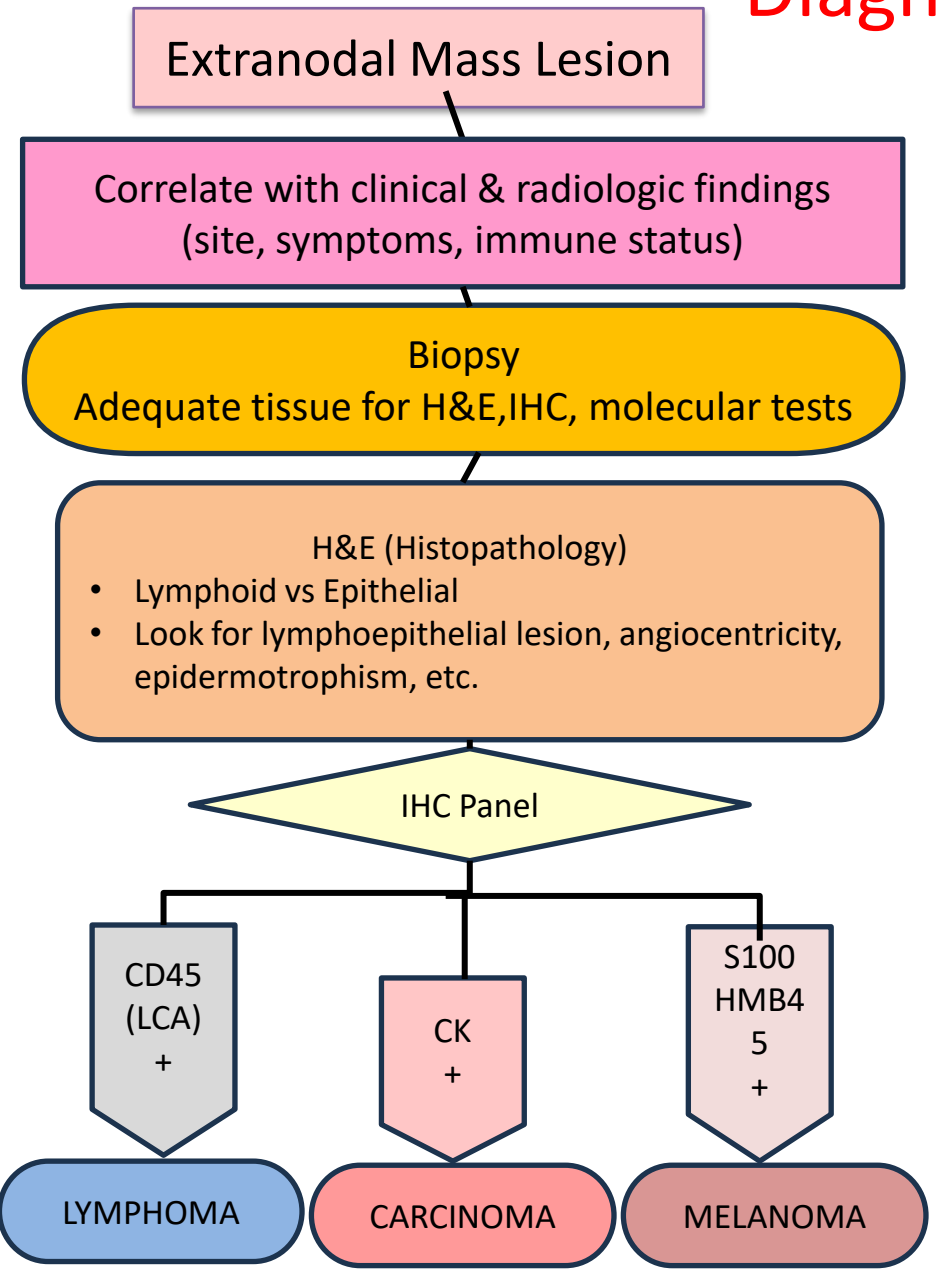
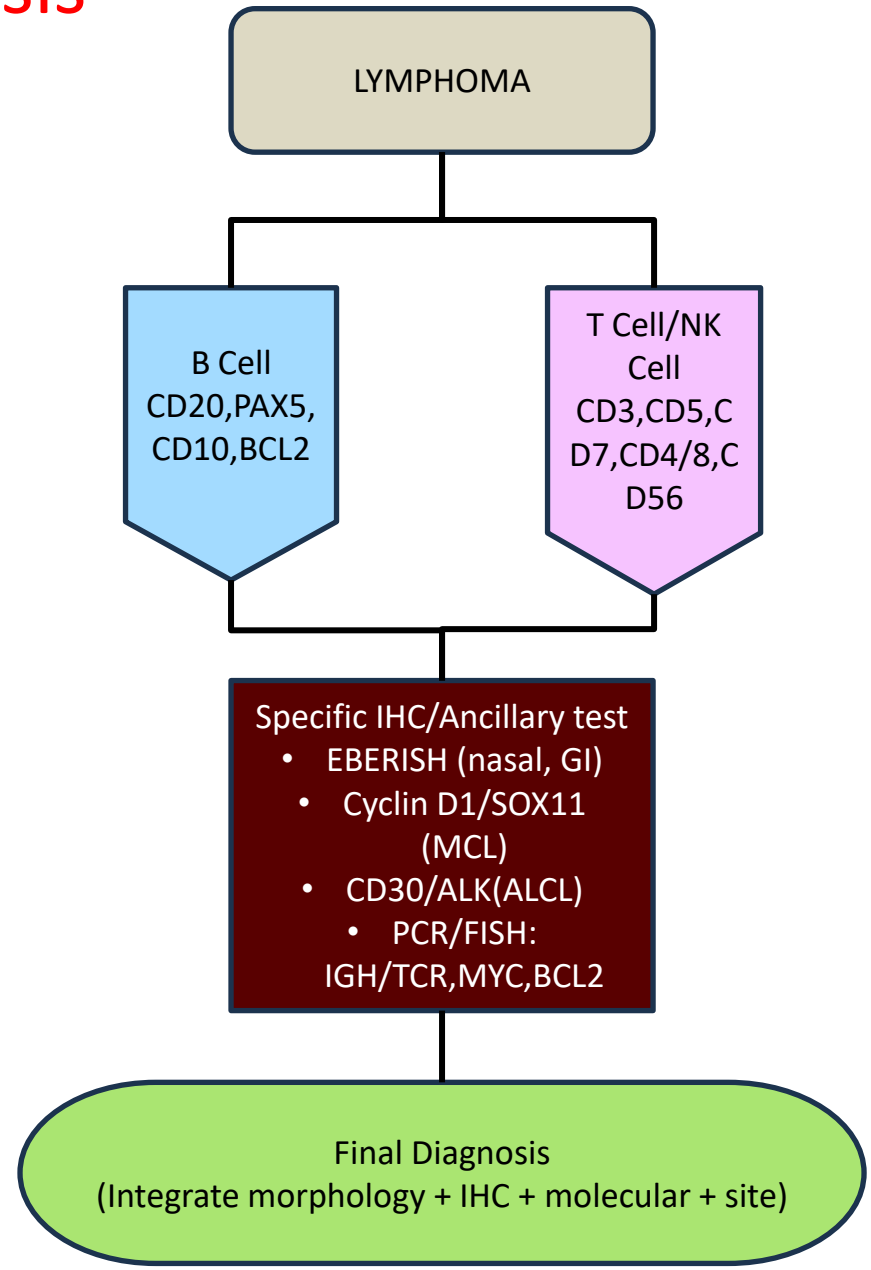
**Abstract**

Extranodal natural kill[er] (NK)/T cell lymphoma is a highly aggressive non-Hodgkin lymphoma that predominantly affects the upper aerodigestive tract. The nasal type accounts for ~80% of cases of NK/T cell lymphomas. In advanced stages, the disease can disseminate to various sites such as skin, testis, eyes, gastrointestinal tract, and soft tissue. NK/T cell lymphoma presenting as lesion in penis is extremely rare. While reviewing the published literature, we found only three reported cases of NK/T cell lymphoma involving the penis. Among them, none was primary NK/T cell lymphoma of

# Diagnosis


Extranodal Mass Lesion
Correlate with clinical & radiologic findings (site, symptoms, immune status)
Biopsy
Adequate tissue for H&E,IHC, molecular tests
H&E (Histopathology)
• Lymphoid vs Epithelial
• Look for lymphoepithelial lesion, angiocentricity, epidermotrophism, etc.
IHC Panel
CD45 (LCA) +
CK +
S100 HMB45 +
LYMPHOMA
CARCINOMA
MELANOMA


LYMPHOMA
B Cell CD20,PAX5, CD10,BCL2
T Cell/NK Cell CD3,CD5,CD7,CD4/8,CD56
Specific IHC/Ancillary test
• EBERISH (nasal, GI)
• Cyclin D1/SOX11 (MCL)
• CD30/ALK(ALCL)
• PCR/FISH: IGH/TCR,MYC,BCL2
Final Diagnosis
(Integrate morphology + IHC + molecular + site)

**Key Histologic Patterns**

- **Diffuse infiltrate:** DLBCL, T-cell lymphoma
- **Follicular pattern:** Follicular lymphoma
- **Lymphoepithelial lesions:** MALT lymphoma
- **Starry sky:** Burkitt lymphoma
- **Angiocentric/angiodestructive:** NK/T- cell lymphoma

**Molecular & Ancillary Tests**

- **Clonality testing:**
  - PCR for IGH / TCR rearrangements
- **Translocations:**
  - *t(11;18)(q21;q21)* in gastric MALT
  - *MYC, BCL2, BCL6* in double/triple-hit lymphomas
- **EBER (ISH):** Nasal NK/T-cell, EBV+ DLBCL
- **Flow cytometry:** When fresh tissue available

| IHC Markers | Common Sites |
|---|---|
| **B-cell:** CD20, PAX5, CD79a | GI, thyroid, breast |
| **T-cell:** CD3, CD5, CD7, CD4/8 | Skin, gut, nasal cavity |
| **MALT:** CD20+, CD5-, CD10-, BCL6- | Stomach, salivary gland |
| **DLBCL:** CD20+, BCL6+, MUM1 variable | Any extranodal site |
| **NK/T-cell:** CD56+, EBER+, cytoplasmic CD3ε | Nasal/upper aerodigestive |
| **Plasmablastic:** CD138+, MUM1+, EBER+, CD20– | Oral cavity, HIV+ patients |

# Extranodal B-cell Lymphomas (WHO 5th Edition)

- Extranodal Marginal Zone Lymphoma (MALT type): Stomach, salivary gland, thyroid – CD20+, CD79a+, BCL2+, CD5–, CD10–
- Diffuse Large B-cell Lymphoma (DLBCL), NOS: GI, CNS, testis – CD20+, BCL6+, MUM1+/–
- Primary CNS DLBCL: Brain, meninges – CD20+, BCL6+, MUM1+, MYD88 mutation
- Primary Cutaneous DLBCL, leg type: Skin (leg) – CD20+, MUM1+, BCL2+
- Primary Mediastinal (Thymic) Large B-cell Lymphoma: Mediastinum – CD20+, CD23+, MUM1+
- Plasmablastic Lymphoma: Oral cavity, GI – CD138+, MUM1+, EBER+, CD20–
- Burkitt Lymphoma: Jaw, ileocecal – CD20+, CD10+, BCL6+, Ki67 ≈100%
- EBV-positive DLBCL: Elderly, skin, GI – CD20+, EBER+, CD30+
- Primary Effusion Lymphoma (HHV8+): Serous cavities – HHV8+, CD138+, EBER+, CD20–

# Extranodal T/NK-cell Lymphomas (WHO 5th Edition)

- Extranodal NK/T-cell Lymphoma, Nasal Type: Nasal cavity, palate – CD3ε+, CD56+, EBER+, cytotoxic markers+
- Enteropathy-associated T-cell Lymphoma (EATL): Small intestine – CD3+, CD7+, CD103+, CD30+
- Monomorphic Epitheliotropic Intestinal T-cell Lymphoma (MEITL): Jejunum, ileum – CD3+, CD8+, CD56+
- Hepatosplenic T-cell Lymphoma: Liver, spleen – CD3+, CD56+, TCR-γδ+
- Subcutaneous Panniculitis-like T-cell Lymphoma: Subcutaneous fat – CD3+, CD8+, βF1+, Granzyme B+
- Primary Cutaneous ALCL: Skin – CD30+, CD4+, ALK– (except ALK+ variant)
- Primary Cutaneous γδ T-cell Lymphoma: Skin – CD3+, CD56+, TCR-γδ+, cytotoxic+
- Peripheral T-cell Lymphoma, NOS (Extranodal): GI, skin – Variable T-cell markers, CD30+ subset
- Adult T-cell Leukemia/Lymphoma (HTLV-1+): Skin, GI – CD3+, CD4+, CD25+, FoxP3+, HTLV-1+

# Staging: Ann-Arbor staging

| Stage | |
|---|---|
| I | Involvement of a single lymphatic region (I) or localised involvement of single extralymphatic organ or site (IE) |
| II | Involvement of two or more lymphatic regions on the same side of the diaphragm (II) or localised involvement of a single extralymphatic organ or site and of one or more lymphatic regions on the same side of the diaphragm (IIE) |
| III | Involvement of lymphatic regions on both sides of the diaphragm |
| IV | Diffuse or disseminated involvement of one or more extralymphatic organs with or without lymphatic involvement |

# Organ confined stage IE-IIE.

Slight variation depending on the site.

