

London Cancer
Head and Neck
Radiotherapy Protocol

June 2014

Head and Neck Squamous Carcinoma

Cancer definition

- Cancers of the upper aero-digestive tract, predominately squamous cell carcinomas :
 - Oral cavity
 - Oropharynx
 - Hypopharynx
 - Larynx
 - Nasopharynx
 - Paranasal sinuses
- Salivary gland tumours
- Associated level I-V cervical lymph nodes

Indications

- Radical radiotherapy may be used in:
 - Primary treatment for unresected cancers of the head and neck
 - Treatment of benign disease rarely e.g. recurrent inoperable salivary gland pleomorphic adenomas
- Post-operative radiotherapy (PORT) may be indicated:
 - For positive resection margins
 - For extra-capsular spread in lymph node metastases
 - If any two of the following factors are present, PORT is also indicated:
 - Close margins (<5mm)
 - Invasion of soft tissues such as skeletal muscle
 - ≥ 2 lymph nodes positive for metastatic spread
 - 1 lymph node region positive of metastatic spread
 - Involved node >3cm in size ($\geq N_{2a}$ disease)
 - Multicentric primary
 - Peri-neural invasion

The following factors should also be borne in mind when considering a patient for PORT but are of lesser importance:

- Lymphovascular invasion
- Poorly differentiated (grade 3) disease
- T₃₋₄ disease
- Carcinoma in situ or dysplasia at the resection margins where further surgery would be difficult
- Carcinomas of the oral cavity
- In cases where there are uncertainties regarding the surgical or histopathological findings.

PLUS

- Performance status ≤ 2
- Clinical benefit from organ preservation or improved PTV coverage likely (consultant decision)

Intent

- Radical

Timing

- A patient's 1st treatment (IMRT or neo-adjuvant chemotherapy) to start within 31 days from referral to the service, or within 62 days from referral if the patient is on the 'two-week wait' pathway as per nationally set targets.
- Post-operative radiotherapy to start within 6 weeks of primary surgery wherever possible.

Chemotherapy and EBRT/IMRT

- Induction Chemotherapy
 - There is no level 1 evidence for an advantage to induction chemotherapy before chemoradiotherapy. It can be considered in the following situations
 - i. Primary treatment of Nasopharyngeal Carcinoma (NPC)
 - ii. Primary treatment of rapidly progressive disease where urgent treatment is required
 - Cisplatin/5FU should be used. TCF can be considered
- Chemo-radiotherapy (CRT)
 - Primary treatment of NPC in combination with neo-adjuvant/adjuvant chemotherapy
 - Primary treatment of $\geq T_3$ or node positive squamous cell carcinomas and may be considered in earlier disease if there are other high risk factors
 - In addition to surgery in esthesioneuroblastoma
 - Cisplatin should be used using either a 3-weekly, 4 weekly or weekly regimen
- Post-operative chemo-radiotherapy (POCRT) may be used in:
 - Incomplete resections
 - Extra-capsular spread in lymph node metastases
 - Soft tissue invasion
 - Selected cases where risk is increased such as resected pN_{2c-3} disease, resected pT₃₋₄ disease and where there is extensive peri-neural or lympho-vascular invasion
 - Age less than 70 years, although 'Biological Age' should be considered
 - Cisplatin should be used using either a 3-weekly, 4 weekly or weekly regimen
- Cetuximab may be used when there are contraindications to Cisplatin-based chemo-radiotherapy such as: renal failure, pre-existing peripheral neuropathy, hearing impairment.

Essential investigations and information required prior to decision to treat for EBRT and chemotherapy

- Performance Status assessment
- Height and Weight
- Clinical examination including Flexible Nasendoscopy (FNE)
- EUA and biopsy
- Operation note in post-operative cases
- Contrast-enhanced CT Chest
- Contrast-enhanced MRI/CT of Head and Neck
- Ultrasound Neck +/- Fine-Needle Aspiration of suspicious nodes
- Histology/cytology and Imaging review in Head and Neck MDT
- Full blood count, serum urea and electrolytes, liver function tests.
- Serum Haemoglobin should be optimised to $>12\text{g/dl}$ prior to radical radiotherapy start.
- Dental assessment with any remedial work done before beam immobilisation shell is made.

