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CLINICAL INVESTIGATION

Hypofractionated Versus Normofractionated Accelerated Radiation Therapy With or Without Cisplatin for Locally Advanced Head and Neck Squamous Cell Carcinoma (HYPNO): A Randomized, Open-Label, Phase 3, Noninferiority Trial

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Data Sharing Statement: The HYPNO (HYPo-fractionated vs NOrmofractionated radiation therapy for HNSCC) TMG will consider data sharing requests by academic groups to the corresponding author for deidentified patient data on a case-by-case basis. The study protocol is provided in the appendix of this publication.

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Purpose: Based on bioeffect modeling of published outcomes after radiation therapy for head and neck squamous cell carcinoma with various time-dose-fractionation, we hypothesized that a 20-fraction hypofractionated (HFX) schedule delivering 55 Gy in 20 fractions, 5 fractions per week, over 4 weeks would be noninferior to a 33-fraction accelerated, normofractionated (NFX) 2 Gy per fraction schedule, delivering 66 Gy in 2-Gy fractions, 6 fractions per week over 5.5 weeks with respect to both local tumor control and late adverse events.

Methods and Materials: The HYPNO (HYPo-fractionated vs NOrmo-fractionated radiation therapy for head and neck squamous cell carcinoma) trial was designed as a multicenter, pragmatic, embedded, 2-arm, unblinded, randomized controlled noninferiority trial with dual primary endpoints, loco-regional tumor control, and grade 3 or higher late adverse events with a 10% noninferiority margin for both endpoints. The trial was open for enrollment in 12 centers, each adhering to their standard of care to the extent that it was consistent with the requirements of the trial protocol. Concurrent chemoradiation therapy with 35 mg/m^2 cisplatin weekly was permitted.

Results: Between March 2014 and February 2020, 792 patients were centrally randomized: 395 to HFX and 397 to NFX. Accrual closed, with all outcome data still blinded, with 792 of a planned 836 patients (94.7%) enrolled, in part due to the emerging COVID-19 pandemic. The HYPNO test arm passed the separate noninferiority tests for both loco-regional tumor control ($P = .04$) and grade 3+ late adverse events ($P = .004$). At 3 years, the absolute difference in outcome between the 2 arms was ≤1.4 percentage points for overall survival, progression-free survival, loco-regional control, and grade 3+ late adverse events. The planned subgroup analyses showed no statistically significant heterogeneity of effect estimates for loco-regional control between the 2 trial arms.

Conclusions: The HYPNO test arm schedule was shown to be noninferior with respect to both loco-regional tumor control and grade 3+ late adverse events.

Introduction

A series of randomized controlled trials (RCTs) conducted in the 1990s and early 2000s explored 2 biological hypotheses[1-3]: (1) delivering radiation therapy with an increased number of smaller dose fractions would spare late adverse events and thereby allow escalation of the dose to tumor for the same level of late toxicity; and (2) increasing the rate of dose delivery beyond the standard 10 Gy per week would improve tumor control with an unchanged level of late toxicity. The synthesis of data from these trials allowed statistical estimates of the dose-time-fractionation biology of locally advanced head and neck squamous cell carcinoma (HNSCC) quantified using the linear-quadratic (LQ) model with a linear correction for overall treatment time.[4,5] Interest in schedules delivering multiple fractions per day was tempered by the outcome of the thrice-a-day Continuous Hyperfractionated Accelerated Radiation Therapy trial,[6] which showed less sparing than anticipated, supporting the hypothesis that recovery kinetics of sublethal radiation injury in humans were much slower than in rodent models.[7] This realization, together with the model parameters estimated from the published outcomes of RCTs available at the time, led the investigators to explore shorter, HFX schedules for definitive treatment of locally advanced HNSCC. Specifically, we hypothesized that shortening the overall treatment time from around 7 to 4 weeks, by delivering an increased dose in each daily fraction, would allow a sufficient reduction of total dose to ensure noninferiority with respect to late toxicity and at the same time maintain noninferiority with respect to tumor control due to the accelerated dose accumulation.

Each year 7 million people die of cancer, 5 million of these in low-and-middle-income countries (LMICs). Although HNSCCs account for 4% to 5% of incident cancers worldwide, it is more frequent in many LMIC, as an example, HNSCC account for 30% of incident cancers in India. Fractionated radiation therapy remains a standard option for definitive treatment for locally advanced HNSCC as an organ-preserving alternative to surgery or in cases that are medically or technically inoperable. One challenge, however, is that the access to state-of-the-art radiation therapy in many LMIC is limited. An HFX schedule delivering a lower number of larger dose fractions would be attractive as it would free-up capacity in the treatment room as well as being more convenient for patients.

On this background, the proposal to test a short HFX schedule as an alternative to a 33 or 35 fraction schedule in an RCT was presented by the PI, among other proposals, at an advisory meeting organized by the Applied Radiation Biology and Radiotherapy Section in the Division of Human Health, Department of Nuclear Sciences and Applications, International Atomic Energy Agency (IAEA) in June 2008. The primary aim of the HYPNO (HYPo-fractionated vs NOrmo-fractionated radiation therapy for HNSCC) trial was to test for noninferiority with respect to both tumor control and late adverse events of such a moderately HFX treatment schedule. The trial was designed as a pragmatic, embedded randomized trial conducted in LMICs with high incidence and mortality of HNSCC. The IAEA requested a full proposal and decided to sponsor the trial as Coordinated Research Project E3.30.35 "Resource Sparing Curative Radiotherapy for Locally Advanced Squamous Cell Cancer of the Head and Neck."

Methods

Study design

HYPNO was designed as a pragmatic, embedded RCT. Each participating center was allowed to use its standard

radiation therapy planning and delivery techniques as long as they complied with the protocol requirements.

The contents of the case record forms (CRFs) and a draft of the protocol were defined by the trial management group (TMG) at an investigators' meeting at IAEA in Vienna, Austria, in March 2010. Data were transferred by the local study team to a "live" pdf form that was subsequently submitted to the data center as an attachment to an email. This asynchronous solution was devised as an alternative to real-time online data entry as not all centers had a reliable internet connection. At the data center, all data were electronically extracted from the form, missing-value and consistency checks were conducted, and, where relevant, blood biochemistry units used by the local laboratory were converted into a standard set of units. Any issues identified by the data center would be sorted by contacting the local site PI or a delegate as needed. No statistical imputation was performed for missing data in any case.

