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Background

Intensity-modulated radiotherapy (IMRT) is the accepted standard radiotherapy for patients undergoing primary and adjuvant radiotherapy for head and neck squamous cell carcinomas (HNSCC); exceptions are T1/T2N0 glottic cancer. The international standard for definitive treatment remains 70 Gy in 35 daily fractions of 2 Gy over 7 weeks, although altered fractionation regimens have been widely used. In the UK, many centres have adopted 65–66 Gy in 30 fractions over 6 weeks as a standard regimen. A simultaneous integrated boost technique with IMRT is routinely used to treat all target volumes and elective lymph node regions to varying dose levels in each fraction.

Role of modified fractionation in head and neck squamous cell carcinoma (non-nasopharyngeal)

An updated meta-analysis[1] compared conventional with altered fractionation across 34 trials including 11,969 patients in both radical and adjuvant settings. Altered fractionation was associated with a 3.1% survival benefit at 5 years, with the benefit being restricted to hyperfractionation (8.1% survival benefit at 5 years) (Level 1a). Moderately accelerated radiotherapy was only associated with a reduction in local failures, while hyperfractionated radiotherapy was associated with improved local and regional control. There was a reduced impact with increasing age. Altered fractionation schedules had higher rates of acute toxicity with no difference in late toxicity. Hyperfractionation is difficult to implement and not widely used. Based upon the absence of benefit for regional control, it was suggested that pure acceleration is only considered for patients with low nodal burden.[1] Most of the data pre-dates the human papilloma virus (HPV) era and the applicability of altered fractionation to HPV-related oropharyngeal disease is uncertain. A second comparison was performed between altered fractionation and the use of conventionally fractionated concurrent chemoradiotherapy in five trials with 986 patients; overall survival was inferior with altered fractionation (−5.8% survival difference at 5 years) (Level 1b). Several randomised trials have failed to show any benefit of combining moderate acceleration with concurrent chemotherapy.[2–5]

T1/2N0 glottic carcinoma

There is a dose response relationship in the treatment of early glottic cancer.[6] A meta-analysis of 1,762 patients with early-stage glottic carcinoma reported that altered fractionation was associated with a lower rate of local failure in a pooled analysis of randomised trials (hazard ratio 0.62) and retrospective studies (hazard ratio 0.40).[7] Both hypofractionation (HR 0.55; 95% CI 0.33–0.91) and hyperfractionation (HR 0.65; 95% CI 0.43–0.97) were superior to conventional fractionation (Level 1a). The benefit of altered fractionation is likely to at least in part be related to reduced overall treatment time, consistent with prior analyses.[8] The benefit was pronounced for T1 glottic disease and included anterior commissure involvement.[7] Several UK series have reported high rates of local control with short hypofractionated

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schedules including 50–52.5 Gy in 16 fractions over 3 weeks for T1 disease and 55 Gy in 20 fractions for T1 and T2 disease.[9–11] Patients with T2 glottic cancers are underrepresented and the impact of altered fractionation for this group remains an open question.[7] Treatment approaches in line with those for advanced disease may be appropriate for higher-risk T2 glottic disease (eg bulky, transglottic).

Recommendations

For irradiation of primary site only (when elective lymph node irradiation is not required):

- 63 Gy in 28 fractions over 5.5 weeks (Grade B)
- 50 Gy in 16 fractions over 3 weeks (T1 disease only) (Grade C)
- 55 Gy in 20 fractions over 4 weeks (Grade C)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-Based Medicine.[12]

Radiotherapy alone for oropharynx/hypopharynx/larynx cancer (excluding T1/2 glottic carcinoma)

Single-modality treatment with surgery or radiotherapy is the standard of care for early-stage disease. For locoregionally advanced disease, the use of concurrent chemotherapy may not be appropriate for some patients due to co-morbidity or limited performance status.

