6.
Head and neck cancer

Background

Intensity-modulated radiotherapy (IMRT) is the accepted standard radiotherapy for patients undergoing primary and adjuvant radiotherapy for head and neck squamous cell carcinomas; exceptions are T1/T2N0 glottic cancer and the use of low-dose palliative radiotherapy. The international standard for definitive treatment remains 70 Gray (Gy) in daily fractions of 2 Gy over seven weeks, although altered fractionation regimens have been widely used. In the UK, many centres have adopted 65–66 Gy in 30 fractions over six weeks as a standard regimen. Most centres employ a simultaneous integrated boost technique with IMRT to treat all target volumes and elective lymph node regions to varying dose levels in each fraction (rather than the use of multiple phases or a matched neck field). This has led to altered fractionation regimens for either high-dose or elective treatment volumes.[1]

T1/2N0 glottic carcinoma

Hypofractionated regimens are recommended.[2] A randomised trial demonstrated the superiority of modest hypofractionation with 2.25 Gy per fraction and, in large retrospective series, fraction sizes of ≥2.25 Gy compared favourably with other reported series.[2–4] Several UK series have reported high rates of local control with shorter more hypofractionated schedules including 50–52.5 Gy in 16 fractions over three weeks for T1 disease and 55 Gy in 20 fractions for T1 and T2 disease.[5–8] Hyperfractionated schedules have not shown a significant improvement compared with conventional fractionation.[9]

Recommendations

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.[10]

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

A meta-analysis of 15 trials of altered fractionation without chemotherapy in non-nasopharyngeal head and neck squamous cell carcinoma (predominantly oropharynx and larynx cancers) showed a modest benefit in overall survival (3.4% at five years) and local control (6.4% at five years).[11] The overall survival benefit was mainly seen with hyperfractionation (8.2% at five years) although these schedules are difficult to implement and are not widely used (Level 1a).[10] The Danish Head and Neck Cancer Group (DAHANCA) regimen of six fractions per week showed an improvement of 10% in five-year locoregional control in patients treated without chemotherapy with transiently increased acute toxicity.[12] In the meta-analysis the overall survival benefit of acceleration without a total dose reduction was 2% at five years, and 1.7% at five years with a total dose reduction.[11] There was no benefit of altered fractionation for patients age >70 years old (Level 1b).[10,11]

Elective lymph node and mucosal doses with IMRT

A biological equivalent dose (EQD2) of 50 Gy in 25 fractions is a standard dose to electively treat lymph node regions. Although there is no direct evidence of the need for higher doses for microscopic disease, some centres favour the use of an additional 'intermediate' risk higher elective dose, such as a biological equivalent to 60 Gy in 30 fractions, to regions deemed to be at higher risk of harbouring disease, particularly radiologically equivocal areas for nodal disease (Level 4).[10,13]

In the management of head and neck carcinomas of unknown primary, commonly used mucosal doses are the biological equivalent of 50–60 Gy in 25–30 fractions.[14–17] Several series have suggested that doses at the lower end of this dose range are associated with very low rates of subsequent emergence of a mucosal primary (Level 4).[10,15–17]

To incorporate elective lymph node and mucosal doses into a single phase IMRT plan, two approaches to dose fractionation can be adopted: i) accept moderate hypofractionation to sites of known disease while retaining a conventional fraction size (1.8–2 Gy) for elective lymph node treatment or ii) retain a conventional fraction size to known disease and deliver a reduced fraction size to the elective lymph node regions (for example, 1.5–1.6 Gy). An increasing number of series suggest that elective lymph node irradiation may be safely delivered with a reduced fraction size (Level 4).[11,18]

Recommendations

For elective nodal treatment using IMRT with a matched lower neck technique:

50 Gy in 25 fractions over 5 weeks to the matched neck (Grade C)

Elective treatment within the 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)
60 Gy in 30 fractions over 6 weeks or 63 Gy in 35 fractions over 7 weeks may be additionally used for 'intermediate' risk regions (Grade D)

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.[10]