Dose-fractionation and bioeffect modeling

Time-dose-fractionation biology for HNSCC has been a recurring theme for preclinical and clinical radiobiology throughout the history of radiation therapy for cancer. In the 1980s, with the teaching and wider use of the LQ model, it was often argued that because of the alleged differential in the α/β ratios for HNSCC and most late adverse effects, fraction sizes >2.0 Gy would be associated with an unfavorable therapeutic ratio. This simple argument, however, assumes that the overall treatment time is the same in the 2 schedules. A typical HFX schedule is shortened compared with a NFX 2 Gy per fraction schedule. As the effect of shortening overall treatment time is much larger on HNSCC than for late effects, the so-called time-factor allows revisiting hypofractionation as a treatment principle in light of our present understanding of time-dose-fractionation biology. In the early 2000s, emerging clinical evidence pointed to a 4-week accelerated, HFX schedule as a radiobiologically interesting alternative to accelerated schedules using more fractions for the treatment of HNSCC. A series of exploratory calculations suggested that an attractive candidate schedule could be 55 Gy in 20 fractions (2.75 Gy per fraction), and this schedule was chosen for the test arm of HYPNO. For convenience, this schedule will be referred to as the "HYPNO schedule" in the following. Interestingly, there is historical experience with this schedule in the North of the UK and in several countries in the British Commonwealth. Tweaking this schedule was considered, but using the available modeling parameters, the expected therapeutic gain from doing this is very limited. Further, it was seen as a strength to use a well-established schedule in the test arm of the HYPNO trial.

As regards the control arm of the trial, a previous trial sponsored by the IAEA had shown that reducing the overall treatment time to 5.5 weeks by delivering 66 Gy in 2-Gy fractions with 6 fractions per week was superior to a standard schedule delivering 5 fractions per week.[8] This schedule is 9 days shorter than a schedule delivering 70 Gy in 35 fractions with 5 fractions per week, which was considered as an alternative control. Using the well-established estimate of 0.65 Gy/day recovered in HNSCC due to accelerated proliferation, the HYPNO control arm was estimated to produce an equivalent dose in 2-Gy fractions of 71.85 Gy if delivered over the same overall time as the 70 Gy schedule, thus it is predicted to be slightly hotter than that schedule. Consequently, it was decided to use the 5.5-week schedule as the control arm of the HYPNO trial.

Thus, the 2 schedules to be compared were (Fig. 1):

(1) Hypofractionated, accelerated radiation therapy (HFX): 55 Gy delivered in 20 fractions of 2.75 Gy, 5 fractions per week (test arm).
(2) Normofractionated, accelerated radiation therapy (NFX): 66 Gy in 33 fractions of 2.0 Gy, 6 fractions per week (control arm).

If both schedules start on a Monday and are delivered without any unplanned interruptions of the daily treatments, the difference in overall treatment time is 12 days. If they start uniformly on 1 of the 5 weekdays, the average difference in overall treatment time is 11.2 days. This shortening of the overall treatment time, combined with the higher dose per fraction, was hypothesized to allow the total dose to be lowered from 66 to 55 Gy while maintaining efficacy. The historical concern with HFX radiation therapy has been that it would lead to increased

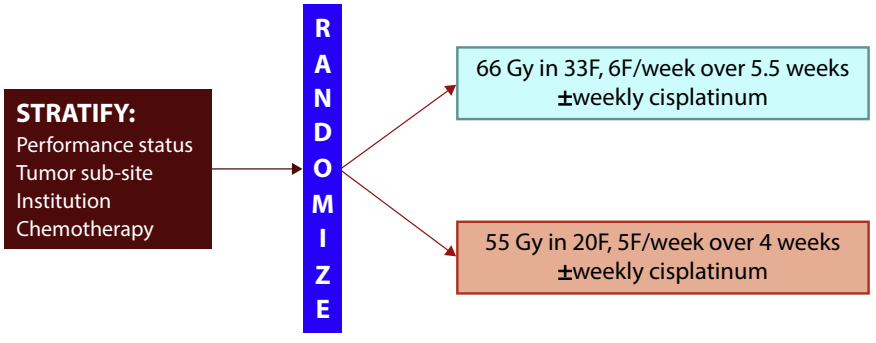

Fig. 1. Trial schema. Patients were assigned to the 33-fraction control arm or the 20-fraction test arm by central, stratified randomization with a uniform allocation ratio.

incidence of late adverse events. Bioeffect calculations, summarized in the protocol, showed that the HYPNO schedule would have about the same anticancer effect with similar or less late toxicity. We therefore designed the HYPNO trial as a dual noninferiority study, aiming for noninferiority with respect to both tumor control and late adverse events.

Patients

Key eligibility criteria were as follows: age >18 years; histopathological diagnosis of invasive HNSCC classified as stage I-IV located in oropharynx, hypopharynx, larynx (excluding glottic stage I-II), or oral cavity according to the TNM classification; WHO performance status of 0-2. Main exclusion criteria were as follows: distant metastases; major comorbidity that could be expected to influence the outcome of treatment or interfere with the assessment of treatment outcome at follow-up, or considerably reduce the life expectancy. Patients should be candidates for definitive external beam radiation therapy and must be expected to be available for long-term follow-up. Written informed consent was obtained before randomization. For details, see the trial protocol (Appendix E1). Centers were not required to maintain a screening log.

Randomization and masking

Concealed, central randomization was initiated by sending the on-study CRF by email to the HYPNO Trial Management Unit at the University of Maryland, Baltimore. The on-study form was reviewed for completeness, and the eligibility of the case for enrollment was verified based on the submitted information. Patients were randomly assigned to a trial arm with a 1:1 allocation ratio using permuted blocks generated with a validated random number generator. Randomization was stratified according to 3 factors: institution, performance status (0-1 vs 2), and prescription of concurrent cisplatin (yes or no). The block size in each stratum had been chosen as 6 by the study statisticians and was not revealed to the participating centers. The allocated trial arm, a unique study identification number assigned to the case, and confirmation of the assigned stratum were returned by email to the center, in general, within 24 hours. Masking was judged not to be feasible. However, the decision to use a specific radiation therapy planning and delivery technique (2 dimensional [2D], 3 dimensional [3D], Intensity Modulated Radiation Therapy [IMRT]) as well as the decision to prescribe concurrent chemoradiation therapy was made *before* randomization to avoid a bias resulting from treatment selection according to randomization arm.