Conventional fractionation remains standard. A retrospective multicentre comparison of patients treated with radiotherapy alone with schedules of 70 Gy in 35 fractions or 65–66 Gy in 30 fractions showed no difference in disease outcomes or late toxicity.[13] In the meta-analysis of altered fractionation, there was no interaction between tumour stage and the impact of altered fractionation; based upon the local control benefit modest acceleration can be considered when treating patients with low nodal burden with radiotherapy alone.[1]

Recommendations

- 70 Gy in 35 fractions over 7 weeks (Grade A)
- 65–66 Gy in 30 fractions over 6 weeks (Grade C)
- 70 Gy in 35 fractions, 6 fractions per week over 6 weeks (Grade B)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-Based Medicine.[12]

Radiotherapy with concomitant chemotherapy for oropharynx/hypopharynx/larynx cancer

Radiotherapy with concurrent chemotherapy is the current standard of care for the definitive management of patients with more advanced disease. The international standard schedule

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is 70 Gy in 35 fractions. The ongoing Torpedo trial[14] in oropharynx cancer patients has adopted a similar dose fractionation of 70 Gy in 33 fractions over 6.5 weeks. Although not directly compared, a modestly hypofractionated schedule of 65–66 Gy in 30 fractions has been adopted as standard practice in a number of UK trials and centres.[4,15] HPV status in oropharyngeal carcinoma is a strong independent prognostic factor for survival.[16] However, in the anticipation of robust phase III evidence from ongoing de-escalation studies, radiotherapy dose and fractionation for HPV-positive oropharyngeal carcinomas should be no different to that for HPV-negative oropharyngeal tumours (Grade D).

Recommendations

- 70 Gy in 35 fractions over 7 weeks (Grade B)
- 70 Gy in 33 fractions over 6.5 weeks (for oropharyngeal carcinomas) (Grade C)
- 65–66 Gy in 30 fractions over 6 weeks (Grade C)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-Based Medicine.[12]

Elective lymph node irradiation

The dose to elective lymph node regions is based upon historical consensus and is generally delivered as a radiobiological equivalent dose of approximately 50 Gy (EQD2). This is usually achieved as part of a single radiotherapy plan with a reduced fraction size (eg 1.5–1.6 Gy) to elective lymph node volumes compared with conventional fractionation to high-dose target volumes. Data suggest that elective lymph node irradiation may be safely delivered with a reduced fraction size.[17] Although an elective lymph node EQD2 of 50 Gy remains standard there is ongoing interest in dose de-escalation. A randomised trial of 200 patients compared an elective nodal EQD2 dose of 50 Gy versus 40 Gy and reported long-term results showing no difference in elective nodal failure between these doses.[18] In a retrospective cohort of 233 HNSCC patients (90% HPV negative) who received an elective nodal dose of 40 Gy, the 2-year actuarial rate of elective volume recurrence was low (3.9%).[19]

Recommendations

- Standard dose for elective lymph node target volumes is to deliver an EQD2 50 Gy (using α/β=10).

Within a single-phase IMRT plan the following dose levels are appropriate:

- 54 Gy in 30 fractions over 6 weeks (Grade C)
- 56–57 Gy in 35 fractions over 7 weeks (Grade C)

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Head and neck squamous cell carcinoma of unknown primary

Dose fractionation to the neck for gross disease, in the adjuvant setting and to elective nodal volumes will parallel that for HNSCC of known primary sites. Rates of primary emergence are low, with a meta-analysis of retrospective series showing lower rates of primary site emergence for patients treated with neck and mucosal radiotherapy versus neck only (12% versus 16%).[20] These data are largely from an era before positron emission tomography (PET) so relevance to modern practice with the increasing use of base of tongue mucosectomies is uncertain. Putative mucosal sites of origin may be treated, with selection of mucosal sites dependent upon the clinical scenario/HPV status.[21] An EQD2 dose of 50 Gy (using α/β=10) is recommended if mucosal irradiation is being utilised, with multiple series reporting very low rates of subsequent emergence of a mucosal primary.[22,23] Treating involved neck only is also a valid strategy, with evidence supporting this approach when patients are thoroughly investigated with modern diagnostic techniques.[24]

Recommendations

Dose and fractionation to neck target volumes are the same as those used for HNSCC of known primary sites. When mucosal irradiation is to be delivered to potential mucosal primary sites, the number of fractions is dependent upon neck management. Appropriate doses to the mucosal target are:

- 54 Gy in 30 fractions over 6 weeks (Grade C)
- 56 Gy in 33 fractions over 6 weeks (Grade C)
- 56–57 Gy in 35 fractions over 7 weeks (Grade C)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-Based Medicine.[12]

Postoperative radiotherapy: primary site and neck

Adjuvant doses to both the primary site and dissected neck have been developed on a background of very limited randomised data to guide a dose response relationship.[25] Historical studies showed no clear dose response for radiation doses ≥57.6 Gy (1.7 Gy/fraction), although patients with extranodal extension (ENE) had higher recurrence rates at 57.6 Gy than ≥63 Gy (1.8 Gy/fraction).[26] Postoperative doses of 60–66 Gy in 30–33 fractions were used in the Radiation Therapy Oncology Group (RTOG) and European Organisation for Research and Treatment of Cancer (EORTC) trials investigating the role of concurrent chemotherapy.[27,28] Modern adjuvant studies give a dose of 60 Gy in 30 fractions with an optional boost of 6 Gy in the presence of ENE.[29,30] A recent database analysis of adjuvant radiotherapy for HNSCC in 15,836 patients did not demonstrate a survival benefit from dose escalation beyond EQD2 60 Gy even in the presence of high-risk factors.[28] A meta-analysis of accelerated versus conventionally fractionated radiotherapy in high-risk adjuvant patients did not show a benefit of altered fractionation[31] (Level 1a). De-escalation of dose in the context of HPV-related oropharyngeal disease is currently being investigated.[32]

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There is uncertainty regarding the optimal dose to surgically dissected and pathologically negative neck nodal levels. A dose of 60 Gy in 30 fractions has been commonly used.[33] In ongoing adjuvant studies of HPV-related oropharyngeal disease[32] an EQD2 dose of 50 Gy (using α/β=10) is used.

Recommendations

- 60 Gy in 30 fractions over 6 weeks to surgically treated areas (Grade B)
- A dose of up to 66 Gy in 33 fractions over 6.5 weeks may be delivered to high-risk subvolumes (areas surrounding extracapsular spread and/or positive/close margins) (Grade B)
- 54–60 Gy in 30 fractions to surgically dissected and pathologically node-negative neck nodal levels (Grade C)
- 54–56 Gy in 30–33 fractions over 6 to 6.5 weeks to undissected elective lymph node regions (Grade C)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-Based Medicine.[12]

Sinonasal carcinoma

Sinonasal malignancy is rare and heterogenous with multiple pathological types and patterns of invasion. For most pathological types, the standard of care is surgery followed by consideration of adjuvant (chemo)radiotherapy for resectable disease. Radiotherapy doses used are broadly similar for squamous and non-squamous histological subtypes. In a retrospective analysis, adjuvant doses of ≥60 Gy were associated with improved survival outcomes on univariate analysis.[34] Centres have reported favourable outcomes with a dose of 60 Gy in 30 fractions with a 6 Gy boost if positive surgical margins were present.[35] A UK survey of clinical practice and workshop[36] found consensus for a dose of 60 Gy in 30 fractions following an R0 resection, while for an R1 resection there was a lack of consensus between 60 Gy in 30 fractions and 66 Gy in 33 fractions.

Esthesioneuroblastoma (olfactory neuroblastoma) is a rare malignancy, often treated with a combined modality approach. A wide range of radiotherapy doses have been reported in the literature and it is not possible to define a clear dose response. It has been recommended that similar doses to those used for other sinonasal tumours are appropriate.[37]

Recommendations

- 60 Gy in 30 fractions over 6 weeks (Grade C)
- Increased dose of 66 Gy in 33 fractions over 6.5 weeks can be considered following an R1 resection (Grade C)
- 70 Gy in 35 fractions over 7 weeks for unresectable disease or R2 resection (Grade C)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-Based Medicine.[12]

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Nasopharyngeal carcinoma (NPC)