- EMZL of Stomach: Lugano modified Ann arbor staging. (IE-T1, T2, T3, No/IIE-T1-T3, N1/T4 No.., N1,N2..)
- NK/T cell lymphoma

  IE-Localised(limited) /extensive invasion.
- Bone : I-IIE- Single lesion+/-regional node / IVE(Polyostotic)Multiple lesion/bones.
- PCNLS: Risk categorization.

  IELSG. MSKCC..etc

# Management principle

## General principles:

In line with nodal lymphomas

- Mainly as Indolent vs Aggressive.

- Mainly difference in relation to

  1. RT –intent, 2. Timing, 3. Field definition and 4. Dose.

- Indolent MZL, FL,  -(MALT)
- Aggressive: DLBCL, NK/T cell lymphoma, PCNSL and Testicular ENLs.

IJROBP: Volume 92 Number 1, 2015,
Clinical Oncology 28 (2016) 62-68

# General prin…..

- Indolent lymphomas: MZL, FL
- Localised and organ confined,

**RT as sole Local therapy is curative modality,**

Although indolent ENL is highly responsive to systemic therapy, the curative potential of standard-dose systemic therapy has not been demonstrated

As adjuvant after chemotherapy or as salvage

Palliation: Low dose radiation

**Dose: RT: 20-30Gy, 1.5Gy/#- 2-3 weeks,**

**12Gy/4# still needs robust data.**

**4Gy is effective for palliation.**

# Aggressive localized ENLs

Systemic chemotherapy is primary modality.

RT mainly as consolidative or salvage: potentially translating into an improvement in progression-free and overall survival

Dose: post chemotherapy CR: 30-36GY (same dose in relapse/recurrence)

- PR: 40-45 Gy
- Unsuitable for CT: Monotherapy-45-55Gy
- Palliation: lesser dose is sufficient.
- PCNSLs, NK/T cell Ls, cutaneous Lymphomas different approach to RT dosing.

# Volumes:

**Involved Site Radiotherapy** : ISRT (EFRT-> IFRT-> INRT/ISRT)

ISRT was introduced by the ILROG as a slightly larger treated volume, intended to allow for commonly encountered uncertainties

**GTV:** If RT is sole therapy : GTV tumour evident at diagnosis

RT after course of chemotherapy:

1. **GTV pre-chemo** 2. GTV post-chemo.

**CTV:** Macroscopic disease evident at CT simulation and potential sites of microscopic disease.

ENLs usually multifocal---so whole organ to be treated.

ITV: CTV+margin— uncertainties in size, shape and position.

4D-CT/ fluoroscopy determine –ITV.

**PTV(ITV):** Expansion of the CTV. Uncertainties –patient positioning and beam alignment. Department protocol-0.5-1cm.

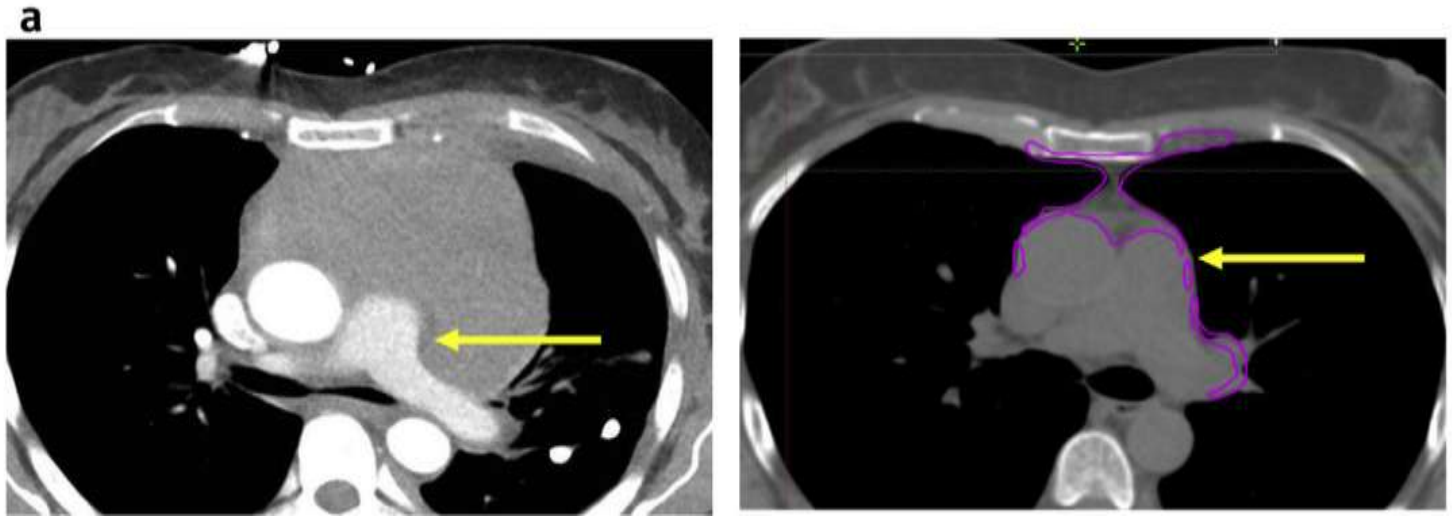
**Requisites:**

- CT based 3-dimensional outlining is recommended in all cases

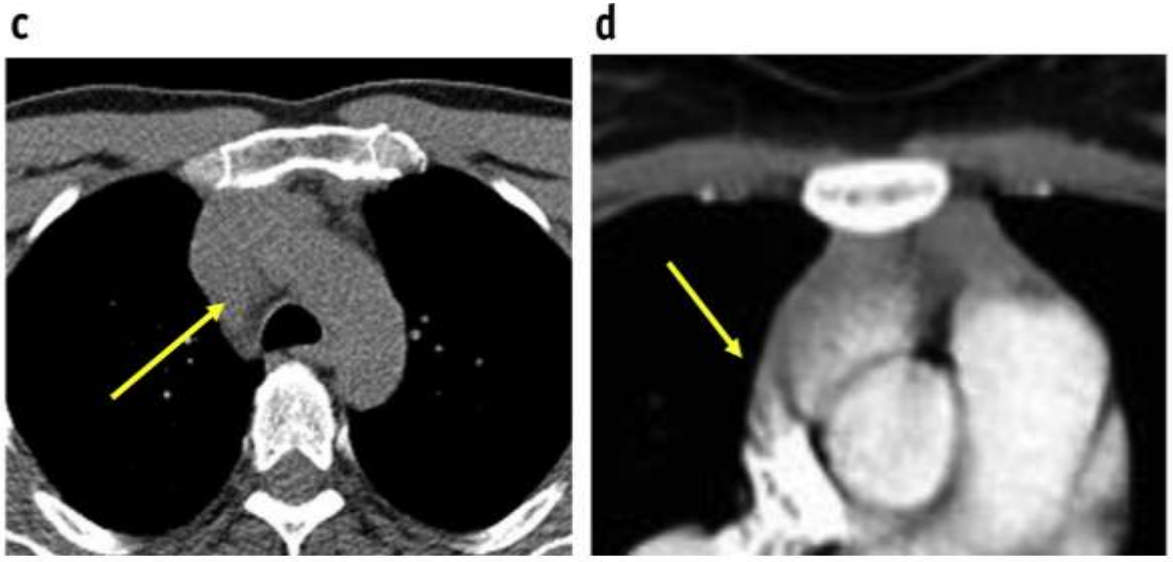
- should be based on all clinical information and imaging studies available, both pre- and post-chemotherapy.

- CT, PET and/or MRI should be available, especially when volumes are reduced to less than an entire extra-nodal structure.
- Imaging and volume uncertainties should be studied.

# Imaging uncertainties:

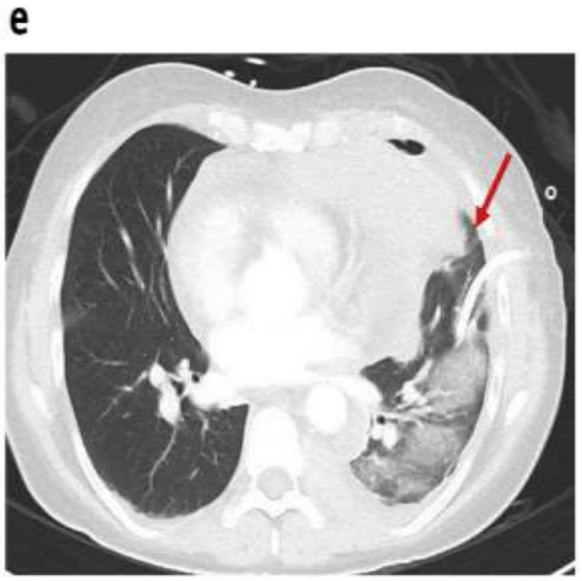


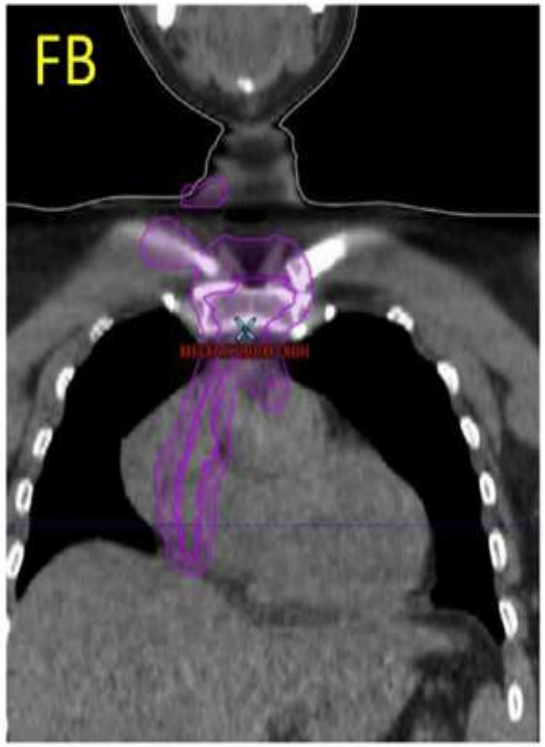

(a) anatomic shifts after chemotherapy (note the shift of the aorta and pulmonary artery);

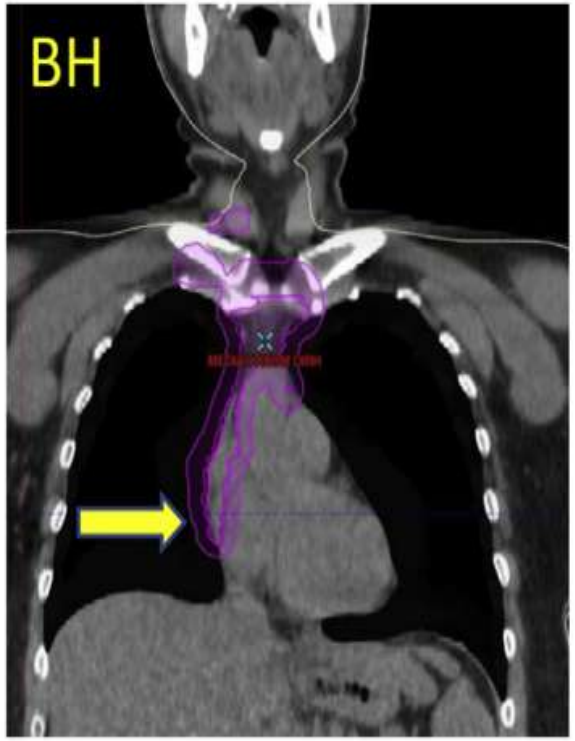



(c) poor anatomic definition with noncontrast computed tomography; (d) ill-defined extent of pericardial infiltration;

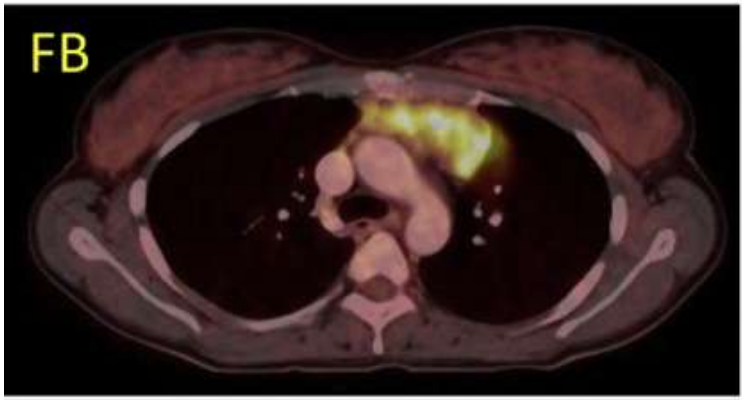
(e) uncertainty whether lung is displaced or infiltrated.