- Nutritional assessment with Percutaneous Endoscopic Gastrostomy (PEG) or Radiologically Inserted Gastrostomy (RIG) insertion in patients who:
 - Have had >10% weight loss in the past 3 months and who are at risk of malnutrition
 - Have nodal involvement and will have > 6cm of mucosa irradiated to >40Gy
 - Will be treated with IMRT where weight loss during treatment may impact on dosimetry
- Specialist Speech and Language Assessment where swallowing may be impaired by the tumour or may become more impaired during therapy. Flexible-Endoscopic Evaluation of Swallowing (FEES) may be performed at baseline and repeated during treatment to assess the risk of aspiration.
- Young male patients for chemotherapy should be counselled regarding the risk of infertility and offered semen cryopreservation. Those considering semen storage must have appropriate tests for Hepatitis B, Hepatitis C and HIV.
- Male and female patients for chemotherapy should be counselled to use effective contraception during chemotherapy and for 6 months after.
- Patients for Cisplatin-based chemoradiotherapy must have:
 - Detailed history taking for potential contraindications such as pre-existing renal failure, peripheral neuropathy or partial deafness.
 - Creatinine Clearance, repeated prior to the next dose of Cisplatin if the calculated GFR drops below 60ml/min. Baseline EDTA-GFR if suspicion of reduced renal function on calculated GFR
 - Baseline Audiometry, repeated if there is change in hearing as clinically indicated.
- Patients for Platinum-Fluoropyrimidine Neoadjuvant Chemotherapy should also have:
 - Detailed cardiac history **and ECG, with assessment of left ventricular function (MUGA or Echocardiogram) as clinically indicated.**
 - Assessment and placement of a Peripherally Inserted Central Catheter (PICC)

Information for patients

- Site-specific information leaflets discussing the diagnosis, preparations for treatment, details of the planning process and potential side-effects of treatment should be given to the patient in the Head and Neck clinic
- Further information may be provided by the Clinical Nurse Specialist.
- Referral to Smoking and Alcohol Cessation services.

Consent

Required for all patients including concurrent chemotherapy/cetuximab if appropriate.

Radiotherapy booking form completed

Trials

- ARTDECO

Position/immobilisation

- Supine
- Immobilisation shell
- Head rest / Knee / Ankle Stocks may be used
- Lymphadenopathy and scars may be marked with wire.
- Mouth bite where it is possible to exclude either the upper or lower half of the mouth from the field e.g. carcinoma of the oral cavity, nasal cavity, ethmoid and maxillary sinuses
- Dentures should be removed unless their presence may reduce mucosal toxicity by acting as a mouth bite
- Shells should not be cut-out over:
 - Tumour extending close to the skin

- Operation and biopsy scars
- Anterior commissure in larynx cancer

Image acquisition

- CT head and neck as per Scanning Level Protocol
- 1.25 - 2mm slices
- i.v. contrast may be considered
- PET-CT or MRI fusion may be used where the clinician feels it will help tumour volume delineation

Volume delineation and nomenclature

- Volumes delineated with aid of diagnostic MRI and CT.
- Clinician delineates GTV, CTV and PTV volumes plus additional/non standard OAR.
- If one positive node in level consider treating all nodes in that level.
- Before contouring identify which nodal levels to include and what dose they should receive whether radical, post op or prophylactic radiation dose;
- 1 cm bolus applied to regions of risk e.g. skin involvement.