Procedures

Radiation therapy planning and delivery

Two clinical target volumes were defined as follows. The high-dose clinical target volume (CTV-Hi) is a volume or fields encompassing the gross tumor volume with a margin of at least 1 cm and any high-risk regions that need a high dose of radiation. In the case of palpable involved lymph nodes, the neighboring (more caudal) lymph node group is included in CTV-Hi, that is, at least 3 cm distally from the lower part of the palpable lymph nodes. The low-dose clinical target volume is a larger volume including the lymph node levels that need elective irradiation. Conventional radiation therapy could be delivered with a 2 to 3 field technique, appropriately documented with projection images. Field-shaping should be used whenever possible. Reflecting the pragmatic nature of the trial, both telecobalt (^{60}Co) and linear accelerator with 6-MV photons were permitted. The photon source should be selected and specified upfront. Two of the centers used ^{60}Co as the photon source, enrolling a total of 163 cases (21% of the total in HYPNO), 79 in the HFX arm, 84 in the NFX arm, all had 2D planning. Of the remaining patients treated on linear accelerators, only 5 had 2D planning. 3D conformal radiation therapy (3DCRT) should be planned using an appropriate number of fields on a treatment planning system, and appropriate quality assurance should be performed according to departmental guidelines. The local procedure for expanding the CTV to a planning target volume (PTV) should be followed, and the appropriate dose prescription rule should be applied. In-room field verifications were performed according to institutional guidelines. In line with the pragmatic design of HYPNO, each department was requested to make its own detailed treatment specifications, taking the available equipment and resources into consideration. These specifications should contain a description of the field arrangements and dose calculations used for the treatment of different tumor sites. IMRT was used in 70% of cases and was planned and delivered according to local institutional guidelines, treating CTV-Hi and low-dose clinical target volume using the sequential boost or simultaneous integrated boost technique. Of the patients treated with IMRT, 97% were treated with IMRT-sib. Compliance with the International Commission for Radiation Units and Measurements (ICRU) Report 83 report on specification and prescription of IMRT was encouraged. This also includes institutional guidelines for contouring relevant structures and organs at risk as well as the procedure for expanding the CTV to a PTV and the prescription rule used. Planning dose constraints in the 33-fraction NFX arm were those employed by the Danish Head and Neck Cancer Group (DAHANCA), see protocol in Appendix E1. These were converted to constraints in the 20F HFX schedule that would produce the same equieffective dose in 2-Gy fractions, EQD2, for a specific value of the α/β-ratio. For all endpoints, except the spinal cord and the brain stem, α/β = 3 Gy was assumed. For the spinal cord and brain stem, α/β = 2 Gy was assumed. It is important to note that these constraints are estimates that presume the validity of the LQ model. For mean doses to a structure (ie, when the constraint does not refer to a point (or limited volume) dose), the LQ fraction-size adjustment should ideally be applied to each bin in the dose−volume histogram before

calculating the mean dose. In most cases, however, this will be a relatively small correction with the schedules compared in HYPNO.

Concurrent cisplatin

Patients treated with chemoradiation therapy received intravenous cisplatin dosed at 35 mg/m^2 weekly throughout the course of radiation therapy, that is, 4 courses in the HFX arm and 5 courses in the NFX arm. Patients were evaluated weekly by the nursing staff and typically seen every other week by the treating physician. A complete blood count and a serum creatinine test should be obtained with each weekly treatment. Cisplatin was administered only if the absolute neutrophil count >1500/μL and platelets ≥100,000/μL. The cisplatin dose was omitted in the event of grade 2 nephrotoxicity, nausea, or vomiting or with any grade 3 nonhematologic toxicity occurring during the preceding week. A single-arm phase 1 trial of the HFX schedule with weekly cisplatin was conducted in Brazil[9] as a condition by the local institutional review board (IRB) for opening the HYPNO trial in that country. Twenty patients were enrolled, and early toxicity was found to be comparable to that of standard concurrent chemoradiation therapy.

Quality control

A panel case review of 3 randomly selected cases from each center, including details of clinical workup, staging, target volume definitions, and radiation therapy planning, was conducted by the TMG at an investigators' meeting in Vienna, June 2015. The aim of the review was to ensure compliance with protocol guidelines and to improve consistency across participating centers.

Outcomes

HYPNO had 2 coprimary endpoints: loco-regional tumor control and grade 3 or higher late adverse events. Secondary endpoints were overall survival, progression-free survival, and early and late adverse events graded according to Common Terminology Criteria for Adverse Events (CTCAE) 4.0. Patients were seen at least once a week during treatment. Time and severity grading of the early radiation reactions in the mucosa and skin were noted. After treatment, the first scheduled follow-up was about 2 months after the end of therapy to record persistent early toxicities and early tumor response. Afterward, patients were seen every 3 months for 2 years, and 6 months for the subsequent 3 years, bringing the total follow-up to 5 years. The detailed follow-up was according to departmental policies. As a minimum, tumor control was evaluated by clinical examination at each follow-up visit. Patients who had a persistent tumor in the primary or nodal position after the end of treatment were recorded as having a loco-regional failure at the follow-up time when this was clinically ascertained. Radiological examinations, x-rays, or computed tomography were performed according to departmental practice. At each post-treatment visit, a follow-up form was filled in with data on overall loco-regional control and late adverse events graded as per CTCAE 4.0. In case of treatment failure, death, new primary tumor, completion of or loss to follow-up, an off-study form was filled in with data on tumor status, type of event, specification of any salvage treatment, and vital status.

Statistical analysis

We required, conservatively, that the outcomes in the HYPNO test arm should meet the separate noninferiority criterion for both coprimary endpoints. Assuming a 3-year loco-regional control (LRC) rate of 42% and a 3-year rate of grade 3+ late adverse events of 35%, sample size estimates were calculated using the 2-sample log-rank test with 80% power and a 1-tailed significance level of 0.05 for a range of noninferiority margins, with the same percentage point margin for tumor control, Δ_T, and normal tissue effect, Δ_N estimated from the hazard ratio (HR) and calculated at 3 years of follow-up. Consideration of the feasibility of reaching the planned sample size within a reasonable time frame led to the choice $\Delta_T = \Delta_N = 10\%$. Under the assumptions made regarding LRC and grade 3+ late adverse events, the target sample size was 836 patients, which was the larger of the sample sizes calculated for the coprimary endpoints: 836 patients for tumor control and 780 patients for late adverse events. No formal statistical analysis plan was developed for the HYPNO trial analysis beyond the general description in the protocol. In February 2020, the TMG decided, blinded to the maturing outcome data at that time, to stop the trial for further accrual, with a sample size of $N = 792$. This was motivated by the emerging COVID-19 pandemic and the fact that the highest-accruing center, Tata Memorial Hospital (TMH), had reached the 200-enrollee ceiling initially approved by the institutional IRB, which had led to a decreasing accrual rate for the trial at that time.

Data analysis

All outcomes were analyzed using a strict intention-to-treat principle. The 792 patients randomized constitute the analysis set for all cancer and survival outcome analyses (see Fig. 2). Early adverse events, scored weekly during and immediately after the end of treatment, were available in 753 of 792 cases (95.1%). Late adverse events were collected from the follow-up form; 11 patients did not have any information regarding late adverse events at any point in time. Late adverse events were defined according to the protocol as events that occurred or persisted 90 days or more after the end of treatment. Time-to-event endpoints, including the coprimary endpoints, were analyzed as a function of time after randomization to the date when the event was first recorded in the case notes using the Kaplan-Meier estimator, groups were compared using the Mantel-Cox log-rank test, and effect sizes were quantified by the HR estimated from a Cox Proportional Hazards Model with