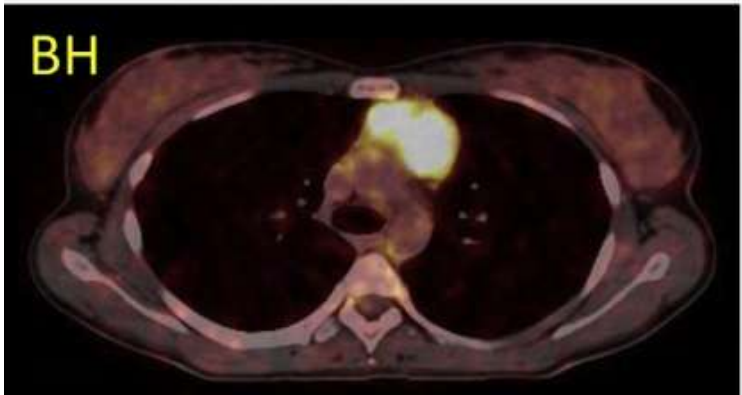





Heart and mediastinal structures in breath-hold (BH) and free-breathing (FB);




positron emission tomography/computed tomography illustrates blurring and widening of a mediastinal mass in FB.

# Important sites and types ( Site wise ……)

- Gastric lymphoma.
- Waldeyars ring lymphoma and Mediastinal lymphomas
- Extranodal NK/T cell lymphoma
- Testicular lymphoma
- PCNSL
- Primary cutaneous lymphoma, CTCL, CBCL.

Annals of Oncology: Volume 27 | Supplement 5 | September 2016

## Gastric Lymphoma:

>2/3rd will have evidence of H. pylori infection, (either on the biopsy, by C14 urease breath test and/or stool antigen).

Treatment: prompt eradication therapy with a proton pump inhibitor plus dual or triple antibiotics.

**H. pylori eradication alone results in gastric MALT lymphoma regression in 75% of cases.**

At least 12 months of endoscopic surveillance is recommended before defining refractory disease and switching to another treatment in most guidelines.
There is a lower response rate to H. pylori eradication in patients carrying the t(11;18) translocation and H. pylori negative cases, and radiotherapy is considered standard of care

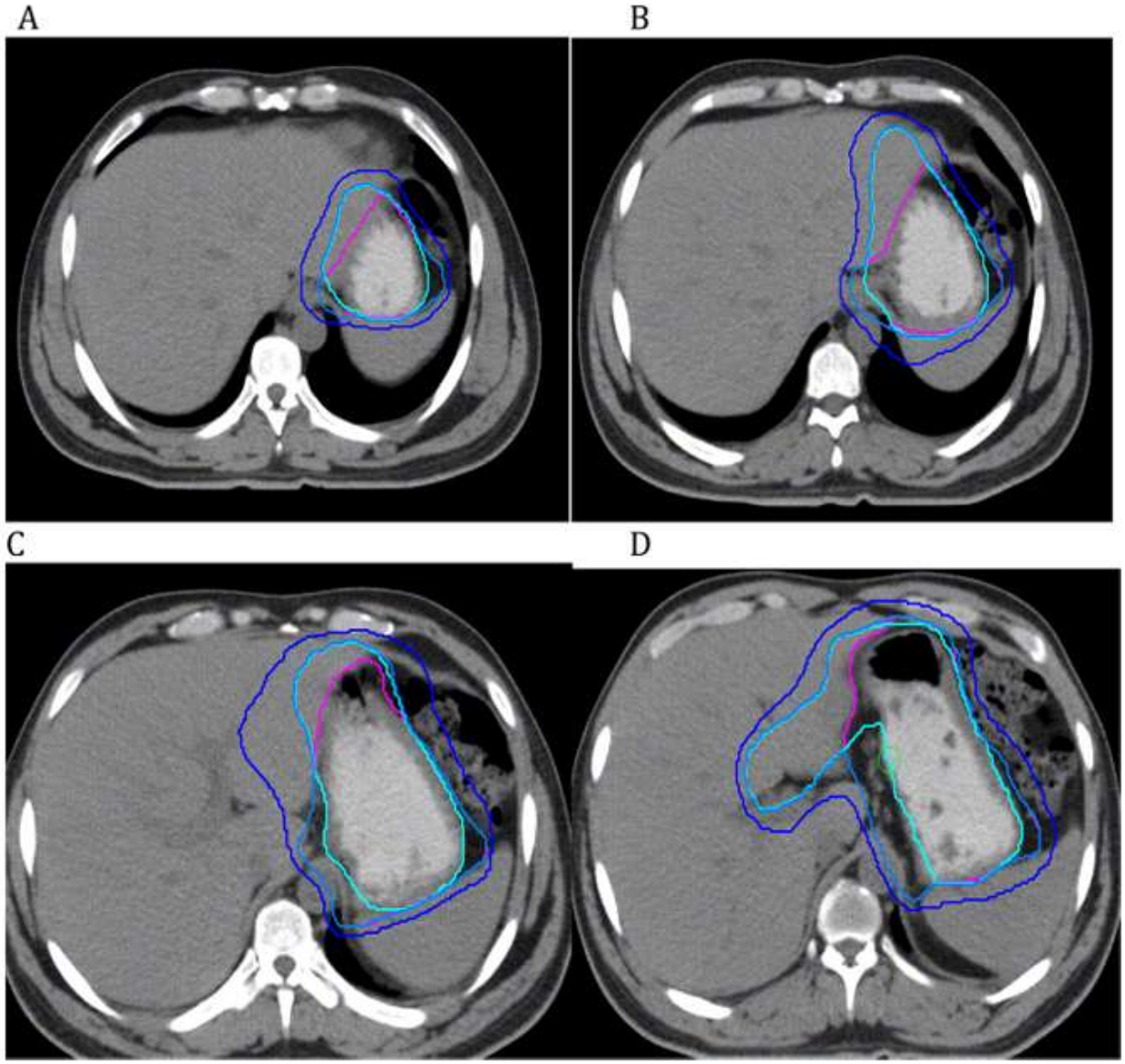
Am J Hematol. 2023;98:1645–1657

# Gastric MZL

CTV: pink,

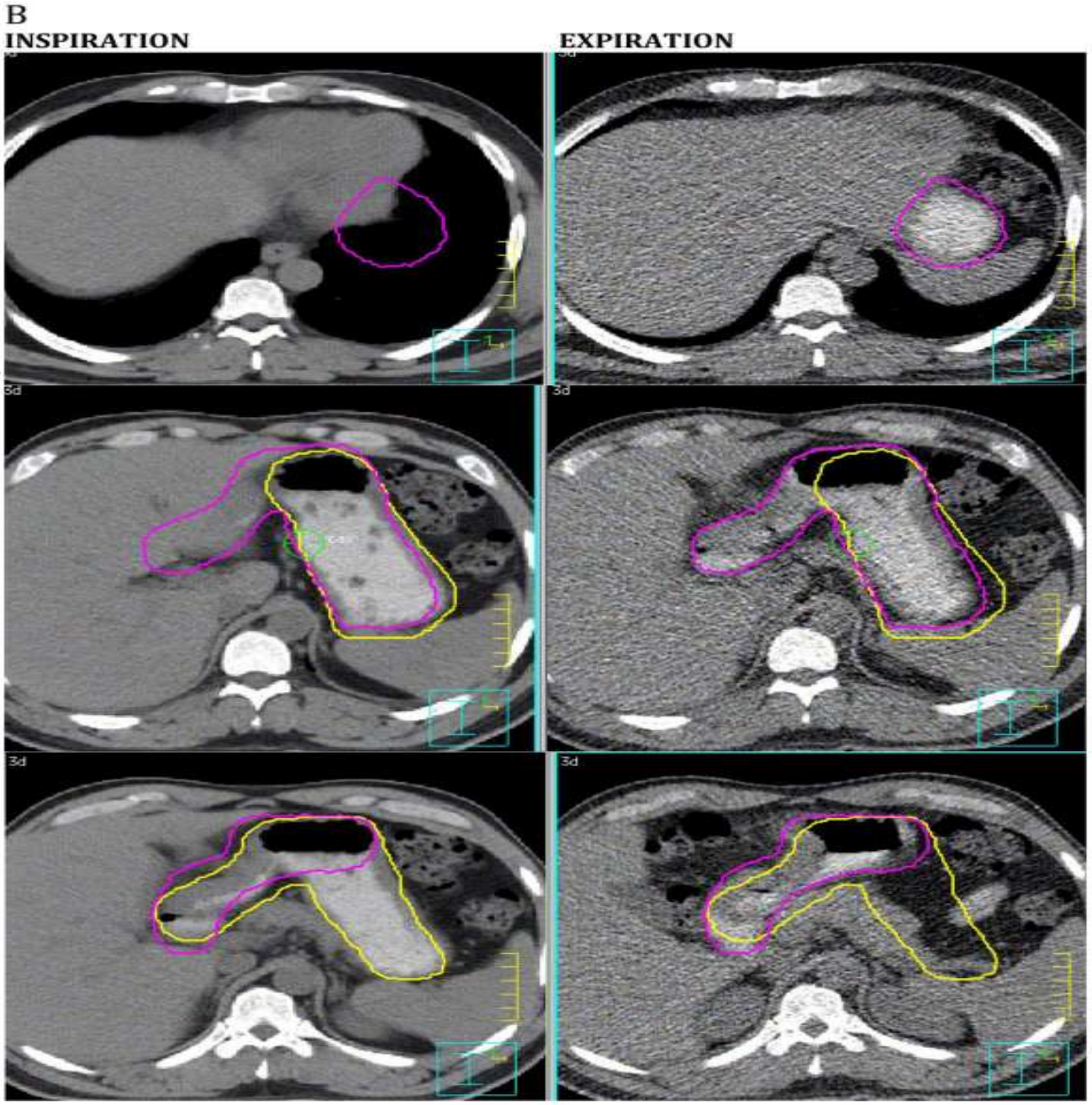
ITV: after 4-D CT, light blue.

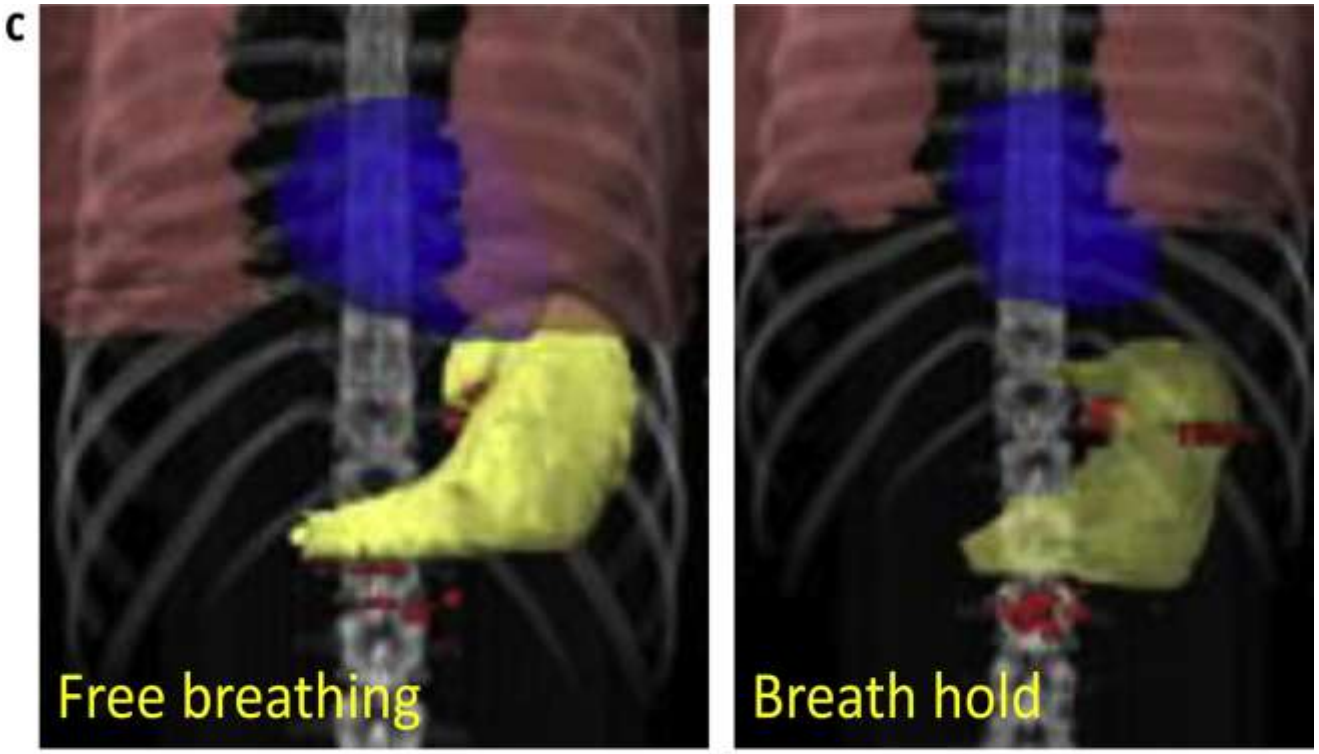
PTV: dark blue.