High dose GTV

- Primary tumour and any involved lymph nodes. Use suffix indicating dose e.g. GTV65 (or v GTV65 if virtual volume i.e. following neo-adjuvant chemotherapy)
- For all tumour sites, outlining of this volume should be done with the aid of:
 - All diagnostic scans: MRI, PET, PET-CT and CT scans (including pre and post-operative imaging).
 - Operation notes (including EUA findings).
 - Clinical examination/ Nasendoscopy.
- If induction chemo used the high dose GTV should include pre-treatment tumour volume (Salama JK et al 2009)

High dose CTV (including post operative CTV)

- $CTV_{dose} = GTV_{dose} + 10\text{-}20\text{mm margin}$ (e.g. CTV65)
- The risk of nodal extracapsular increases with size therefore a 1cm margin in nodes <20mm and 2cm margin if $\geq 20\text{mm}$ is suggested (Chao et al 2002).
- Sternocleidomastoid muscle should be included if there is extracapsular spread in node adjacent to it
- Volume edited to incorporate areas of high risk (often the anatomical region where the tumour arose) and out of barriers to tumour spread (bone, fasciae) provided they are not breached.
- Air is not part of the CTV and, in principle, it should be edited out of the volume
- In the postoperative setting include residual tumour / positive margins if radical dose is required.
- Merge the primary and involved lymph node volumes to create one CTV i.e. CTV65

High dose PTV

- $PTV_{dose} = CTV_{dose} + 3\text{ to }5\text{ mm}$ (e.g. PTV65), dependent on local audit of set up error

Elective CTV

- CTV to be treated to an elective dose. Differentiate between 'high dose microscopic dose' e.g. 60Gy and 'low dose microscopic dose' e.g. 54Gy. Use suffix to denote dose e.g. CTV60 or CTV54
- In patients receiving post-operative radiotherapy the high dose volume will include the anatomical sites at risk of residual disease in addition to the original areas involved.
- Consider sparing normal tissue structures such as superficial parotid in oropharynx/NPC

Elective PTV

- $PTV_{dose} = CTV_{dose} + 3 \text{ to } 5 \text{ mm}$ (e.g PTV65), dependent on local audit of set up error.

DOSE / FRACTIONATION

IMRT			
Tumour type	High dose PTV	Post operative PTV	Elective PTV
Squamous cell carcinoma Adenocarcinoma Adenoid cystic Acinic cell Mucoepidermoid Undifferentiated Salivary duct carcinomas	60-70Gy / 30 - 35 daily fractions *	60-70Gy / 30 - 35 daily fractions *	60-54Gy / 30-35 daily fractions
Pleomorphic adenoma	50-60Gy / 25-30 daily fractions		

*Consider simultaneous boost to GTV 70Gy/33# (2.12Gy/#)

Planning technique

3D-Conformal RT

Fields: Chosen to optimise dose coverage and respect normal tissue tolerance, single isocentre technique, avoid junctions though gross disease.

Energy: 6MV photons

Inverse planned IMRT

Fields: 5-9 co-planar fields
e.g. Gantry: 0°, 51°, 102°, 154°, 206°, 257°, 309°

Energy: 6MV photons

Dose requirements

PTVdose: Dose over 95% prescribed dose (62.7Gy) $\geq 99\%$
No more that 5% volume $\geq 105\%$ dose
No more than 1% volume $\geq 107\%$ dose

Hot spots outside the PTV not to exceed 105%

Deviation from these intended dose levels may be required e.g. to account for OAR DVH and will be made at clinicians discretion.

Plan Approval

Clinician to review and approve the whole plan to assess patient details, laterality, target coverage and DVH, OAR DVH and hotspots outside PTV / unexpected cold spots

Treatment technique

Refer to Local Work Instructions

Treatment verification

- MV Electronic Portal Imaging according to local work instructions
- Additional imaging/reassessment of dosimetry with repeat planning CT scan may be justified by the practitioner where:
 - There is likely to be considerable soft tissue change during treatment, such as that seen in bulky disease or where nutritional status is likely to be affected during therapy
 - There is evidence of increasingly poor setup and a decision needs to be made about re-planning

On treatment review definition and schedule gap category for management of unscheduled interruptions

- Weekly review by clinician, SALT, Dietician, RT nurse
- Weekly weight
- Weekly FBC (aim Hb \geq 12g/dl) plus U&E and LFT's if concurrent chemotherapy
- Continued review until the acute side-effects of treatment have settled
- Clinician to dictate detailed end of treatment summary letter for NHM notes, GP and referring hospital patient notes
- Baseline post-treatment contrast-enhanced MRI/CT or PET scan at 3months following radiotherapy completion

GAP CATEGORY FOR MANAGEMENT OF UNSCHEDULED INTERRUPTIONS

Classified as category 1:

- Category 1 patients will be offered treatment, as detailed below, to prevent prolongation of treatment schedules over Bank Holidays, with the exception of the aforementioned dates.