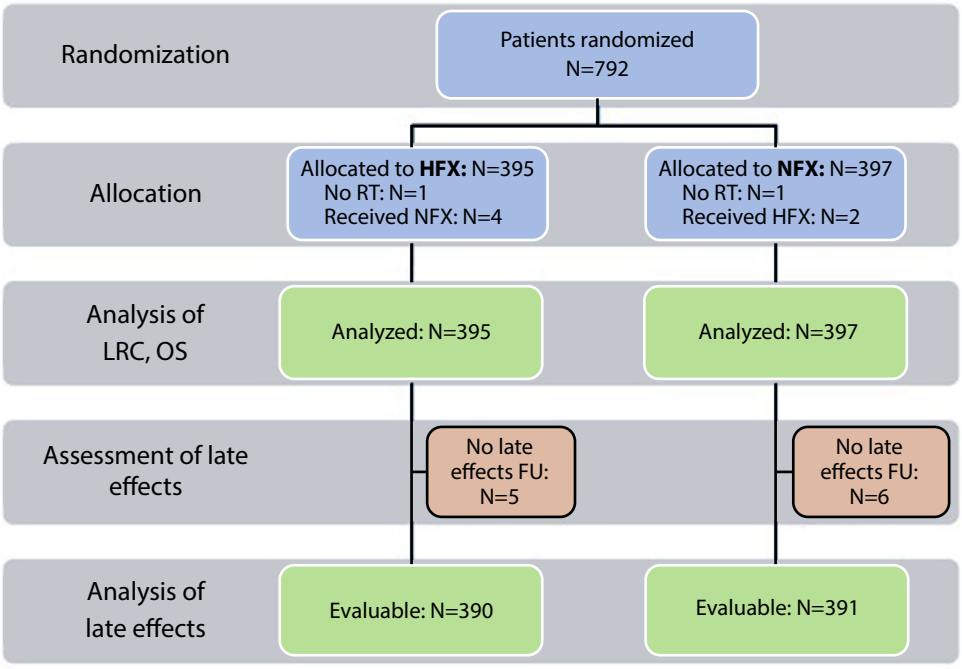

Fig. 2. Study profile. Efficacy outcomes were estimated in the intention-to-treat population. Late adverse events were estimated in the evaluable population, consisting of patients who had at least one assessment of normal tissue effects after therapy. *Abbreviations:* FU = Follow-up; HFX = hypofractionated radiation therapy; LRC = Loco-regional control; NFX = normofractionated radiation therapy; OS = Overall survival; RT: radiation therapy.

treatment arm as the only covariate. The noninferiority margin, Δ, was converted into a critical value of the hazard ratio, HR_c, for each primary endpoint using the observed 3-year estimate of outcome in the NFX arm as a reference value. The value of HR_c was 1.31 for loco-regional control and 1.5 for freedom from grade 3+ late effects. Patients who were alive without having reached a given endpoint were censored at the time of the last follow-up. Planned subgroup analyses compared the trial arms stratified for radiation therapy planning: 2D versus 3DCRT versus IMRT; tumor stage: T1-2 versus T3-4; and nodal stage: N0-1 versus N2-3. Proportions were compared using 2-tailed Pearson Chi-Square or Fisher's Exact test as appropriate. Distributions of scale variables were compared using the nonparametric Mann-Whitney test. All *P*-values were from 2-tailed tests except where explicitly stated.

Governance and oversight

The Trial Management Group was chaired by the Principal Investigator (S.M.B.) and comprised the Lead Clinical Investigator (J.P.A.), the IAEA Study Coordinator (K.H.), the Site Principal Investigators for each participating center, and the study statistician (O.G.). The local site PI was responsible for compliance with all relevant national and/or local research ethics and protocol review procedures and other relevant local regulations. The study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice Guideline. The HYPNO trial is registered with ClinicalTrials.gov, NCT02765503. Registration was completed on April 29, 2016, that is, after the trial had been initiated, because of a change in IAEA policies. Data and safety monitoring was the responsibility of each site IRB according to local policies and regulations. One interim safety analysis of early deaths was conducted at the end of September 2015 at the request of the IRB at the lead accruing center (Tata Memorial Hospital), after 149 patients had been randomized. No other interim analysis for safety or efficacy was planned or undertaken. All investigators were blinded to any emerging outcome signals throughout the duration of the trial. The data center maintained a dashboard of study accrual per center, and annual progress reports were submitted to the IAEA for approval.

Role of the funding source

No financial or logistical support was provided by any for-profit entity. The IAEA provided an annual award to each actively enrolling center in support of conducting the trial. The data center received partial support through a technical contract, and IAEA staff provided logistical support for investigators' meetings, remotely or on-site in Vienna, Austria, as well as IT support for the design and implementation of the electronic CRFs. Staff actively collaborating in the design and conduct of the trial are listed as coauthors of this publication according to ICMJE criteria.

Table 1 Centers enrolling patients on the HYPNO trial

	HFX, *n* (%)	NFX, *n* (%)	All, *n* (%)
Argentina, Mendoza	22 (6)	27 (7)	49 (6)
Brazil, Sao Paolo	75 (19)	73 (18)	148 (19)
Cuba, Havana	39 (10)	36 (9)	75 (10)
Indonesia, Jakarta	3 (1)	5 (1)	8 (1)
India, Coimbatore	15 (4)	11 (3)	26 (3)
India, Mumbai	100 (25)	100 (25)	200 (25)
India, New Delhi	49 (12)	50 (13)	99 (13)
Pakistan, Bahawalpur	38 (10)	42 (11)	80 (10)
Philippines, Quezon City	9 (2)	7 (2)	16 (2)
Thailand, Bangkok	20 (5)	26 (7)	46 (6)
Uruguay, Montevideo	21 (5)	19 (5)	40 (5)
South Africa, Johannesburg	4 (1)	1 (0.3)	5 (0.6)
	395	397	792

Abbreviations: HFX = hypofractionated radiation therapy; HYPNO = HYPo-fractionated versus NOrmo-fractionated radiation therapy for HNSCC; NFX = normofractionated radiation therapy.

Results

Between March 5, 2014, and February 7, 2020, 792 patients were randomized in the 12 participating centers (Table 1). The interim analysis of safety analyzed early deaths according to trial arm, and compared the rate of early deaths with that observed in the previous IAEA HNSCC trial; the results of the analysis were shared with the IRB at TMH, but not with any of the investigators. The IRB concurred that the analysis gave no cause for concern, and enrollment was allowed to proceed. The trial was formally closed for accrual in April 2020 due to declining accrual rates, in part due to the emerging COVID-19 pandemic, with some centers reporting local embargoes on recruitment to clinical trials. It was decided that no formal adjustment of the statistical design was required as the enrollment was within 95% of the originally planned sample size.

Patients were predominantly male with a tobacco history (see Table 2). Tobacco use, current or past, was self-reported by 87% (686/792) of patients, 87% (342/395) in the HFX arm and 87% (344/397) in the NFX arm. Testing for human papilloma virus (HPV) was not required and was not routinely performed in the participating centers. About half of the cancers were oropharyngeal carcinomas, and 59% of cases presented with stage IV disease.