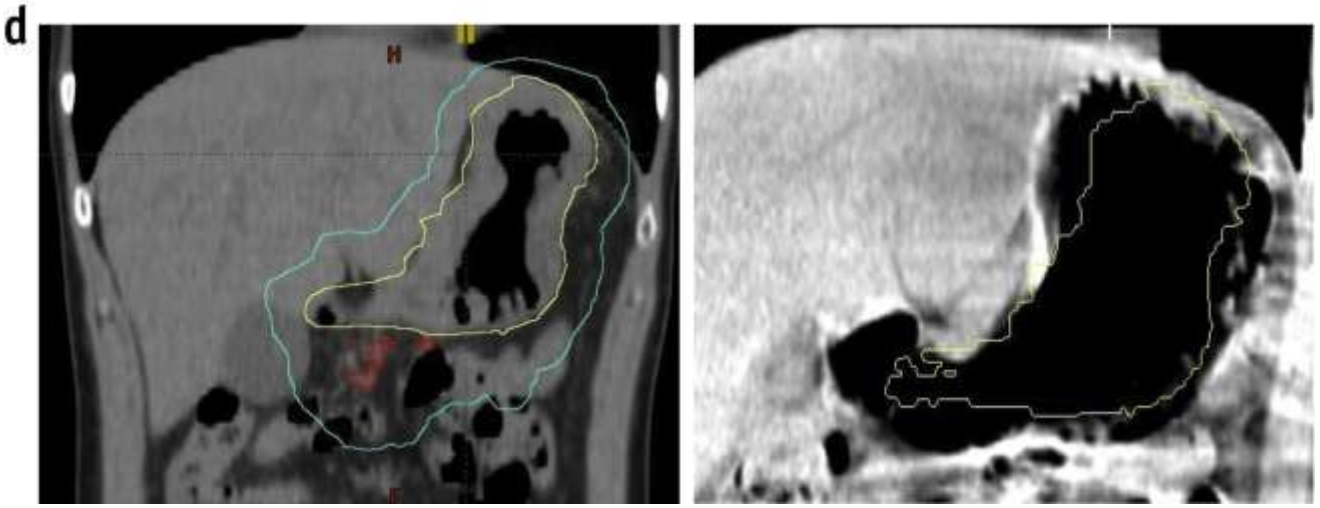



IJROBP; Vol 92,1. 2015. IJROBP: Volume 107 Number 5 2020,.

(B) Volumes for gastric lymphoma. Effect of respiration: CTV at inspiration, yellow; at expiration, pink

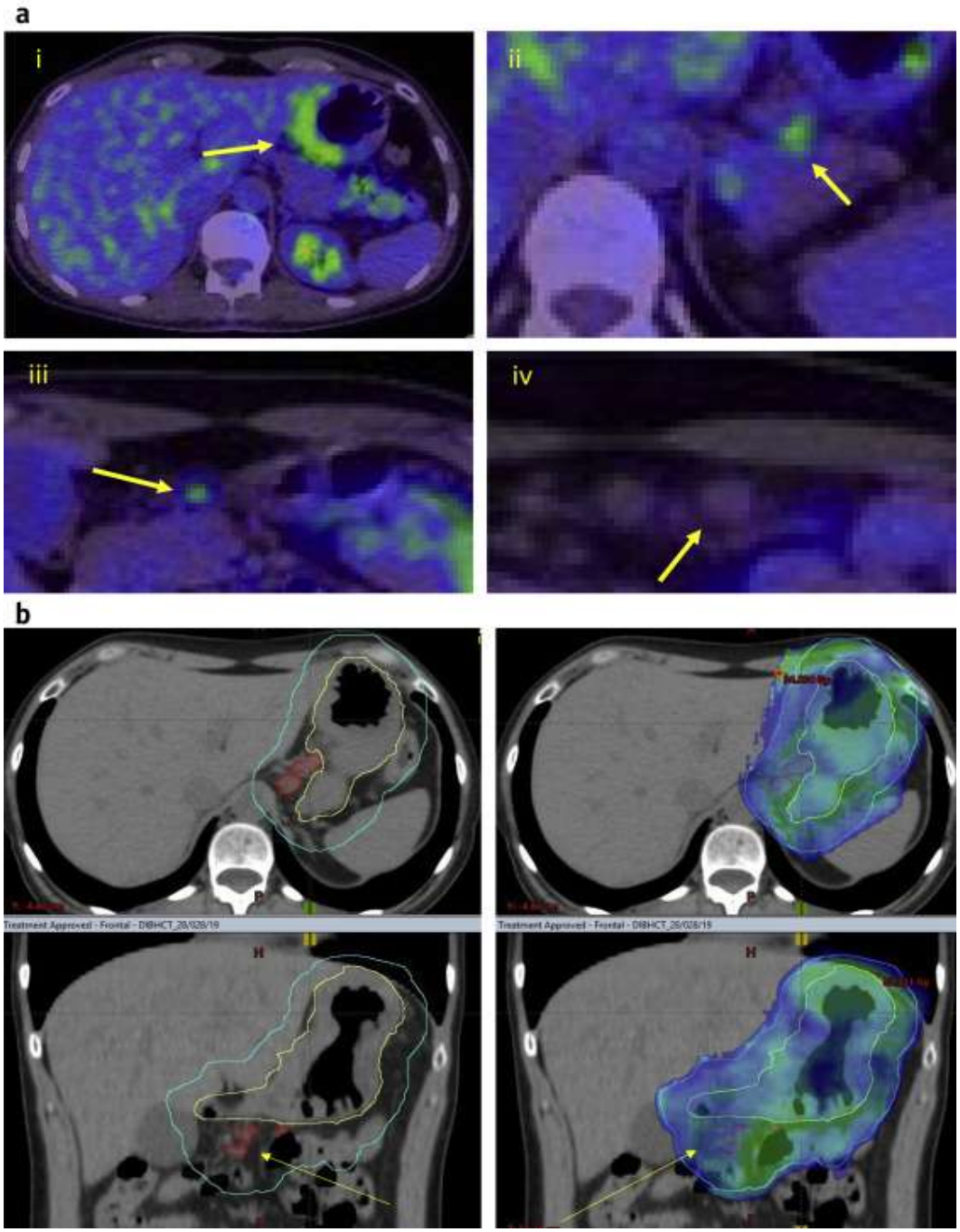





**(c) Note the greater distance from CTV to heart and breast tissue in breath hold.**

**(d) Cone beam computed tomography showing variation in stomach shape and position (CTV in yellow).**




**MZL with nodal involvement:**
**(a) arrows indicate (i) gastric wall involvement, (ii, iii) nodal uptake on positron emission tomography, (iv) enlarged PET –Ve.**

**(b) clinical target volume (CTV) including whole stomach (yellow) and suspicious adjacent nodes (red), planning target volume (blue), and IMRT/VMAT plan.**

# ENK/T cell lymphoma

- Extranodal natural killer/T-cell lymphoma, nasal type (ENKTCL), is a distinct clinicopathologic entity with an aggressive clinical course.
- Although rare globally, it is more prevalent in East Asia and South America.
- ENKTCL is characterized by prior Epstein Barr virus (EBV) infection, is predominant in adult males,
- Large proportion of early-stage cases, is known for its clinically extensive primary tumor invasion, and has a propensity for extranodal failure.
- RT is integral part of treatment, Combined modality – improves outcome.

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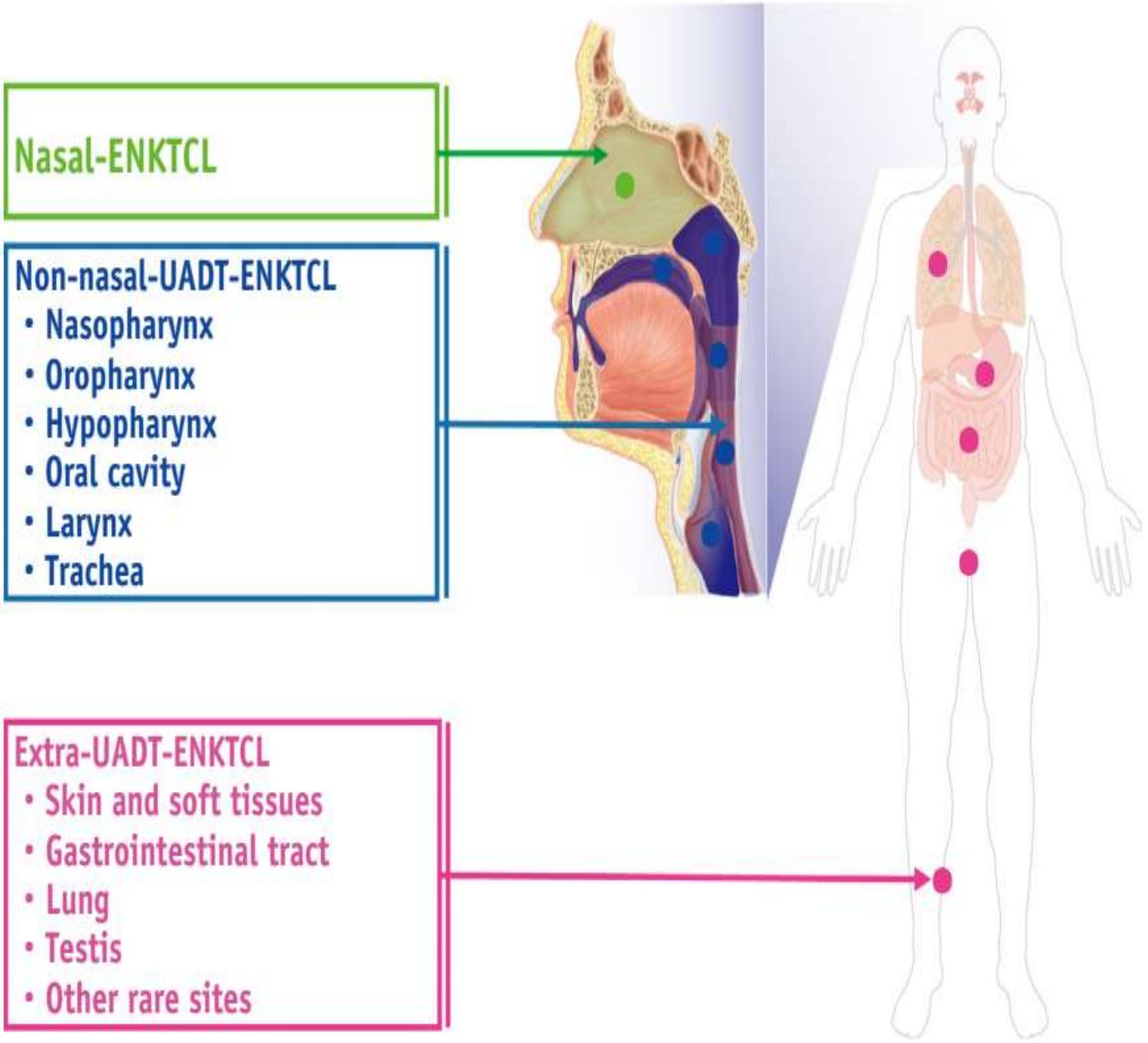
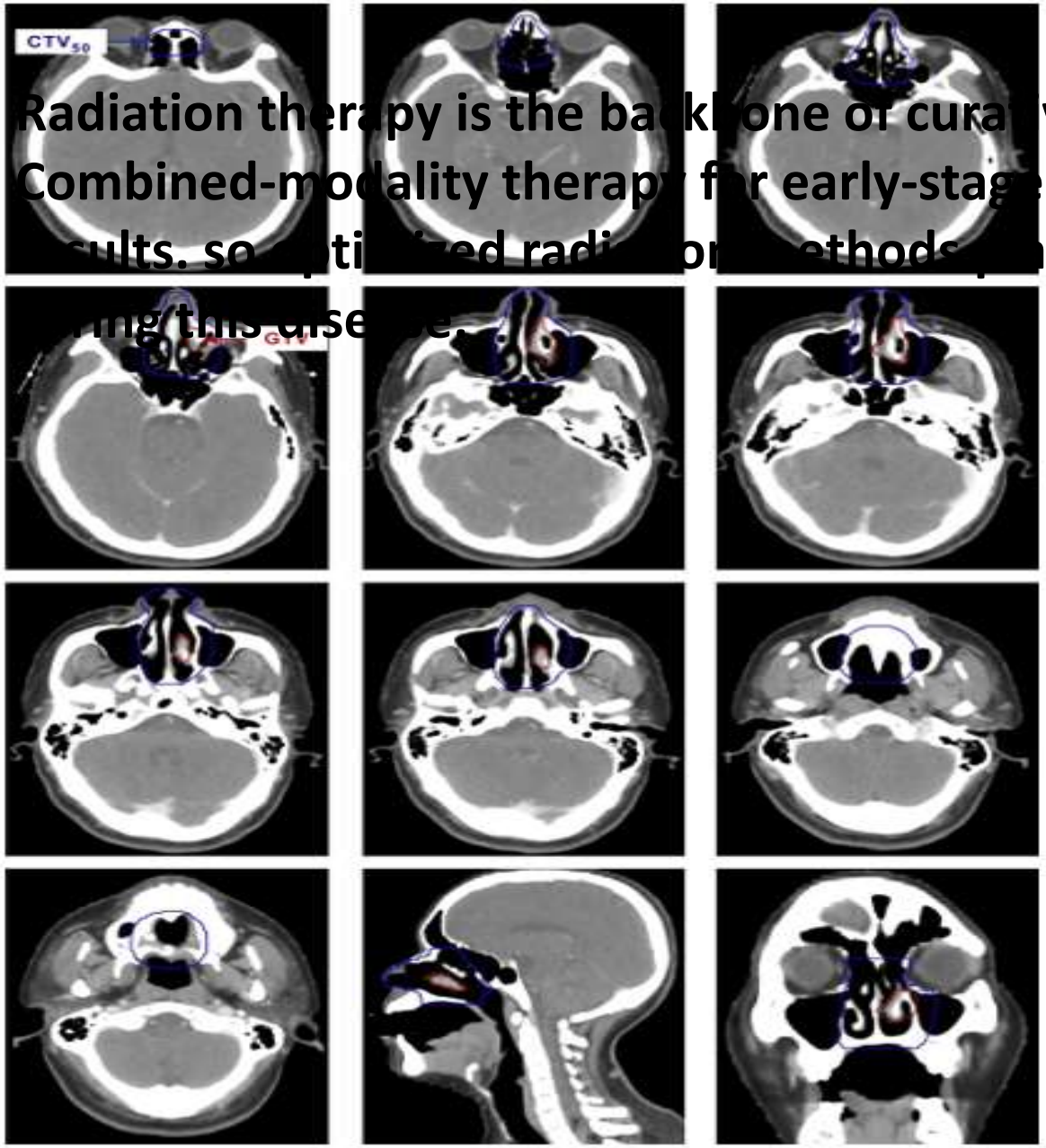



Prognosis Declines from Nasal to aggressive Extra UADT-outcome is poor.