Single bank holidays

When the holiday falls on a Monday patients should ideally be treated on the day or on the previous Saturday (to avoid a 3-day gap).

Two day bank holidays

Treat on one holiday and the following (or previous) Saturday.

Christmas / New Year Period

This period will require a combination of Bank Holiday and Saturday working to be agreed depending on the actual holidays on any particular year. The decision of which days to offer treatment during this period must be presented at Oncology Multi-Professional Meeting well before Christmas.

References

- Chao K S Et Al, Determination And Delineation Of Nodal Target Volumes For Head And Neck Cancer Based On Patterns Of Failure In Patients Receiving Definitive And Postoperative IMRT. *Int. J. Radiation Oncology Biol. Phys.*, Vol 53, No 5, Pp. 1174- 1184, 2002.
- Salama Jk, Haddad Ri, Kies Ms, Busse Pm, Dong L, Brizel Dm, Eisbruch A, Tishler Rb, Trotti Am, Garden As. Clinical Practice Guidance For Radiotherapy Planning After Induction Chemotherapy In Locoregionally Advanced Head-And-Neck Cancer. *Int J Radiat Oncol Biol Phys.* 2009 Nov 1;75(3):725-33.
- Gregoire Et Al. CT- based delineation of lymph node levels and related CTVs in the node negative neck: DAHANCA, EORTC, GORTEC, NCIC, RTOG Consensus Guidelines. *Radiotherapy And Oncology* 69 (2003) 227- 236
- Gregoire V, Eisbruch A, Hamoir M and Levendag P. Proposal for the delineation of the nodal CTV in the node-positive and post-operative neck. *Radiother Oncol* (2006), 79: 15-20
- Som P M et al. An imaging- based classification for the cervical nodes designed as an adjunct to recently clinically based nodal classifications. *Arch Otolaryngol Head Neck Surg.* Vol 125, apr 1999, 388-396.
- MT Guerrero Urbano, CH Clark, C Kong, E Miles, DP Dearnaley, KI Harrington, CM Nutting. Adhering to the PARSPORT study target volume definition guidelines for IMRT planning of oropharyngeal tumours allows sparing of the contralateral parotid glands. *Clin Oncol (R Coll Radiol).* 2007 Oct;19(8):604-13.
- Bonner Ja, Hariri Pm, Giralt J, Et Al. Radiotherapy plus Cetuximab for Squamous Cell Carcinoma of The Head And Neck. *N Engl J Med* 2006; 354: 567-78.
- Carter et al. Radical neck dissections for squamous carcinomas: Pathological findings and their clinical implications with particular reference to transcapsular spread. *Int J Radiat Oncol Biol Phys* 1987; 13: 825- 832.
- Emami B et al. Tolerance of normal tissue to therapeutic irradiation. *Int J Radiat Oncol Biol and Phys* 1991;21:109-122
- Huang et al. Postoperative radiotherapy in head and neck carcinoma with extracapsular lymph node extension and/ or positive resection margins. A comparative study. *Int J radiat Oncol Biol Phys* 1992; 23: 737- 742.
- Pignon JP, Bourhis J, Domenge C, Designe L. Chemotherapy added to locoregional treatment for head and neck squamous cell carcinoma: three meta-analyses of updated individualised patient data. *Lancet* 2000, 355: 949-955
- Tobias JS, Ball D, Synchronous chemo-radiation for squamous cell carcinomas *BMJ* 2001, 322: 876-78
- Zackrisson B, Mercke C, Strander H, et al. A systemic overview of radiation therapy effects in head and neck cancer. *Acta Oncol* 2003, 42:443-461
- Bernier J, Domenge C, Ozsahin M, et al. EORTC 22931. Post-operative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. *N Engl J Med* 2004, 350: 1945-1952
- Cooper JS et al Postoperative Concurrent Radiotherapy and Chemotherapy for High-Risk Squamous-Cell Carcinoma of the Head and Neck. *N Engl J Med* 2004, 350: 1937-1944
- Kirkpatrick JP, van der Kogel AJ, Schultheiss TE. Radiation dose-volume effects in the spinal cord. *Int J Radiat Oncol Biol Phys.* 2010 Mar 1;76(3 Suppl):S42-9.