The compliance with the radiation dose prescription was excellent: the full prescribed dose was delivered to 95% and 99% of all patients in the NFX and HFX arms, respectively. Also, the compliance with the prescribed overall treatment time was very good (Fig. E1) and, important for testing the radiobiological rationale of the HYPNO trial, the difference in mean

Table 2 Distribution of patient and treatment characteristics in the 2 trial arms and overall

	HFX	NFX	All
Sex, *n* (%)			
Male	344 (87)	344 (87)	688 (87)
Female	51 (13)	53 (13)	104 (13)
Subsite, *n* (%)			
Oral cavity	33 (8)	34 (9)	67 (9)
Oropharynx	200 (51)	200 (50)	400 (51)
Hypopharynx	53 (13)	54 (14)	107 (14)
Larynx	99 (25)	95 (24)	194 (25)
Other	10 (3)	14 (4)	24 (3)
T category, *n* (%)			
T1	15 (4)	11 (3)	26 (3)
T2	88 (22)	101 (25)	189 (24)
T3	189 (48)	174 (44)	363 (46)
T4a	83 (21)	99 (25)	182 (23)
T4b	19 (5)	12 (3)	31 (4)
N category, *n* (%)			
N0	118 (30)	129 (33)	247 (31)
N1	82 (21)	71 (18)	153 (19)
N2a	29 (7)	24 (6)	53 (7)
N2b	73 (19)	77 (19)	150 (19)
N2c	76 (19)	76 (19)	152 (19)
Missing	0	3 (1)	3 (0)
Stage, *n* (%)			
I	5 (1)	5 (1)	10 (1)
II	23 (6)	43 (11)	66 (8)
III	140 (35)	108 (27)	248 (31)
IVA	192 (49)	207 (52)	399 (50)
IVB	35 (9)	34 (9)	69 (9)
Grade, *n* (%)			
G1	56 (14)	69 (17)	125 (16)
G2	218 (55)	212 (53)	430 (54)
G3	73 (19)	69 (17)	142 (18)
G4	47 (12)	43 (11)	90 (11)
Missing	1 (0.3)	4 (1)	5 (0.6)
Performance status, *n* (%)			
0	173 (44)	171 (43)	344 (43)
1	206 (52)	213 (54)	419 (53)
2	16 (4)	13 (3)	29 (4)

(*Continued*)

Table 2 (*Continued*)

	HFX	NFX	All
Smoking history, *n* (%)			
Never	91 (23)	87 (22)	178 (23)
Stopped	152 (39)	159 (40)	311 (39)
Current	151 (38)	151 (38)	302 (38)
Missing	1 (0.3)	0	1 (0.1)
Betel nut/ tobacco chewing, *n* (%)			
Never	313 (79)	311 (78)	624 (79)
Stopped	62 (16)	75 (19)	137 (17)
Current	20 (5)	11 (3)	31 (4)
Alcohol, *n* (%)			
Never	191 (48)	205 (52)	396 (50)
Stopped	137 (35)	129 (33)	266 (34)
Current	67 (17)	62 (16)	129 (16)
Missing	0	1 (0.3)	1 (0.1)
Chemotherapy, *n* (%)			
No	99 (25)	96 (24)	195 (25)
Yes	296 (75)	301 (76)	597 (75)
RT technique, *n* (%)			
2D	89 (23)	89 (22)	178 (23)
3DCRT	29 (7)	27 (7)	56 (7)
IMRT-seq. boost	7 (2)	12 (3)	19 (2)
IMRT-sib. boost	270 (68)	267 (67)	537 (68)
Missing	0	2 (0.5)	2 (0.3)
Age, median and IQR (y)*	57.9 (49.8, 65.5)	58.4 (50.7, 65.1)	
Max tumor diameter, median, and IQR (cm)†	4.0 (2.8, 5.0)	4.0 (3.0, 5.0)	
Max node diameter, median, and IQR (cm)‡	2.1 (1.4, 3.5)	2.0 (1.5, 3.4)	

Abbreviations: HFX = hypofractionated radiation therapy; IMRT-sib. Intensity Modulated Radiation Therapy using the simultaneous integrated boost; IMRT-seq: Intensity Modulated Radiation Therapy using the sequential boost; NFX = normofractionated radiation therapy; RT: radiation therapy; 2D = 2 dimensional; 3DCRT = 3D conformal radiotherapy.

* Date of birth missing in 18 patients.

† Primary tumor maximum diameter missing in 33 cases.

‡ In patients with positive nodes; missing in 2 cases.

overall treatment time was 11.5 days, very close to the 11.2-day difference presumed when conducting the bioeffect modeling underpinning our sample size estimation. Weekly cisplatin was prescribed in 75% of all cases. Again, the compliance was very good; in the NFX arm, 59% (171 pts) received 5 of 5 courses of chemotherapy, 81% (236 pts) received at least 4 courses; in the HFX arm, 64% (176 pts) received 4 of 4 courses (1 patient received 5 courses in the HFX arm), 86% (237 pts) received at least 3 courses. The cumulative dose of cisplatin in the HFX arm was 121 mg/m^2 versus 149 mg/m^2 in the NFX arm.

In terms of early radiation reactions, radiobiological modeling had suggested that the incidence and severity of these would be similar in the 2 trial arms. In total, 753 patients (95.1%), 373 in the HFX arm and 380 in the NFX arm, were evaluable with respect to early adverse events during and immediately after treatment. A maximum grade of mucositis of 3+ was seen in 50.9% (190/373, 16 grade 4) and 54.7% (208/380, 22 grade 4) of patients in the HFX and NFX arms, respectively. Opioid analgesics were prescribed during or immediately after treatment in 41.6% (155/373) and 47.4% (180/380) of patients in the HFX and NFX arms, respectively, $P = .12$. Grade 3+ dysphagia, that is, tube feeding, or total parenteral nutrition, or hospitalization indicated, was seen in 40.5% (151/373, 7 grade 4) and 41.6% (158/380, 6 grade 4) after HFX and NFX, respectively, $P = .34$. Grade 2+ weight loss at the end of therapy, that is, a loss of more than 10% compared to before the start of treatment, occurred in 29.2% (107/366) and 42.1% (154/366) of patients in the HFX and NFX arms, respectively, $P < .001$. The median weight loss over the course of treatment was lower after HFX, 4.1 kg, than after NFX, 5.2 kg, $P = .010$. Grade 3 skin reactions were less common in the HFX arm, 8.6% (32/373) versus 22.1% (84/380), $P < .001$.

Figure 3 shows Kaplan-Meier plots comparing the 2 trial arms with respect to the coprimary endpoints and overall survival. Table 3 contains the corresponding 3-year point estimates for the same endpoints. The test for noninferiority was performed on basis of 3-year estimates for the coprimary endpoints derived from the HR estimated using the Cox Proportional Hazards Model with trial arm as the only covariate (Fig. 4). The $\Delta = 10\%$ noninferiority margin was rejected at the 95% CI for both loco-regional tumor control ($P = .04$) and for grade 3+ late adverse events ($P = .004$). The absolute difference in the 3-year outcome estimates between the 2 arms was less than or equal to 1.4 percentage points for overall survival, progression-free survival, loco-regional control, and grade 3+ late adverse events (see Table 3). The most frequently recorded grade 3+ late adverse event was dysphagia seen at 1 or more follow-up visits in 26 (7.7%) and 29 (8.8%) of cases in the HFX and NFX arms, respectively. Other grade 3+ effects were recorded in less than 3% of cases for each of the recorded endpoints. Three cases of grade 3 osteoradionecrosis were reported, 2 in the NFX arm and 1 in the HFX arm. One

