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Critical Review Article

Summary of major radiation fractionation and chemotherapy trials for organ preservation therapy in locally advanced head and neck squamous cell carcinoma

James T. Parsons MD [a,*], Bruce D. Greene MD [b]

[a]*South Florida Radiation Oncology, Boynton Beach, Florida*
[b]*Valley View Hospital, Glenwood Springs, Colorado*

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Abstract

Purpose: To review radiation fractionation and chemotherapy trials for patients undergoing organ preservation therapy for locally advanced head and neck squamous cell carcinoma.

Methods and materials: Radiation therapy fractionation and chemotherapy trial results as well as historical evidence are systematically reviewed.

Results: Trial results, which involve nearly 30,000 patients, have been interpreted, compared, and presented in a structured manner to demonstrate the changing approaches in treatment over the years from the 1960s to the present. The review includes data from the split-course radiation therapy era, meta-analyses of chemotherapy and radiation therapy fractionation trials, cetuximab trials, "triple-drug trials," and modern trials of induction chemotherapy followed by concomitant chemotherapy and radiation therapy.

Conclusions: This summary will be useful to clinicians making treatment decisions today and to investigators designing trials in the future.

Introduction

Approximately 70% to 75% of patients with head and neck squamous cell cancers (HNSCC) arising from the oropharynx, hypopharynx, or supraglottic larynx have stage III or IV ("moderately advanced" or "advanced") disease at presentation with 5-year survival rates of 30% to 40%. Numerous radiation therapy (RT) and chemotherapy (chemo) strategies have evolved over the past several decades to improve these results, including split-course RT, altered fractionation RT, concomitant chemo-RT, induction chemotherapy (IC), and various combined strategies. Following is a review of those data.

Split-course RT

Planned split-course RT is a program that introduces an interruption into the treatment schedule during which no RT is given. It was developed in the 1970s to reduce mucosal toxicity and remained popular until retrospective

Conflicts of interest: None.

* Corresponding author. South Florida Radiation Oncology, 2301 W. Woolbright Rd, Boynton Beach, FL 33426.
E-mail address: jtparsons007@yahoo.com (J.T. Parsons).

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analyses showed it produced significantly worse locoregional control and survival.[1,2] Furthermore, it did not reduce late effects, which depend on total dose and dose per fraction rather than overall treatment time.[3,4] Attempts to "overcome the split" by increasing total dose produced high rates of late complications.[1]

Altered fractionation RT

Altered fractionation (AltFx) refers to deviation from conventional once-daily RT (CnvRT) and includes both hyperfractionated RT (HFRT) and accelerated fractionation RT (AcFRT). Although some use the AcFRT and HFRT terms interchangeably, there are important differences.

AcFRT refers to abbreviating treatment duration using conventional or slightly less than conventional fractions (ie, 1.6-2.0 Gy), usually with twice-daily (BID) RT. Total dose is similar to or slightly less than CnvRT (ie, MD Anderson's "concomitant boost" technique of 72 Gy/42 fractions/6 weeks).[4]

HFRT uses a larger number of smaller than conventional fractions with an overall treatment time similar to or slightly less than CnvRT, typically with BID RT. Total dose is higher than CnvRT (ie, University of Florida's 74.4-76.8 Gy/62-64 fractions at 1.2 Gy BID/6-6.5 weeks).[5]

Meta-analysis of RT in cancer of the head and neck (MARCH)

MARCH included 6515 patients from 15 randomized trials comparing CnvRT to AcFRT or HFRT without chemotherapy.[6]

Findings of the MARCH study

1. AltFx schedules (AcFRT, HFRT) yielded an 8.5% absolute (23% relative) reduction in local failure and significantly higher locoregional control ($P < .001$).
2. AltFx produced a 3.4% 5-year survival benefit ($P = .01$), with the main benefit in the HFRT (8% absolute, 29% relative) rather than the AcFRT group (2% absolute, 5.6% relative).

The authors noted the 8% survival benefit with HFRT alone exceeded the 6.5% survival benefit of concomitant chemo-CnvRT in the Meta-Analysis of Chemotherapy in Head and Neck Cancer (MACH-NC) analysis.[7]

Radiation Therapy Oncology Group 9003

Final results of Radiation Therapy Oncology Group (RTOG) 9003, the largest fractionation trial, support the MARCH conclusions.[8] RTOG 9003 included 1076 patients with stage III-IV disease randomly assigned to receive RT alone by 1 of 4 schedules:

1. CnvRT (70 Gy at 2 Gy/fraction/7 weeks).
2. HFRT (81.6 Gy at 1.2 Gy/fraction BID, "University of Florida protocol" albeit with higher doses).[5]
3. AcFRT split-course (67.2 Gy at 1.6 Gy BID with a 2-week interruption after 38.4 Gy, "Massachusetts General protocol").[9]
4. AcFRT-concomitant boost ("MD Anderson protocol").[4]

Only the HFRT arm significantly improved locoregional control ($P = .05$) and 5-year survival ($P = .05$). HFRT did not increase late toxicity. AcFRT concomitant boost produced more late grade 3-5 toxicities ($P = .06$). "From the late toxicity and long-term efficacy endpoints, RTOG 9003 suggested that HFX [HFRT] yielded the optimal results."[8]

Concomitant chemo-HFRT versus HFRT alone

Five randomized trials asked whether concomitant chemo-HFRT provides benefit over HFRT alone.

1. Brizel et al[10] compared HFRT (1.25 Gy BID to 75 Gy) with chemo-HFRT (1.25 Gy BID to 70 Gy plus concomitant cisplatin/fluorouracil [5-FU] ×2). At 3 years, chemo-HFRT produced higher locoregional control (70% vs 44%, $P = .01$), overall survival (55% vs 34%, $P = .07$), and relapse-free survival (61% vs 41%, $P = .08$) without additional toxicity.
2. Jeremic et al[11] compared HFRT (77 Gy at 1.1 Gy BID) with HFRT plus concomitant cisplatin. Chemo-HFRT produced significantly higher 5-year survival (46% vs 25%, $P = .0075$), progression-free survival (46% vs 25%, $P = .0068$), locoregional progression-free survival (50% vs 36%, $P = .041$), and distant metastasis-free survival (86% vs 57%, $P = .0013$) without additional acute or late high-grade toxicity.
3. Ghadjar et al[12] compared HFRT (74.4 Gy at 1.2 Gy BID) with HFRT plus cisplatin. At 10 years, chemo-HFRT produced significantly higher locoregional failure-free survival (40% vs 32%, $P = .049$), distant metastasis-free survival (56% vs 41%, $P = .02$), and cancer-specific survival (55% vs 43%, $P = .03$). Five-year survival (estimated from survival curves) favored chemo-HFRT (46% vs 32%, $P = .11$). Acute and major late toxicities were similar.[13]
4. Budach et al[14] compared dose escalated hyperfractionated accelerated radiation therapy (HART) alone (14 Gy/7 fractions once daily, then 1.4 Gy BID to 77.6 Gy) with C-HART (30 Gy/15 fractions once daily, then 1.4 Gy BID to 70.6 Gy plus concomitant 5-FU/mitomycin C). C-HART produced higher 5-year locoregional