- Radiotherapy Dose–Volume Effects On Salivary Gland Function. J O. Deasy et al Int. J. Radiation Oncology Biol. Phys., Vol. 76, No. 3, Supplement, pp. S58–S63, 2010
- Radiation Dose–Volume Effects In The Larynx And Pharynx Tiziana Rancati Et Al Int. J. Radiation Oncology Biol. Phys., Vol. 76, No. 3, Supplement, Pp. S64–S69, 2010
- Radiation Therapy And Hearing Loss Niranjana Bhandare, Int. J. Radiation Oncology Biol. Phys., Vol. 76, No. 3, Supplement, Pp. S50–S57, 2010
- Radiation Dose–Volume Effects In The Spinal Cord John P. Kirkpatrick, Int. J. Radiation Oncology Biol. Phys., Vol. 76, No. 3, Supplement, Pp. S42–S49, 2010
- Radiation Associated Brainstem Injury Charles Maymont. J. Radiation Oncology Biol. Phys., Vol. 76, No. 3, Supplement, Pp. S36–S41, 2010
- Radiation Dose–Volume Effects Of Optic Nerves And Chiasm Charles Mayo, Int. J. Radiation Oncology Biol. Phys., Vol. 76, No. 3, Supplement, Pp. S28–S35, 2010
- Takeda A, Shigematsu N, Suzuki S, et al. Late retinal complications of radiation therapy for nasal and paranasal malignancies: relationship between irradiated-dose area and severity. Int J Radiat Oncol Biol Phys 1999;44:599-605.
- Lawrence YR, Li XA, el Naqa I, Hahn CA, Marks LB, Merchant TE, Dicker AP. Radiation dose-volume effects in the brain. Int J Radiat Oncol Biol Phys. 2010 Mar 1;76(3 Suppl):S20-7.
- Henk JM, Whitelocke RA, Warrington AP, Bessell EM. Radiation dose to the lens and cataract formation. Int J Radiat Oncol Biol Phys. 1993 Apr 2;25(5):815-20.
- Bhide S, Clark C, Harrington K, Nutting CM. Intensity modulated radiotherapy improves target coverage and parotid gland sparing when delivering total mucosal irradiation in patients with squamous cell carcinoma of head and neck of unknown primary site. Med Dosim. 2007 Fall;32(3):188-95.
- Madani I, Vakaet L, Bonte K, Boterberg T, De Neve W. Intensity-modulated radiotherapy for cervical lymph node metastases from unknown primary cancer. Int J Radiat Oncol Biol Phys. 2008 Jul 15;71(4):1158-66.
- Lefebvre JL, Chevalier D, Lubinski B et al. Larynx preservation in pyriform sinus cancer: preliminary results of a European Organization for Research and Treatment of Cancer phase III trial. EORTC Head and Neck Cancer Cooperative Group. J Natl Cancer Inst. 1996 Jul 3;88(13):890-9
- Wiernik G, Bates TD, Berry RJ, et al. Seventh interim progress report of the British Institute of Radiology fractionation study of 3F/week versus 5F/week in radiotherapy of the laryngo-pharynx. Br J Radiol. 1982 Jul;55(655):505-10
- Sanguineti G, Adapala P, Endres EJ, et al. Dosimetric predictors of laryngeal edema. Int J Radiat Oncol Biol Phys 2007;68:741–749.
- Wiernik G, Alcock CJ, Bates TD, et al. Final report on the second British Institute of Radiology fractionation study: short versus long overall treatment times for radiotherapy of carcinoma of the laryngo-pharynx. Br J Radiol. 1991 Mar;64(759):232-41
- Al-Sarraf M, LeBlanc M, Giri PG, et al. Chemoradiotherapy versus radiotherapy in patients with advanced nasopharyngeal cancer: phase III randomized Intergroup study 0099. J Clin Oncol. 1998 Apr; 16(4):1310-7
- Baujat B, Audry H, Bourhis J, et al. MAC-NPC Collaborative Group. Chemotherapy in locally advanced nasopharyngeal carcinoma: an individual patient data meta-analysis of eight randomized trials and 1753 patients. Int J Radiat Oncol Biol Phys. 2006 Jan 1; 64(1):47-56