Radiotherapy alone for early stage (I/II) oropharynx/hypopharnx/larynx cancer (excluding T1/2 glottic carcinoma)

Single modality treatment with surgery or radiotherapy is the standard of care. The relative merits of conventional versus altered fractionation remain unclear. IMRT with modest acceleration has shown high rates of local control with low rates of late toxicity.[19] Patients with early stage disease accounted for >50% of patients in the DAHANCA 6 and 7 trial which demonstrated a substantial benefit of shortening overall treatment time without reduction in total dose (66–68 Gy in 33–34 fractions delivered at five versus six fractions per week).[12] In a meta-analysis, there was no clear benefit for altered fractionation for the subgroup with stage I/II disease (Level 1a).[10,11]

Recommendations

Stage I/II oropharynx, hypopharynx or non-glottic larynx cancer:

70 Gy in 35 fractions over 7 weeks (Grade C)
65–66 Gy in 30 fractions over 6 weeks (Grade C)
66 Gy in 33 fractions or 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.[10]

Radiotherapy with concomitant chemotherapy for stage III/IVa/b HNSCC (excluding nasopharyngeal carcinoma)

Radiotherapy with concurrent cisplatin is the current standard of care for the definitive management of stage III/IV patients <70 years of age with adequate performance status.[20] The international standard schedule is 70 Gy in 35 fractions.[20] 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.[21] There has been considerable interest in combining perceived benefits of altered fractionation with concurrent chemotherapy. However, the Radiation Therapy Oncology Group (RTOG) 0129 trial compared 72 Gy in 42 fractions delivered over six weeks with two cycles of concurrent chemotherapy with a standard arm of 70 Gy in 35 fractions over seven weeks with three cycles of concurrent chemotherapy with no difference seen between the arms.[22] The three arm Groupe d'Oncologie Radiothérapie Tête et Cou (GORTEC) 99-02 phase III trial compared 70 Gy in 35 fractions over seven weeks with three cycles of concurrent chemotherapy with 70 Gy over six weeks with two cycles of concurrent chemotherapy and a very accelerated radiotherapy alone arm of 64.8 Gy in 3.5 weeks; there was no benefit of modest acceleration with concurrent chemotherapy while the accelerated radiotherapy alone arm was inferior (Level 1b).[10,23] These data support a hypothesis that concurrent cisplatin may suppress tumour repopulation during radiotherapy, leading to a lower than expected tumour biologically equivalent dose with modestly accelerated schedules.[24] Reported outcomes for hypofractionated IMRT schedules with concomitant chemotherapy (65 Gy in 30 fractions over six weeks or 55 Gy in 20 fractions over four weeks) do not as yet support this hypothesis (Level 2b).[10,21,25]

In patients with oropharyngeal cancer, the tumour human papilloma virus (HPV) status has been identified as a strong and independent prognostic factor for survival.[26] In the anticipation of robust 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).[10]

Recommendations

Radiotherapy with concomitant chemotherapy:

70 Gy in 35 fractions over 7 weeks (Grade A)
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.[10]

Radiotherapy alone for stage III/IVa/b HNSCC (excluding nasopharyngeal carcinoma)

The meta-analysis does not show a benefit of concomitant chemotherapy in patients >70 years old (Level 1a).[10,20] Concomitant chemotherapy or cetuximab may not be appropriate for some patients <70 years old due to co-morbidity, fitness or patient choice. Altered fractionation is an option for fit patients <70 years old treated with radiotherapy alone with superior local control and no increase in late toxicity; meta-analysis of altered fractionation studies did not show a benefit for alterated fractionation in patients ≥70 years old (Level 1a).[10,11,12,27]

Recommendations

Radiotherapy without concomitant radiotherapy:

66 Gy in 33 fractions or 70 Gy in 35 fractions, 6 fractions per week, over 6 weeks (Grade A)
70 Gy in 35 fractions over 7 weeks (Grade B)
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.[10]