Distribution of 3 ENKTCL subgroups based on primary tumor location.



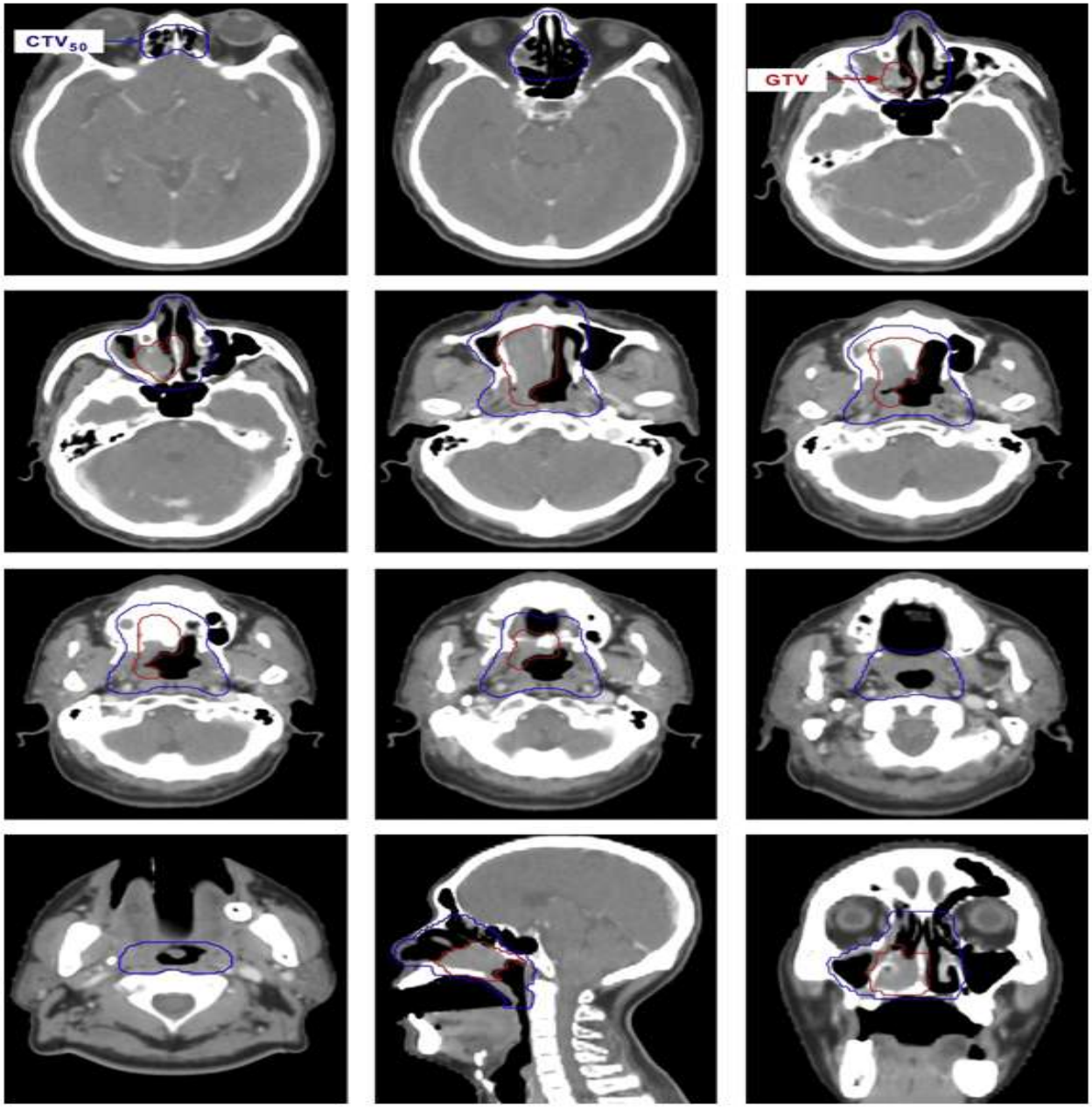

Radiation therapy is the backbone of curative treatment

Combined-modality therapy for early-stage ENKTCL has

results, so optimized radiation methods may assume a

ing this disease.

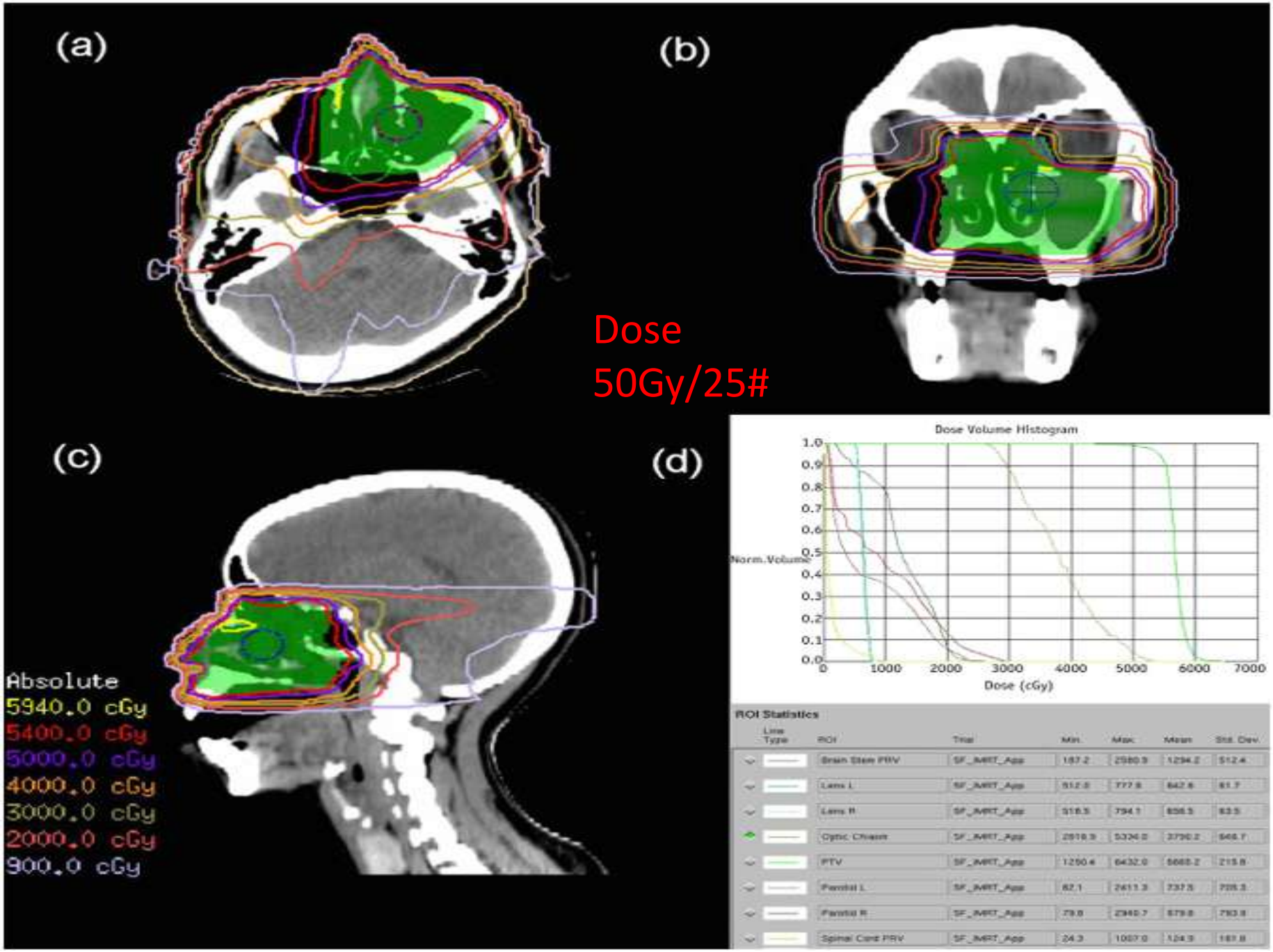
stage I nasal ENKTCL localized (disease confined to the nasal cavity without primary tumor invasion- GTV (red line) and CTV (blue line)