- Baujat B, Audry H, Bourhis J, et al. MAC-NPC Collaborative Group. Chemotherapy as an adjunct to radiotherapy in locally advanced nasopharyngeal carcinoma. *Cochrane Database Syst Rev*. 2006 Oct 18; (4):CD004329
- Hunt MA, Zelefsky MJ, Wolden S, Chui CS, LoSasso T, Rosenzweig K, Chong L, Spirou SV, Fromme L, Lumley M, Amols HA, Ling CC, Leibel SA. Treatment planning and delivery of intensity-modulated radiation therapy for primary nasopharynx cancer. *Int J Radiat Oncol Biol Phys*. 2001 Mar 1;49(3):623-32.
- Lee AW, Ng WT, Hung WM, Choi CW, Tung R, Ling YH, Cheng PT, Yau TK, Chang AT, Leung SK, Lee MC, Bentzen SM. Major late toxicities after conformal radiotherapy for nasopharyngeal carcinoma-patient- and treatment-related risk factors. *Int J Radiat Oncol Biol Phys*. 2009 Mar 15;73(4):1121-8.
- Lee N, Harris J, Garden AS, Straube W, Glisson B, Xia P, Bosch W, Morrison WH, Quivey J, Thorstad W, Jones C, Ang KK. Intensity-modulated radiation therapy with or without chemotherapy for nasopharyngeal carcinoma: radiation therapy oncology group phase II trial 0225. *J Clin Oncol*. 2009 Aug 1;27(22):3684-90.
- Lin S, Pan J, Han L, Zhang X, Liao X, Lu JJ. Nasopharyngeal carcinoma treated with reduced-volume intensity-modulated radiation therapy: report on the 3-year outcome of a prospective series. *Int J Radiat Oncol Biol Phys*. 2009 Nov 15;75(4):1071-8.
- Xia P, Lee N, Liu YM, Poon I, Weinberg V, Shin E, Quivey JM, Verhey LJ. A study of planning dose constraints for treatment of nasopharyngeal carcinoma using a commercial inverse treatment planning system. *Int J Radiat Oncol Biol Phys*. 2004 Jul 1;59(3):886-96.
- Xia P, Fu KK, Wong GW, Akazawa C, Verhey LJ. Comparison of treatment plans involving intensity-modulated radiotherapy for nasopharyngeal carcinoma. *Int J Radiat Oncol Biol Phys*. 2000 Sep 1;48(2):329-37.
- O'Sullivan B, Warde P, Grice B, et al. The benefits and pitfalls of ipsilateral radiotherapy in carcinoma of the tonsillar region. *Int J Radiat. Oncol. Biol. Phys* 2001, 332-343.
- Rusthoven KE, Raben D, Schneider C, Witt R, Sammons S, Raben A. Freedom from local and regional failure of contralateral neck with ipsilateral neck radiotherapy for node-positive tonsil cancer: results of a prospective management approach. *Int J Radiat Oncol Biol Phys*. 2009 Aug 1;74(5):1365-7