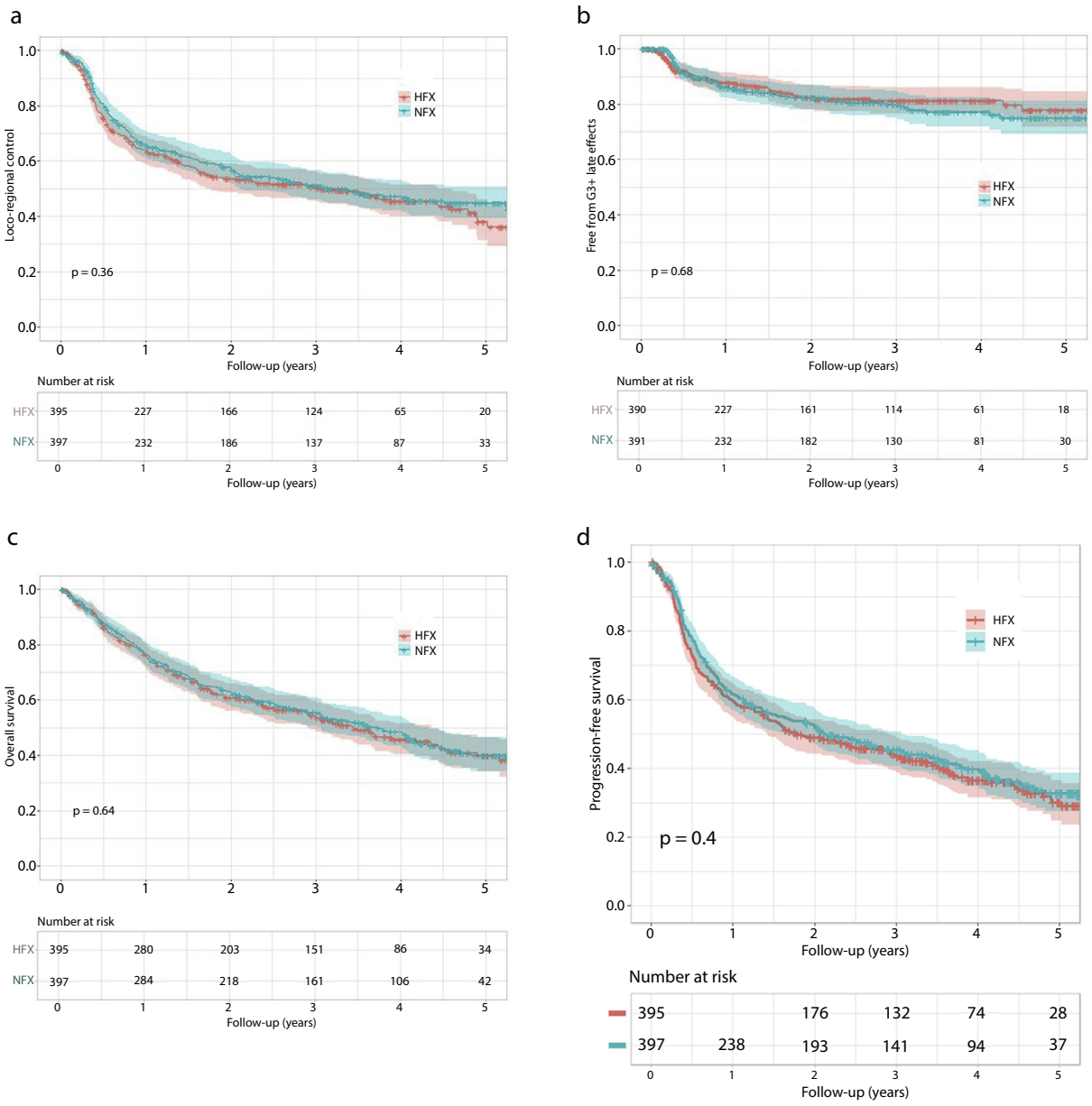

Fig. 3. Kaplan-Meier estimates of loco-regional control (a), freedom from G3+ late adverse events (b), overall survival (c), and progression-free survival (d) according to randomization arm. The P-value is from a two-tailed Mantel-Cox logrank test of the hypothesis HR=1. The shaded region is the 95% confidence interval for the point estimate at a given point in time. The vertical bars indicate censoring times. *Abbreviations:* HFX = hypofractionated radiation therapy; NFX = normofractionated radiation therapy.

patient, in the HFX arm, developed grade 3 soft tissue necrosis.

The prespecified subgroup analyses are summarized in Figure 5. No statistically significant heterogeneity of treatment effect was seen when comparing subsites within the head and neck region or stage groups. The subgroup analyses showed no heterogeneity of treatment effect in relation to photon source (^{60}Co vs 6-MV linac) or type of treatment planning and delivery. Importantly, there was no significant difference between the groups who did or did not have cisplatin.

Discussion

The HYPNO HFX arm met the predefined noninferiority criteria for both efficacy and late toxicity, and with similar early toxicity compared to the control arm. This is consistent with the modeling performed when designing the trial. It is important, however, that the outcome of HYPNO does not depend on the presumed validity of the LQ model for dose-fractionation. The modeling was used to generate a testable hypothesis; the trial provided the test. The choice of the noninferiority Δ was made in part from feasibility considerations. Tightening Δ to, say, 8%

Table 3 Kaplan-Meier point estimates of 3-year outcomes ±1 SE of the estimate and hazard ratios (HR) between trial arms with 90% CIs

	Loco-regional control	Grade 3+ late effects	Overall survival	Progression-free survival
HFX (%)	50.7 ± 2.7	18.8 ± 2.4	54.1 ± 2.7	44.0 ± 2.6
NFX (%)	51.2 ± 2.7	20.2 ± 2.4	55.5 ± 2.6	45.3 ± 2.6
HR (HFX/NFX) 90% CI	1.098 (0.93, 1.30)	0.926 (0.68, 1.25)	1.068 (0.90, 1.26)	1.12 (0.95, 1.33)
P value*	0.36	0.68	0.64	0.42

Abbreviations: HFX = hypofractionated radiation therapy; NFX = normofractionated radiation therapy.
* Testing the null hypothesis, HR = 1.0, Mantel-Cox log-rank test.

would have increased the target sample size to 1304 patients, which was felt to be unrealistic in view of the expected annual accrual in the participating centers.

The HYPNO schedule reduces the number of daily fractions by 13 or 15 compared with the DAHANCA 6-fractions per week or a standard 70 Gy in 35 fractions schedule, respectively. This represents a reduction of 39% or 43% in the number of treatment days per patient. In addition, the concurrent cisplatin was delivered as 4 courses in the 4-week schedule instead of 5. Both the reduced number of fractions and the shorter overall treatment time are attractive in terms of resource sparing. Patient convenience is another important consideration. Finishing a course of definitive radiation therapy in 4 weeks rather than 5.5 to 7 weeks is a major convenience and will represent a sizeable saving of out-of-pocket costs for the patient. Furthermore, unplanned gaps in the planned course of fractionated radiation therapy are less likely to occur with a shorter schedule. Comparing the actual overall treatment time versus the expected overall time for a schedule without gaps in the 2 treatment arms showed that the proportion of patients who had a difference exceeding 5 days was 10% in the HFX arm versus 18% in the NFX arm, $P = .002$.