There is a clear radiotherapy dose response relationship; underdose of the tumour target (≥65 Gy when treating 2 Gy per fraction) is associated with inferior local control and survival.[38] A commonly agreed standard total dose is in the order of 70 Gy in 33–35 fractions or equivalent (2–2.12 Gy per fraction), with 54–60 Gy for at-risk areas.[39,40] Use of a dose of 65 Gy in 30 fractions has also been reported within the UK.[41] Lower radiotherapy doses are routinely used for the treatment of children and adolescents with NPC.[42]

Recommendations

- 70 Gy in 35 fractions over 7 weeks (Grade A)
- 70 Gy in 33 fractions over 6.5 weeks (Grade A)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-Based Medicine.[12]

Salivary gland malignancies

Surgery is the primary treatment modality and adjuvant radiotherapy is routinely recommended for T3/4 disease, adenoid cystic carcinoma or other adverse pathological features. Dose response data are lacking and postoperative radiotherapy is given at a dose of at least EQD2 of 60 Gy (using α/β=10) to the high-dose target volume.[43,44] A dose of EQD2 66 Gy can be considered in the event of positive margins. Perineural infiltration is a risk factor for recurrence; adenoid cystic carcinomas are particularly prone to nerve invasion. Nerves at risk may be treated electively to the skull base;[44] a dose in the order of EQD2 50–60 Gy is appropriate (Grade D).

Recommendations

For adjuvant radiotherapy:

- 60 Gy in 30 fractions over 6 weeks (Grade C)
- Increased dose of 66 Gy in 33 fractions over 6.5 weeks can be considered following an R1 resection (Grade C)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-Based Medicine.[12]

Reirradiation

Reirradiation for recurrent or second primary head and neck cancers with curative intent is highly challenging and individualised in a heterogenous group of patients. Appropriate patient selection is addressed in the RCR *Head and neck consensus statements 2022*.[45]

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An analysis of volume, dose and fractionation by the Multi-Institution Reirradiation (MIRI) Collaborative[46] has suggested that elective nodal irradiation does not improve locoregional control rates. Altered fractionation, including hyperfractionation, was not advantageous compared with conventional fractionation in terms of disease control or late toxicity (Grade C). There was a dose response relationship for definitive reirradiation, with reirradiation IMRT to doses of ≥66 Gy (conventionally fractionated) appearing safe and associated with improved disease outcomes (Grade C). Following surgery with no residual gross disease, conventionally fractionated doses of 50–66 Gy appeared adequate (Grade C). There is growing evidence that stereotactic body radiotherapy (SBRT) reirradiation is relatively safe with, to date, no clear evidence of benefit compared with IMRT for disease control.[46–49] Brachytherapy either as definitive or adjuvant treatment is a further option with acceptable toxicity.[50,51]

Palliative radiotherapy

Palliative radiotherapy is used in a very heterogenous group of patients and may range from the use of a single fraction to stop bleeding or fungation to the use of high doses to achieve longer-term disease control while accepting that a cure is not possible. Hypofractionated palliative radiotherapy can be used for symptoms such as pain, swallowing, breathing and speech.[52] Response is dose related so some selected patients with good performance status and more limited disease burden may benefit from more intensive schedules.[52] There is no high-level evidence on which to recommend a specific palliative radiotherapy schedule,[52] with a survey of UK practice showing a host of different schedules in use.[53] The use of conformal radiotherapy techniques is appropriate to facilitate the delivery of higher-dose schedules.

Recommendations

Examples of some appropriate dose fractionation schedules include:

- 8–10 Gy in 1 fraction (Grade D)
- 25 Gy in 5 fractions over 1 week[54] (Grade C)
- 20 Gy in 5 fractions over 1 week[53] (Grade D)
- 30 Gy in 10 fractions over 2 weeks (Grade D)
- 24 Gy in 3 fractions over 3 weeks (fractions on day 1, 8, 22)[55] (Grade C)
- 40 Gy in 10 fractions over 4 weeks ‘split course’[56] (Grade C)
- 14 Gy in 4 fractions, which may be repeated 2 further times every 4 weeks (Grade C)[57]

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-Based Medicine.[12]

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