Postoperative radiotherapy

There are few studies of radiation dose with postoperative radiotherapy with or without chemotherapy. Historical studies suggest that for adjuvant radiotherapy alone, patients with extracapsular extension benefitted from doses of 63 Gy and for other patients there was no benefit >57.6 Gy (Level 2b).[10,28] Adjuvant doses of 60–66 Gy in 30–33 fractions were used in the RTOG and European Organisation for Research and Treatment of Cancer (EORTC) trials investigating the role of concurrent chemotherapy.[29,30] A pooled analysis identified subgroups with close/positive margins and/or extracapsular spread as benefiting from concurrent cisplatin (Level 2a).[10,31] Based on limited evidence of a dose-effect in the adjuvant setting, a dose of 66 Gy in 33 fractions is considered standard in the presence of high-risk pathological findings, and 60 Gy in 30 fractions is widely used in the absence of high-risk features.[32,33] Doses equivalent to 50–54 Gy in 2 Gy per fraction are commonly used for lower risk areas at risk of microscopic disease (Level 4).[10,33]

Recommendation

Postoperative radiotherapy:

60 Gy in 30 fractions over 6 weeks (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)

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.[10]

Nasopharyngeal carcinoma

Radiotherapy alone is used for early stage nasopharyngeal carcinoma.[34] For locally advanced disease, conventionally fractionated radiotherapy combined with chemotherapy is currently recommended. RTOG phase 2 trials have used a high, intermediate and elective three dose level approach of 70 Gy, 59.4 Gy and 54 Gy in 33 fractions (Level 2b).[10,35] A case series of altered fractionation using 65 Gy in 30 fractions with an elective dose level of 54 Gy in 30 fractions has reported disease outcomes and toxicity (Level 4).[10,36] Doses biologically equivalent to 50–60 Gy in 2 Gy per fraction are commonly used to treat at-risk sites.[34]

Recommendations

Nasopharyngeal cancer:

70 Gy in 35 fractions over 7 weeks (Grade A)
70 Gy in 33 fractions over 6.5 weeks (Grade B)
65 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.[10]

Palliative radiotherapy schedules

Palliative radiotherapy is used in a very heterogenous group of patients, and may range from the use of a single fraction to stop bleeding/fungation to the use of high doses to achieve longer-term disease control while accepting that a cure is not possible. Decisions with regard to palliative radiotherapy dose fractionation take into account symptoms, disease extent and co-morbidity. When higher doses are delivered, three-dimensional (3D) conformal radiotherapy or IMRT are often required due to proximity to critical structures.

There is no consensus for palliative radiotherapy for locally advanced head and neck cancer.[37]

Recommendations

Examples of appropriate dose fractionations include:

40 Gy in 10 fractions over 4 weeks 'split course' (Level C)[38]
*24 Gy in 3 fractions over 3 weeks (Level C)[39]
20 Gy in 5 fractions over 1 week (Level C)[40]
14 Gy in 4 fractions which may be repeated 2 further times every 4 weeks (Level C)[41]

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.[10]

*Please note this recommendation was corrected on 2 December 2020 from 8 Gy in 3 fractions over three weeks (Level C). It had been previously updated on 20 November 2020 from the original schedule which incorrectly stated 21 Gy in 3 fractions over 3 weeks (Level C).

Re-irradiation

Re-irradiation with curative intent can be an option for selected patients with limited local recurrence or new primary disease who are unsuitable for surgical treatment/decline surgery. Re-irradiation may also be considered following salvage surgery with adverse histological features (for example, positive margins, extracapsular spread). Patient selection, choice of dose fractionation and dose constraints are individualised dependent on the extent of recurrence, time from previous radiotherapy, sequalae of prior treatment, proximity to organs at risk, performance status, co-morbidity and nutritional status. Radiotherapy target volumes are limited to high-risk areas only and do not include elective regions. Ideally the aim should be to deliver a dose equivalent of ≥60 Gy in 2 Gy per fraction, although the dose may need to be reduced on an individual basis if organ at risk tolerances are exceeded.[40,41] Hyperfractionation with bi-daily irradiation at approximately 1.2 Gy per fraction can be considered (Grade C).[10,41] The use of concomitant radiosensitising agents should only be used with extreme caution.

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