The embedded pragmatic design and a desire to improve the generalizability of study findings across centers in LMIC led to the decision to invite centers using ^{60}Co external beam radiation therapy and 2D planning to participate in the HYPNO trial. In the subgroup analyses, participants treated with ^{60}Co and 2D planning met the noninferiority criterion too. It is also noteworthy that the subgroup treated with IMRT using the sequential boost and using the simultaneous integrated boost (pooled together as the latter technique was by far the most frequently used) also met the noninferiority criterion. With advances in in-room image guidance, many centers have moved toward narrower margins than what was deemed feasible when designing the HYPNO study. Arguably, HYPNO's margin requirements are conservative in the sense that the traditional concern with hypofractionation has been late toxicity, which would be more likely to become overt with larger margins.

One limitation of the HYPNO trial is that HPV testing was not required and, in practice, not performed in the trial participants. Although 87% of all enrollees reported current or past use of tobacco products, it is impossible to assess the prevalence of HPV-related HNSCC in the HYPNO trial. From a radiobiology perspective, it is the magnitude of the dose recovered per day that allows us to devise a schedule with noninferiority with respect to both tumor control and late adverse events. There are no direct estimates of the dose recovered per day as a function of HPV status in the published literature. There are, however, data from the DAHANCA 6/7 trials[10] where Lassen et al[11] performed a stratified analysis of the benefit of accelerated radiation therapy according to p16 status

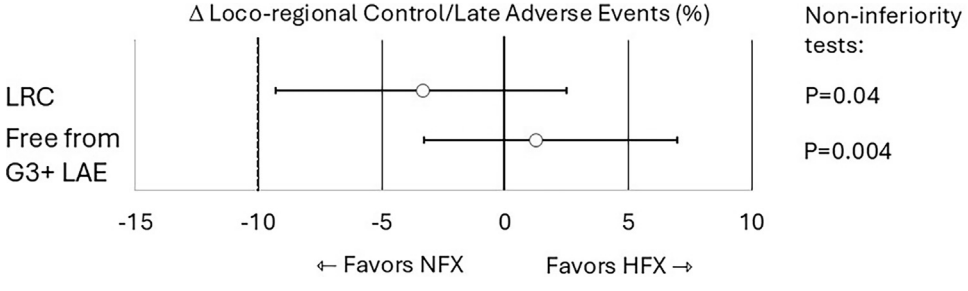

Fig. 4. The estimated difference in percentage point in 3-year loco-regional tumor control and freedom from Grade 3+ late adverse events in the HFX arm minus the NFX arm. Fiducials indicate 1-sided 95% confidence limits. Non-inferiority testing of the co-primary endpoints showed that the 10% non-inferiority threshold was rejected, P-values on the right-hand side of the figure. *Abbreviations:* LAE = Late adverse events; LRC = Loco-regional control.

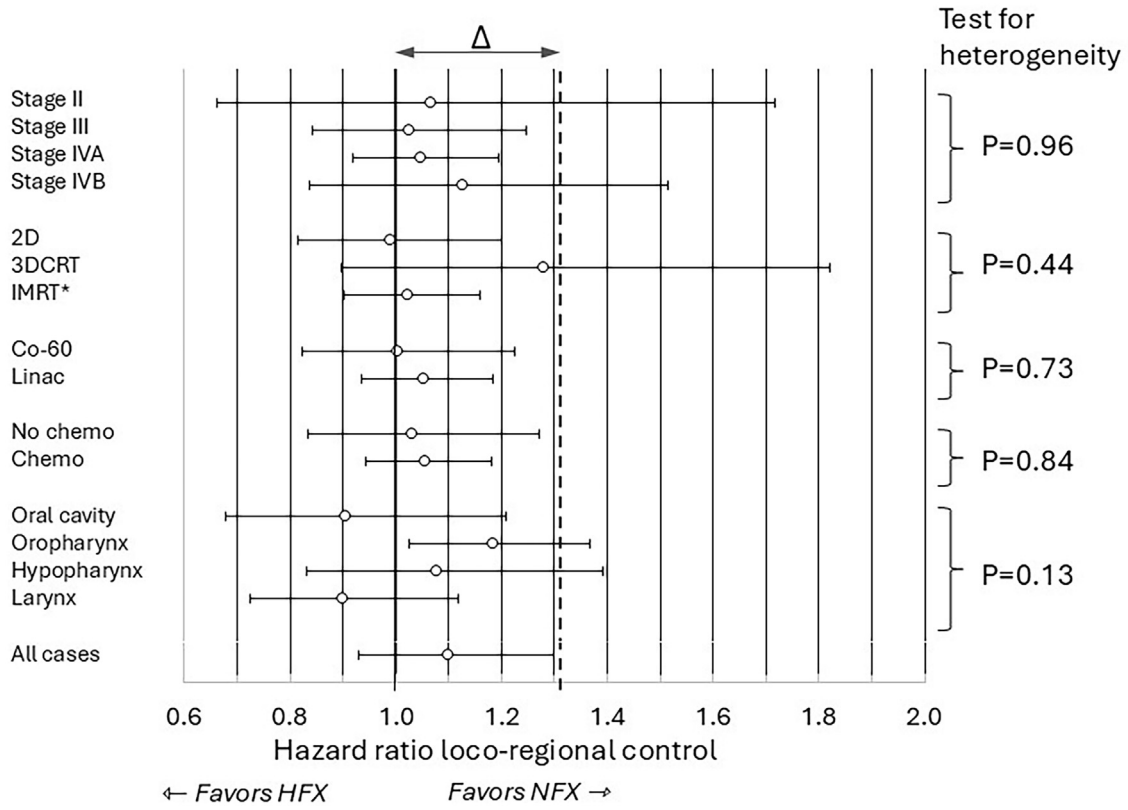

Fig. 5. Planned subgroup analyses of heterogeneity of treatment effect. Hazard ratios were estimated from a Cox Proportional Hazards Model of patients in each stratum with trial arm as the only covariate. Fiducials are 90% confidence intervals on the estimate. P values on the right are from a test for heterogeneity *Abbreviations:* HFX = hypofractionated radiation therapy; IMRT = Intensity Modulated Radiation Therapy; LRC = Loco-regional control; NFX = normofractionated radiation therapy; 2D = 2 dimensional; 3DCRT = 3D conformal radiotherapy.

assessed retroactively by immunohistochemistry staining of Formalin-Fixed Paraffin-Embedded (FFPE)-pre-treatment tumor tissue. The benefit of accelerated radiation therapy was statistically significant in both the p16-positive and p16-negative subgroups and with similar HRs, HR = 0.56 [0.33-0.96] and HR = 0.77 [0.60-0.99], respectively. Also, cause-specific survival was significantly improved after accelerated radiation therapy in the p16-positive group. This provides at least indirect support for the proposition that the accelerated HYPNO schedule would also be noninferior in HPV-related HNSCC. This is consistent with the analysis of HYPNO showing that the test for heterogeneity of treatment effect across the subsites within the head and neck region was not statistically significant.