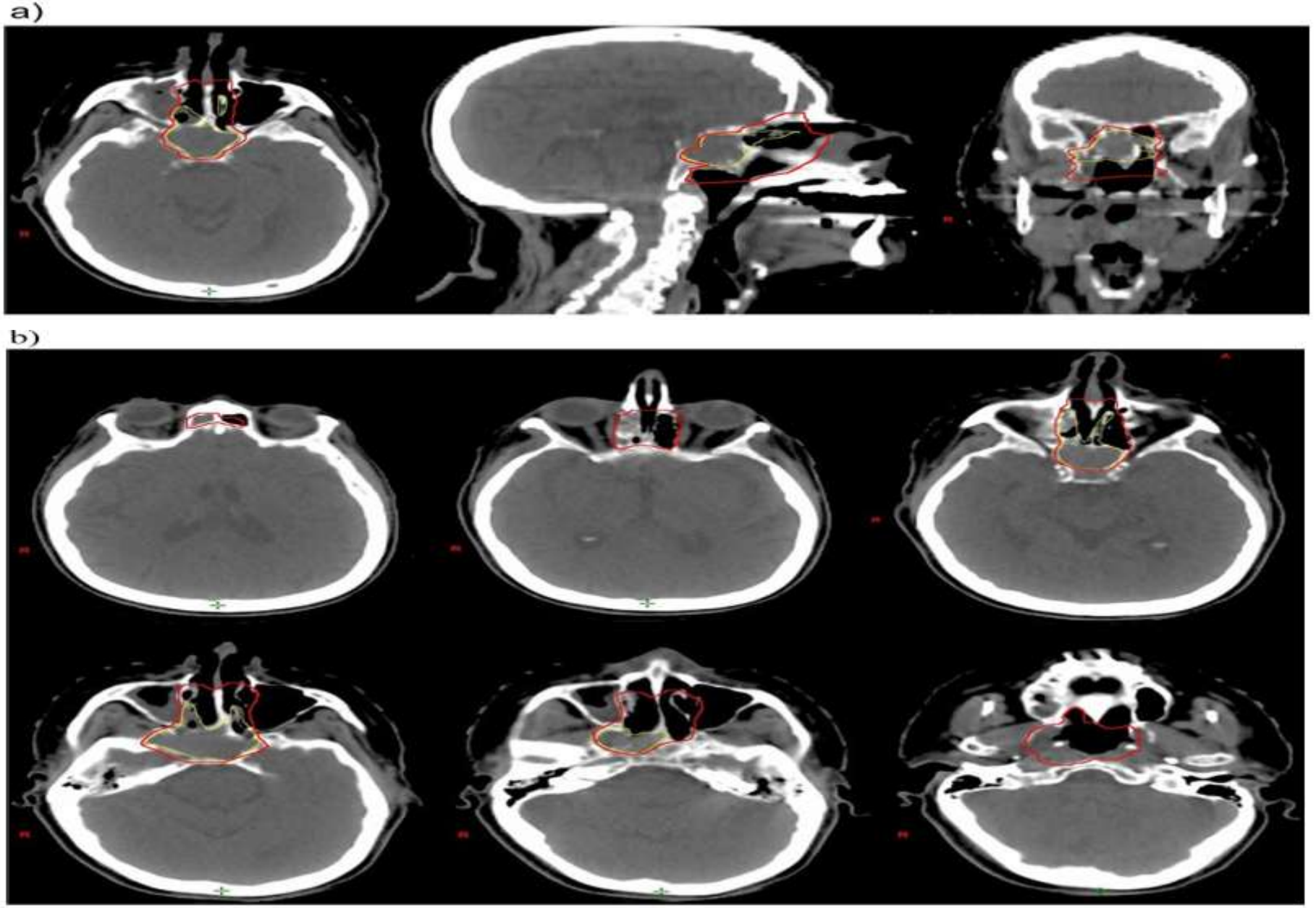

**Satge I extended.**

**CTV:**

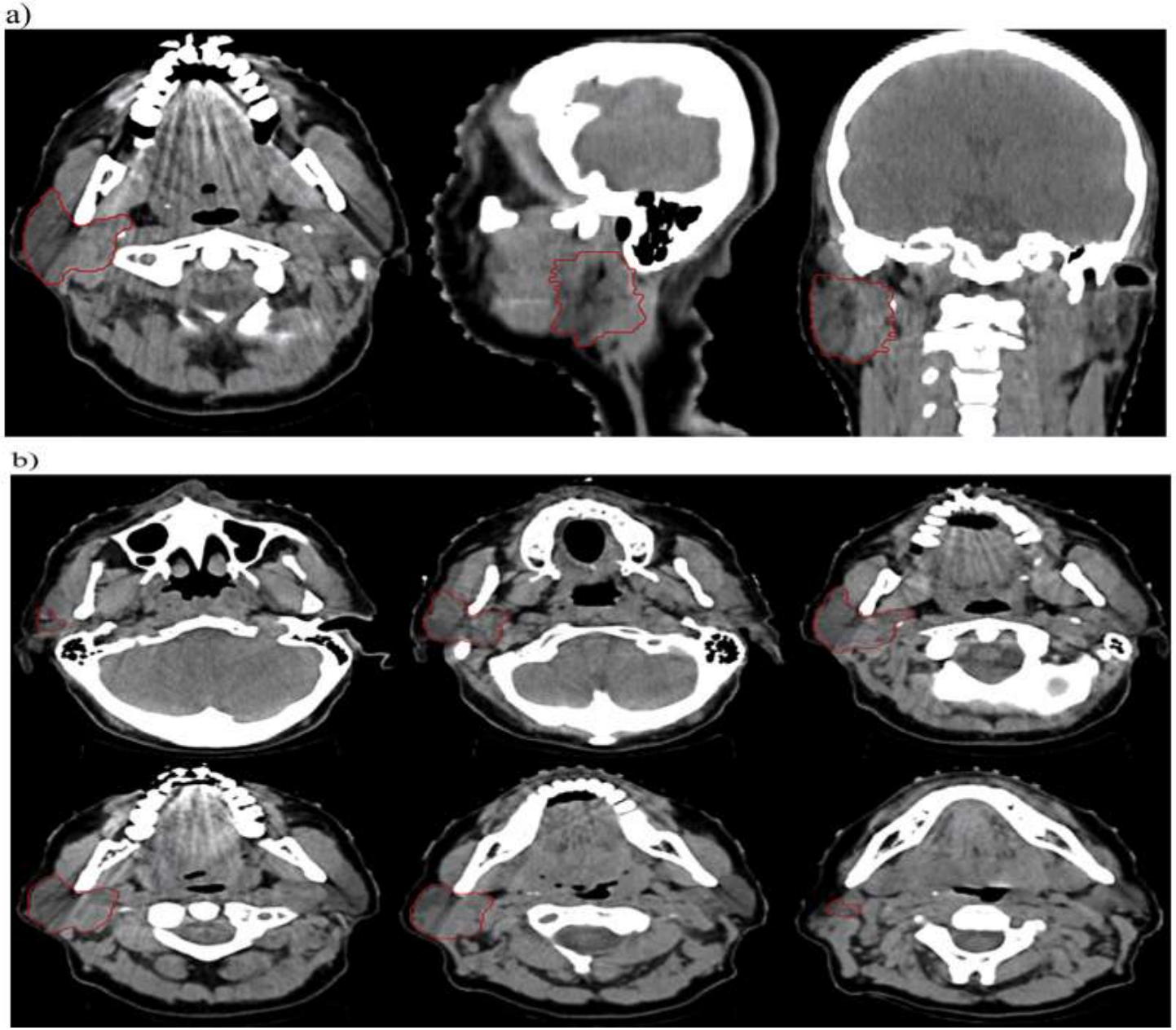
**The nasal cavity and bilateral antra should be included, although a reduction to the involved cavity alone may be considered if there has been a complete or near CR to CT**


(a)
(b)
Dose
50Gy/25#
(c)
(d)
Absolute
5940.0 cGy
5400.0 cGy
5000.0 cGy
4000.0 cGy
3000.0 cGy
2000.0 cGy
900.0 cGy
Dose Volume Histogram
Norm. Volume
Dose (cGy)
ROI Statistics

# Nasopharynx

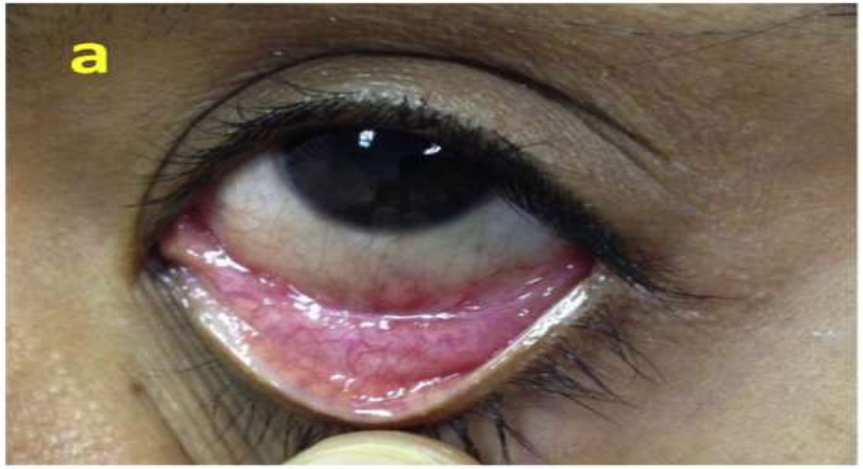


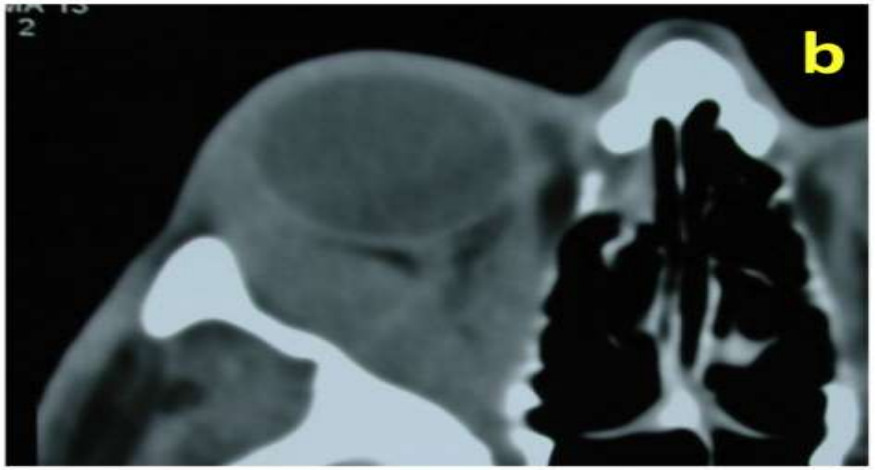
# Parotid gland lymphoma

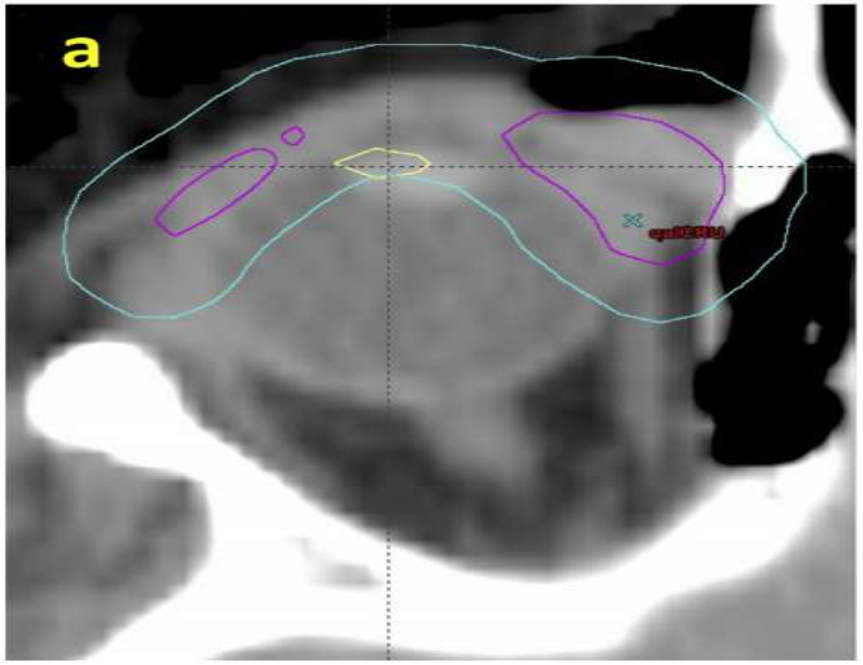


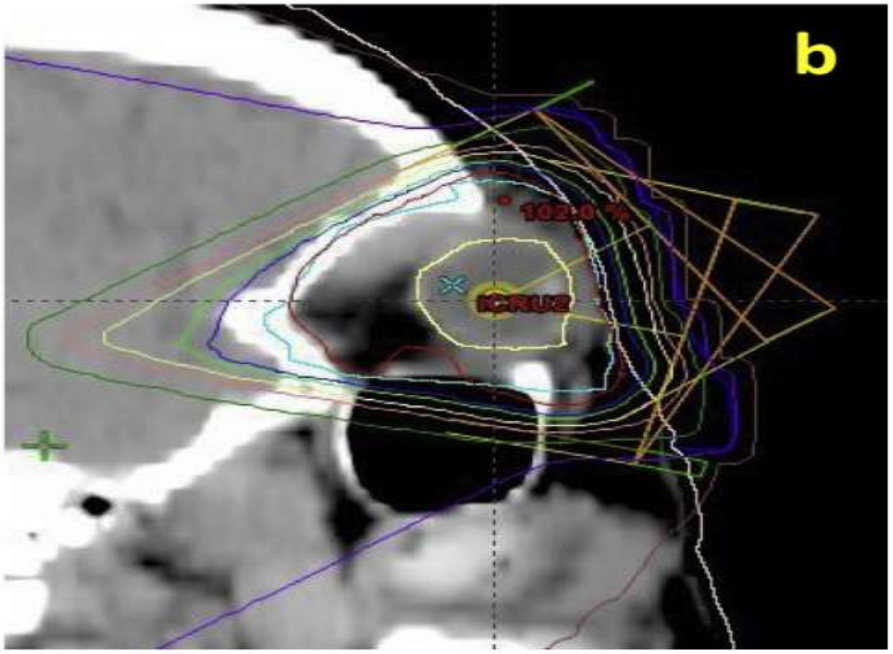

**CTV: the entire ipsilateral gland unless there is extra-capsular spread prechemotherapy In this instance the GTV will be the pre-chemotherapy volume and the CTV a 10 mm expansion of this in all directions.**