Another limitation of the HYPNO trial is that Quality of Life data were not collected. When designing the trial, it had been considered to collect such data on an institutional opt-in basis, but this was never activated.

At the time of designing the HYPNO trial, early results from the phase 3 RTOG 0129 trial had been presented at the 2010 annual scientific meeting of the American Society for Radiation Oncology. This trial showed no statistically significant benefit of accelerated versus standard chemoradiation therapy for locally advanced HNSCC, a conclusion confirmed in the 2014 publication of mature results from the trial. Speculations at the time proposed that the biological mechanism targeted by concurrent chemotherapy and accelerated fractionation might be the same, namely, tumor cell repopulation. In the RTOG trial, cisplatin was delivered every third week at a dose of 100 mg/m^2, meaning that the standard arm received 3 cycles rather than 2 cycles of cisplatin. This hampers the interpretation of the study findings, as the biological effect of acceleration may have been at least partly offset by the delivery of 1 fewer cycle of cisplatin. Also, the phase 3 GORTEC 99-02 trial[12] compared accelerated versus standard chemoradiation therapy and found no statistically significant benefit of the acceleration. In the GORTEC trial, patients in the standard arm received 3 cycles of 4 days of carboplatin 70 mg/m^2 per day plus fluorouracil 600 mg/m^2 per day from day 1 to 4, day 22 to 25, and day 43 to 46. In the accelerated arm, patients received 1 cycle fewer of both carboplatin and fluorouracil, leading to a similar possibility that the putative biological effect of acceleration was in part offset by less dose of chemotherapy. In the HYPNO trial, 75% of the enrolled patients received weekly cisplatin concurrent with the radiation therapy, but due to the weekly dosing of cisplatin and a slightly better compliance in the HFX arm, the difference in cumulative

dose of cisplatin between the 2 trial arms was just 28 mg/m^2. The planned subgroup analysis showed no statistically significant heterogeneity between the chemoradiation versus radiation alone groups, $P = .80$. In fact, the subgroup analysis had sufficient statistical power for the noninferiority criterion to be met in both groups separately. The decision to prescribe concurrent intravenous cisplatin at 35 mg/m^2 rather than 40 mg/m^2 weekly was taken at the investigators' meeting in Vienna out of concern about the early toxicity from the higher rate of radiation dose accumulation in the HFX schedule together with the chemotherapy. In view of the early toxicity observed in the HFX arm, this decision was perhaps overly cautious, although this cannot be known with certainty. Also, the decision to prescribe 4 courses of chemotherapy in the HFX arm versus 5 courses in the NFX arm was made after careful consideration. It was noted that the main biological rationale for these doses of cisplatin is to modulate the effects of the ionizing radiation and therefore that the 2 modalities should be given concurrently for the duration of the radiation therapy course. As noted above, the total difference in cumulative dose of cisplatin between trial arms was just 28 mg/m^2 in practice.

Currently, several early-phase clinical trials of HFX radiation therapy for HNSCC are in progress. Lester et al[13] listed 8 HNSCC trials, 4 of which are combinations with surgery. The 4 trials of definitive radiation therapy are all single-arm trials, 2 phase 1 and 2 phase 2. The trials deliver 15 or 18 fractions with a range of total dose and overall time. Two of the trials allow weekly cisplatin and 2 use MRI guidance or proton therapy. In contrast, HYPNO used current standard planning and delivery technology and tested a pure radiobiology hypothesis.

In summary, the 4-week accelerated HFX schedule used in the HYPNO test arm met the noninferiority criteria for both loco-regional tumor control and for grade 3+ late adverse events relative to the outcome in the control arm. The HYPNO trial shows that hypofractionation is an attractive alternative to standard fractionation for definitive radiation therapy for locally advanced HNSCC. It is convenient for patients; it is resource sparing, and the clinical outcome is comparable to what can be achieved with standard of care fractionation. The test arm of the HYPNO trial explores a region of dose-time-fractionation space for HNSCC that has been only very sparsely studied in a modern setting. The promising outcome of this trial represents an important benchmark for further evolution of fractionation schedules in HNSCC.

References

1. Thames HD, Peters LJ, Withers HR, Fletcher GH. Accelerated fractionation vs. hyperfractionation: Rationales for several treatments per day. *Int J Radiat Oncol Biol Phys* 1983;9:127-138.
2. Bernier J, Bentzen SM. Altered fractionation and combined radio-chemotherapy approaches. Pioneering new opportunities in head and neck oncology. *Eur J Cancer* 2003;39:560-571.
3. Bourhis J, Overgaard J, Audry H, et al. Hyperfractionated or accelerated radiotherapy in head and neck cancer: A meta-analysis. *Lancet* 2006;368:843-854.
4. Bentzen SM, Dorr W, Gahbauer R, et al. Bioeffect modeling and equieffective dose concepts in radiation oncology—terminology, quantities and units. *Radiother Oncol* 2012;105:266-268.
5. Bentzen SM, Joiner MC. The linear-quadratic approach in clinical practice. In: Joiner MC, van der Kogel AJ, eds. *Basic Clinical Radiobiology*. Edward Arnold; 2009:120-134.
6. Saunders MI, Dische S, Parmar MKB, Harvey A, Gibson D. Randomised multicentre trials of CHART vs conventional radiotherapy in head and neck and non-small-cell lung cancer: An interim report. *Br J Cancer* 1996;73:1455-1462.
7. Bentzen SM, Saunders MI, Dische S. Repair halftimes estimated from observations of treatment-related morbidity after CHART or conventional radiotherapy in head and neck cancer. *Radiother Oncol* 1999;53:219-226.
8. Overgaard J, Mohanti BK, Begum N, et al. Five versus six fractions of radiotherapy per week for squamous-cell carcinoma of the head and neck (IAEA-ACC study): A randomised, multicentre trial. *Lancet Oncol* 2010;11:553-560.
9. Jacinto AA, Batalha Filho ES, Viana LS, et al. Feasibility of concomitant cisplatin with hypofractionated radiotherapy for locally advanced head and neck squamous cell carcinoma. *BMC Cancer* 2018;18:1026.
10. Overgaard J, Hansen HS, Specht L, et al. Five compared with six fractions per week of conventional radiotherapy of squamous-cell carcinoma of head and neck: DAHANCA 6 and 7 randomised controlled trial. *Lancet* 2003;362:933-940.
11. Lassen P, Eriksen JG, Krogdahl A, et al. The influence of HPV-associated p16-expression on accelerated fractionated radiotherapy in head and neck cancer: Evaluation of the randomised DAHANCA 6&7 trial. *Radiother Oncol* 2011;100:49-55.
12. Bourhis J, Sire C, Graff P, et al. Concomitant chemoradiotherapy versus acceleration of radiotherapy with or without concomitant chemotherapy in locally advanced head and neck carcinoma (GORTEC 99-02): An open-label phase 3 randomised trial. *Lancet Oncol* 2012;13:145-153.
13. Lester SC, Moon DH, Patel SH, Awan MJ, Bakst RL. Leave no cancer behind: The conformal hypofractionation era and head and neck cancer. *Int J Radiat Oncol Biol Phys* 2024;118:165-168.