# Conjunctival lymphoma



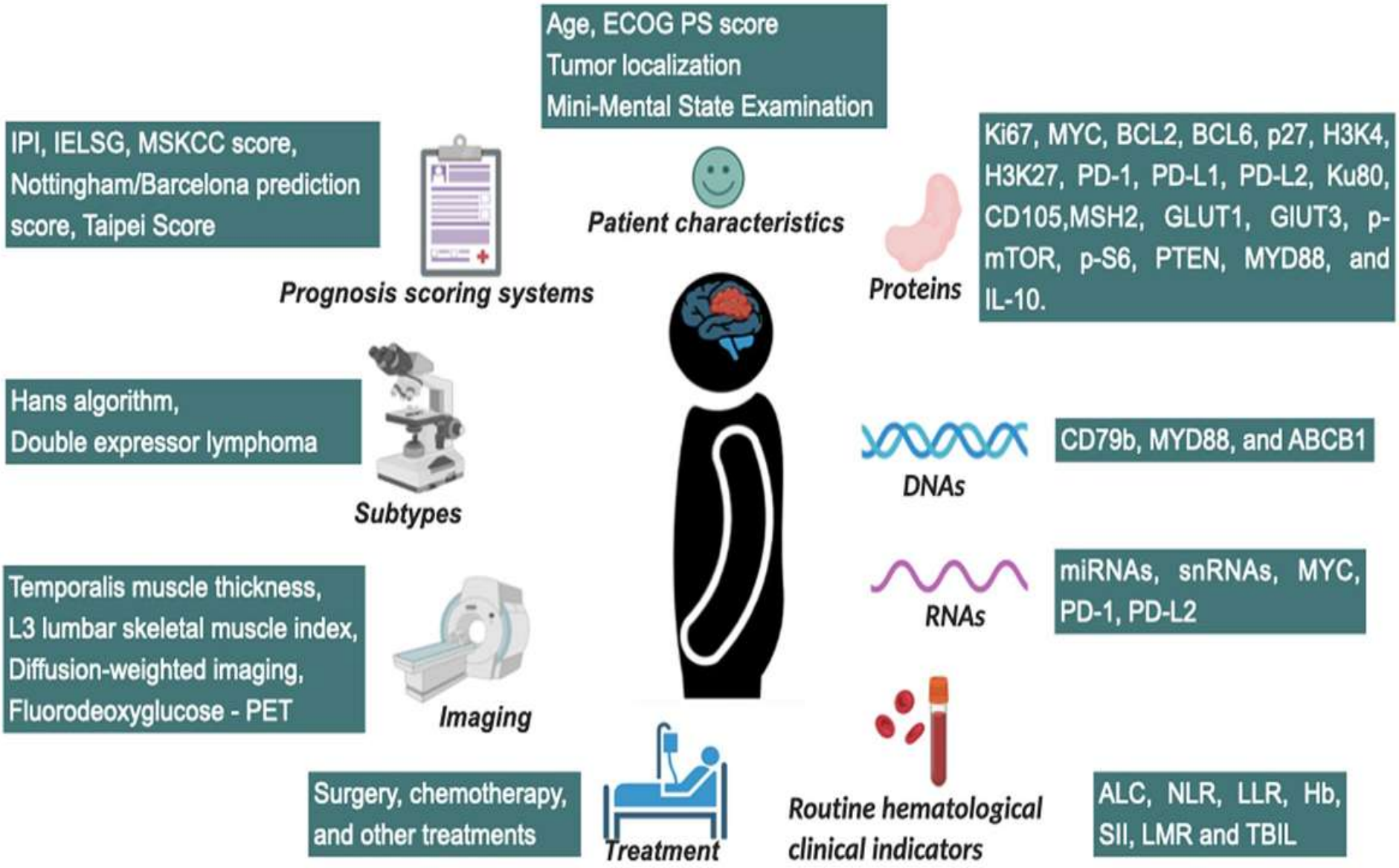



# PCNSLs

Rare diseases defined by involvement of the cerebral parenchyma, leptomeninges, eyes or spinal cord without evidence of systemic disease .
Almost always it is DLBCL

The IELSG has proposed a prognostic system for PCNSL based on the following independent prognostic factors:
**age >60 years, ECOG PS >1, elevated serum LDH, elevated CSF protein concentration and tumour localisation within the deep regions of the brain.**
Three risk classes: are defined for patients
Good-risk: 0–1,
Intermediate-risk: 2–3 or
Poor-risk: 4–5 prognostic factors.

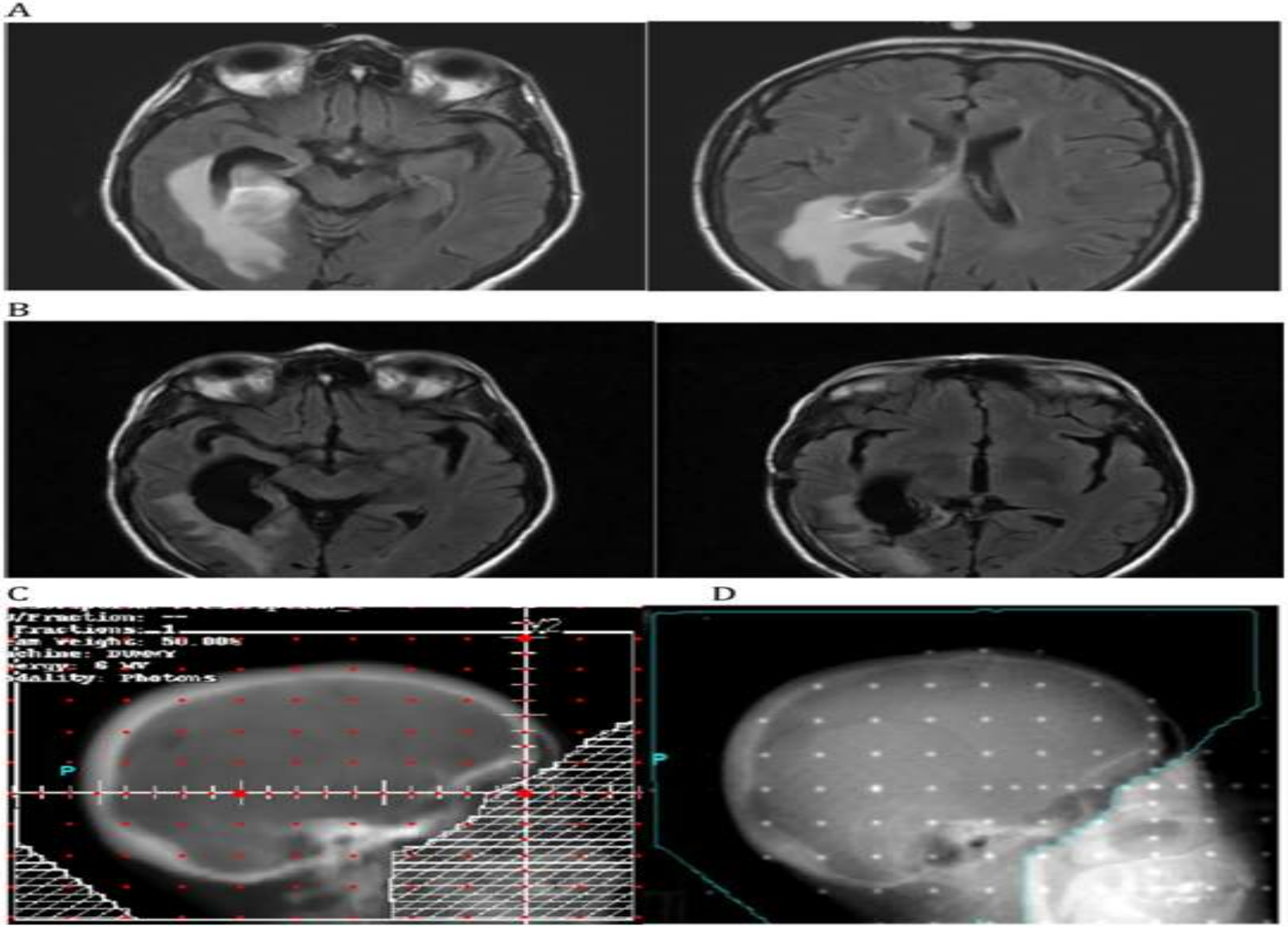



**Prognostic markers for PCNSL**

- Another validated risk score developed by Abrey et al. only requires age and clinical PS to build three different risk groups good risk ( patients <50 years), intermediate risk, ( patients ≥50 years and Karnofsky performance score [KPS] ≥70) and high risk ( patients ≥50; KPS <70).
- MSKCC, Taipei….

- **RT as consolidation treatment after CT(HD-Mtx and HD ara-C)**
- RT dose: CR on MR: 23.4Gy
- PR:36 Gy beyond 36Gy not helpful but increases neurotoxicity
- Additional boost –uncertain.

**The CTV should encompass the whole brain and meninges extending down to the C1-C2 junction and including the cribriform plate, posterior orbit and optic canals.**



| Primary sites | Treatment | Consolidation | CNS prophylaxis |
|---|---|---|---|
| Primary testicular lymphoma | R-CHOP21X6-8 | RT to contralateral testis (25–30 Gy) | IT MTX or i.v. systemic MTX |
| Primary central nervous lymphoma | HD-MTX (MTX $\geq$ 3 g/m$^2$) plus HD-ara-C<br>HD-MTX-based (adjusted dose on ECOG PS, renal function, etc.) in elderly patients | WBRT is not routinely recommended<br>HDCT/ASCT suggested in young patients (clinical trial) | N/A |
| Primary mediastinal lymphoma | R-CHOP or R-V/MACOP-B or R-CHOP14 or DA-EPOCH-R | Mediastinal RT (30 Gy) in responding patients; RT could be omitted in CMR only after DA-EPOCH-R<br>HDCT/ASCT is not recommended in CR1 | Not recommended |
| Primary breast lymphoma | R-CHOP21X6 | Whole ipsilateral breast RT (30–36 Gy). Partial breast RT in selected cases (see text) | To be considered in all patients<br>Mandatory in high risk |
| Primary bone lymphoma | R-CHOP21X6-8<br>RT before chemotherapy is not recommended | RT (30–40 Gy) to involved bone | Only if involvement of the skull and/or spine |

# Cutaneous B cell lymphoma

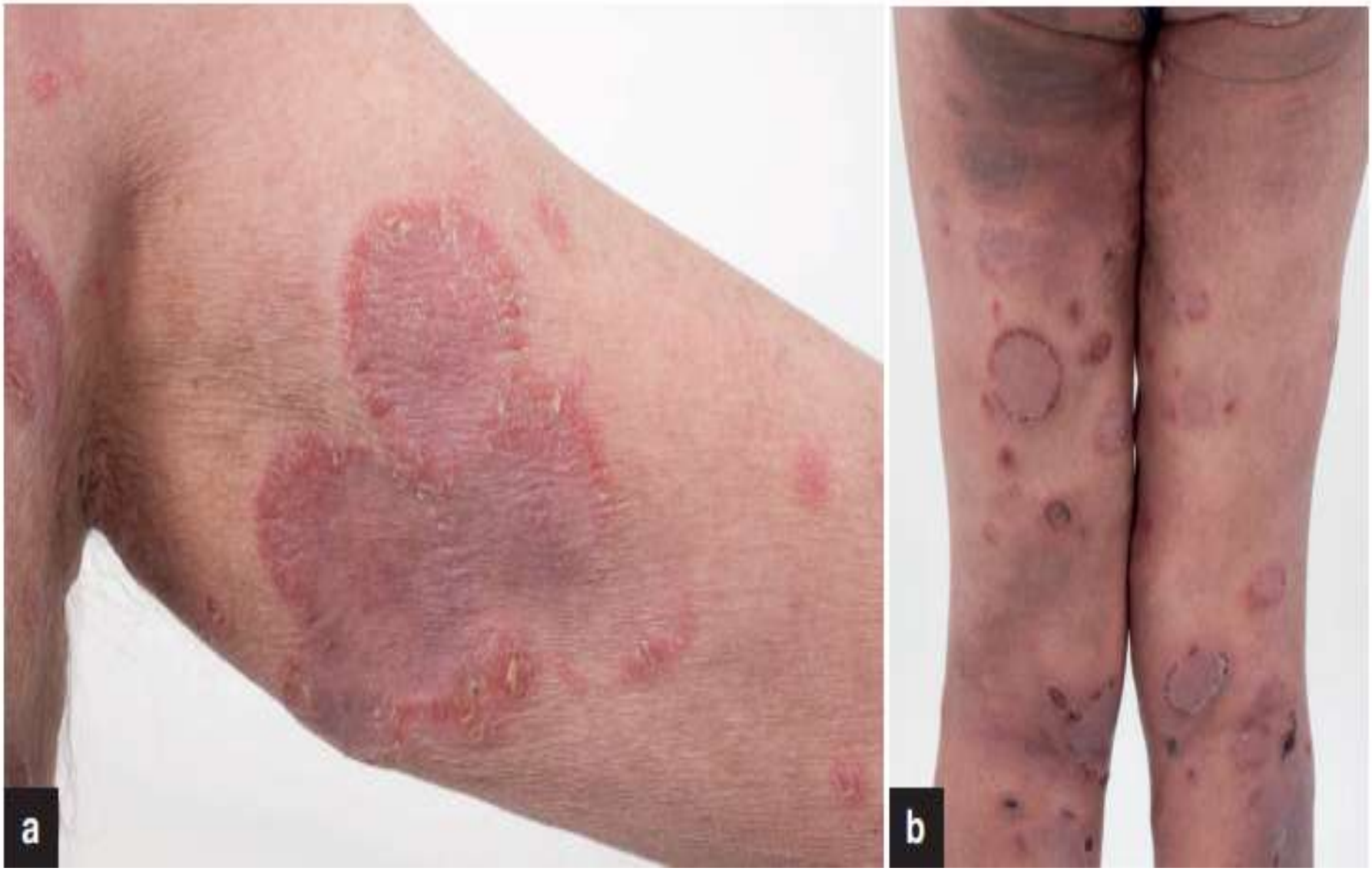
| Primary cutaneous B-cell lymphoma, histological type | Front-line therapy |
|---|---|
| PCMZL | |
| Single lesion/localized disease | RT |
| | Surgical excision (antibiotics[§]) |
| Multiple lesions/disseminated disease | Watchful waiting |
| | RT |
| | CT[§§] intravenously rituximab (antibiotics[§]) |
| PCFCL | |
| Single lesion/localized disease | RT |
| | Surgical excision |
| Multiple lesions/disseminated disease | Watchful waiting |
| | RT intravenously rituximab |
| PCLBCL-LT | |
| Single lesion/localized disease | R-CHOP ± IF-RT |
| Multiple lesions/disseminated disease | R-CHOP |

Chin Clin Oncol 2015:4(1):10

# Cutaneous T-cell lymphoma.

- Cutaneous T-cell lymphoma is a chronic, relapsing illness with treatment aimed at symptomatic relief and improving patient related quality of life.
- The commonest types of cutaneous T-cell lymphoma are mycosis fungoides, Sézary syndrome and primary CD30 positive cutaneous lymphoproliferative disorders.

British Journal of Hospital Medicine | 2022.
Scientific Reports | (2024) 14:20118




Plaque-like lesions, typical of mycosis fungoides, affecting (a) the upper and (b) lower limbs

Histopathological findings of mycosis fungoides. Note the marked epidermotropism with tagging of the basal keratinocytes (white arrows) and collections of atypical lymphocytes forming Pautrier's microabscesses (yellow arrows). Folliculotropism (black arrows) is also present in this example

- The treatment of early-stage disease- skin-directed therapy (topical corticosteroids, narrow band UV- B or psoralen UV-A.
- Radiotherapy - used to treat symptomatic single target lesions, with **TSET** reserved for those with more widespread skin disease
- In advanced stage disease, first-line systemic options include interferon, methotrexate and retinoids, with targeted therapies and chemotherapy kept in reserve
- Extracorporeal photopheresis- photoimmune therapy in which lymphocytes are removed from the blood, and exposed to psoralen and ultraviolet A before being returned to the patient.
- ASCT- used in selected cases of advanced disease. consolidate and achieve a durable remission.

# Outcomes:

- Indolent Lymphomas: 10yr OS 80-90%
- localized gastric or non-gastric MALT lymphoma reported 10-year OS and RFS rates of 87% and 76%, respectively, with cause-specific survival of 98%.
- Aggressive Lymphomas:
- Poorer outcomes in Testicular lymphomas, NK/T cell lymphoma, PCNSL.
- 5yr –OS depending on stage and prognostic factors.
- Treatment outcomes have improved significantly for early-stage disease: 5-year OS rates-
- stage I disease -70% to 90% and stage II disease- 50% to 70%
- stage III/IV disease- 10% to 40%

# Dose volume considerations

| | Optimal* | Acceptable† | If necessary‡ | Avoid |
|---|---|---|---|---|
| Heart (89, 145, 146) | | | | |
| Mean (Gy) | <5 | 5-10 | 10-18 | Coronary arteries and left ventricle |
| V15 | <10% | 10%-25% | 25%-35% | |
| V30 | | <15% | 15%-20% | |
| Lung (147) | | | | |
| V5 | <35% | 35%-45% | 45%-55% | |
| V20 | <20% | 20%-28% | 28%-35% | |
| Mean (Gy) | <8 | 8-12 | 12-15 | |
| Thyroid (148) | | | | |
| V25 | <62.5% | | | Whole thyroid |
| Breast | | | | |
| Mean (Gy) | <4 | 4-15 | >15 | Glandular tissue |
| V4 | <10% | 10%-20% | >20% | |
| V10 | | <10% | >10% | |

* For favorable disease, small-volume early stage lymphoma.

† For bulky mediastinal disease.

‡ Relapse/refractory disease setting. Adapted with permission from Dabaja et al.[49]

## Future directions:

International Collaborative studies: IELSG, ILORG, investigator-initiated, patient-centered independent academic research is the irreplaceable core engine driving progress in clinical understanding and treatment practices

**4 | EXTRANODAL LYMPHOMAS: IMPROVED OUTCOME THROUGH INTERNATIONAL COLLABORATIVE RESEARCH**

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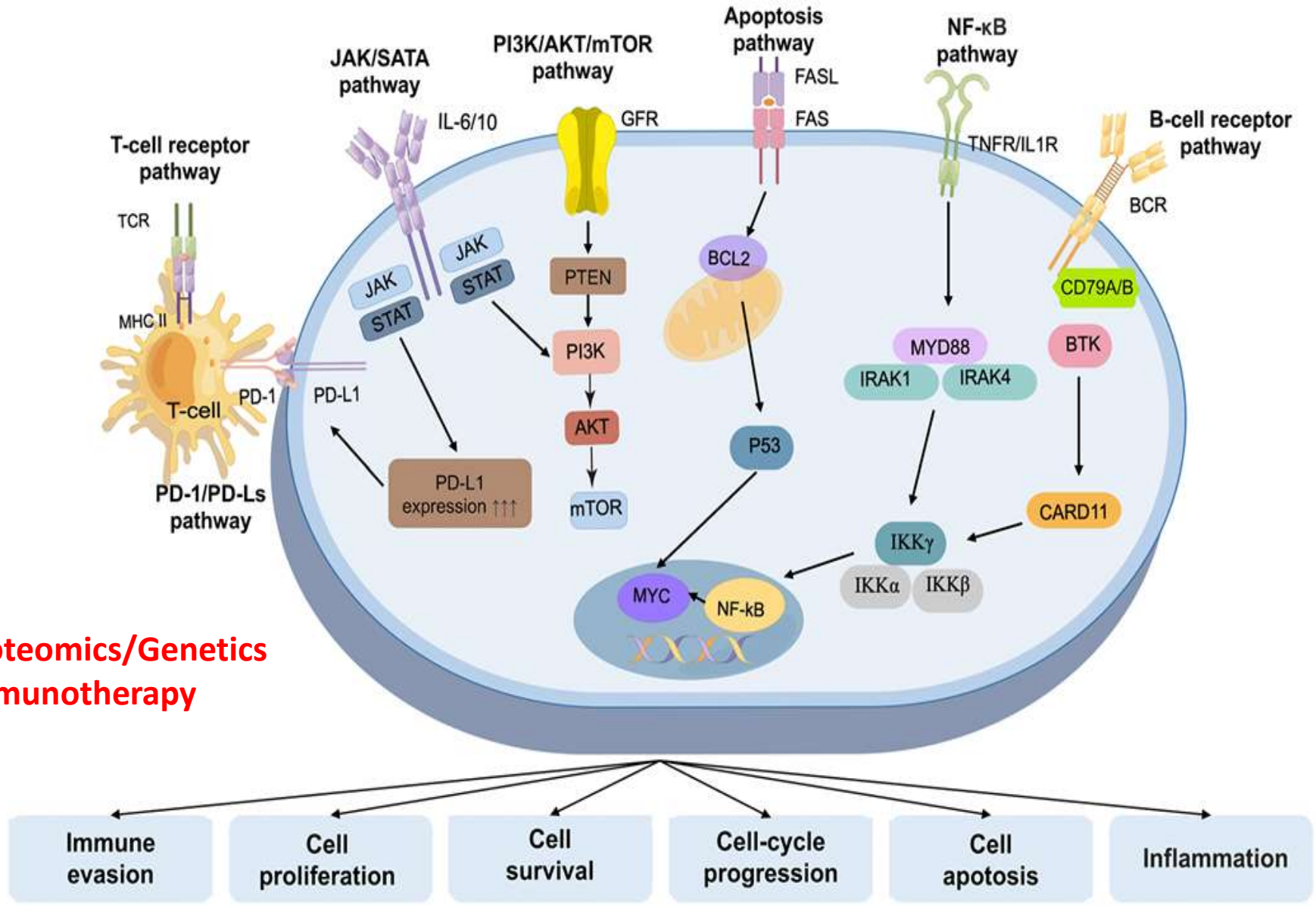


**Fig. 1** Common key signaling pathways in extranodal lymphoma

**Proteomics/Genetics**
**Immunotherapy**

| | |
|---|---|
| **IELSG50** | **Pembrolizumab and radiotherapy for previously untreated patients with limited-stage NK/T cell lymphoma who are not eligible for chemotherapy** |
| **IELSG37** | **A randomized, open-label, multicentre, two-arm phase III comparative study assessing the role of mediastinal radiotherapy after Rituximab containing chemotherapy regimens to patients with newly diagnosed Primary Mediastinal Large B-Cell Lymphoma (PMLBCL** |
| **IELSG33** | **A prospective observational study of newly diagnosed diffuse large B cell primary breast lymphomas treated with R-CHOP with or without radiotherapy** |
| **IELSG30** | **A phase II study of R-CHOP with intensive CNS prophylaxis and scrotal irradiation in patients with primary testicular diffuse large B-cell lymphoma** |

**Table 1** Overview of signaling pathway inhibitors undergoing clinical studies in extranodal lymphoma

| Cancer Type | Signaling Pathway | Drugs |
|---|---|---|
| PCNSL | PD-1/PD-Ls | Camrelizumab, Durvalumab, F520, GNC-038, Nivolumab, Pembrolizumab, Penpulimab, Sintilimab |
| PCNSL | B-cell receptors | Acalabrutinib, Ibrutinib, NX-2127, NX-5948, Orelabrutinib, Tirabrutinib, Zanubrutinib |
| PCNSL | PI3K/AKT/mTOR | Bimiralisib, Buparlisib, Emavusertib, Paxalisib |
| MALT | PD-1/PD-Ls | Pembrolizumab |
| MALT | B-cell receptors | AC-676, Acalabrutinib, AS-1763, BGB-16673, HMPL-760, Ibrutinib, NX-2127, Orelabrutinib, Zanubrutinib |
| MALT | PI3K/AKT/mTOR | BGB-10188, BGB-16673, BR101801, Copanlisib, Duvelisib, GS-9901, HMPL-689, HMPL-760, IBI376, Idelalisib, NX-2127, Orelabrutinib, SHC014748M, Umbralisib, YY-20394, Zandelisib, Zanubrutinib |
| MALT | NF-κB | BGB-21447, CC-99282, LP-168, VAY736, XL114 |
| MALT | JAK/STAT | CpG-STAT3 siRNA CAS3/SS3 |
| MALT | Apoptosis | L-Bcl-2 antisense oligonucleotide |
| PTCL | PD-1/PD-Ls | AB-101, F-520, GB-226, ONO-4685, Sintilimab, Tislelizumab |
| PTCL | NF-κB | Copanlisib, Duvelisib, HMPL-689, IOA-244, Linperlisib, Parsaclisib, SHC014748M, TQ-B3525, YY-20394 |
| PTCL | JAK/STAT | AZD4205, KT-333 |
| PTCL | Apoptosis | ASTX660, L-Bcl-2 antisense oligonucleotide, Tolinapant |
| NK-T | PD-1/PD-Ls | IMC-001, SHR-1210, Sintilimab, Sugemalimab, Tislelizumab, Toripalimab |
| NK-T | NF-κB | YY-20394 |
| NK-T | JAK/STAT | Ruxolitinib, Tofacitinib |

*MALT* Mucosa-associated lymphoid tissue lymphomas, *NKTCL-NT* Natural killer/T-cell lymphoma, nasal type, *PCNSL* Primary central nervous system lymphoma, *PTCL* Peripheral T cell lymphoma

# Conclusion

- Incidence of ENLs is uncommon.
- Treatment depends on nature, site and prognostic features
- Radiation treatment plays important role as sole modality in Indolent lymphomas and consolidative role in aggressive lymphomas .
- Indolent lymphomas outcome is excellent.
- Aggressive lymphomas  steep learning curve.
- Multi-institutional across the globe collaborative studies will be the call of the day which focus on better understanding and evolution in treatment.


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Thank You


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## Diagnosis of ENLS:

Should be carried out in a reference haematopathology laboratory with expertise in morphological interpretation and the facilities to carry out the full range of phenotypic and molecular investigations.

Includes:

- Morphology: Cytology: Small , medium, large cells,
- Pattern: Diffuse, nodular, follicular, Mantle, marginal , sinus
- Location: extranodal.

The typical immunophenotypes :

Naïve B cells: CD5, CD23, IgD,

GCD: CD10, BCL6,

Follicular:CD21, CD23.

Oncogenic products:BCL2, Cyclin D1, MYC, BCL6, ALK.

t(11:18),

- FL: small cell. CD5-ve,CD10+ve, BCL6-Ve
- MZL: Small cell, CD5-Ve, Cd10-ve, Cd105+ve.
- DLBCL: Large cell, CD5+ve, Cy D1-ve.
  -CD5-ve, CD10-Ve, BCL6+ve/IRFU+ve.
- Cutaneous:
- CBCL:CD10+ve–PCFCL
  - CD10-ve, BCL2-ve, BCL6+ve-PCFCL, BCL5-ve-PCMZL
  - CD10-ve, BCL2+ve-PCDLBCL.
- CTCL: CD2, CD3, CD4, CD5, CD7, CD8, CD20, CD30, Clonal T cell receptor (TCR) gene rearrangement.

MF:the presence of CD4+small/medium pleomorphic T-cells-→ the atypical CD4+cerebriform lymphocytes become more prominent-→In the tumor stage of MF, sheets of atypical lymphocytes can be observed. Additionally, Sezary syndrome, the leukemic variant of MF, is characterized by the presence of clonal circulating Sezary cells

NKTCL-NT:

It is characterized by the of CD20 -ve, presence of CD3+, lack of CD5-ve, expression of CD56, high Ki-67 proliferation index, and increased levels of cytotoxic molecules such as granzyme B, perforin, and TIA-1.