1. Title, Protocol ID, IRB number

English: Special Care Patterns for Elderly HNSCC Patients Undergoing Radiotherapy (SENIOR)

German: Klinisches Ansprechen und Verträglichkeit von Radio(chemo)therapie bei älteren Patienten mit Kopf-Hals-Tumoren

Protocol ID: FRKS003723 and NCT05337631

IRB number of the Local Ethics Committee Freiburg: 551/18

Version 4.2 (last update at July 26, 2024)

2. Synopsis

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Title	English: Special Care Patterns for Elderly HNSCC Patients Undergoing Radiotherapy (SENIOR) German: Klinisches Ansprechen und Verträglichkeit von Radio(chemo)therapie bei älteren Patienten mit Kopf-Hals-Tumoren
Patient Population	Elderly (≥65 years) patients with head-and-neck squamous cell carcinoma undergoing definitive (chemo)radiotherapy with curative intention
Aim	To determine the value of concomitant chemotherapy of concomitant chemotherapy in elderly patients with locally advanced head-and-neck squamous cell carcinoma (HNSCC) undergoing definitive (chemo)radiotherapy
Intervention	No intervention
Inclusion and Exclusion Criteria	**Inclusion Criteria:** • definitive (chemo-)radiotherapy with curative intention of a locally advanced (cT3-4 and/or cN+) head-and-neck squamous cell carcinoma (HNSCC) of the oral cavity, oropharynx, hypopharynx or larynx • (chemo-)radiotherapy between 2005 and 2019 • age ≥65 years at the time of (chemo-)radiotherapy

	Exclusion Criteria: • adjuvant (chemo-)radiotherapy • induction chemotherapy • history of previous head-and-neck cancer • distant metastases at (chemo-)radiotherapy initiation (M1) • HNSCCs of the nasopharynx, salivary glands, skin or with unknown primary
Outcome Measure	Primary: • Overall survival (OS) Secondary: • Progression-free survival (PFS) • Type of concomitant chemotherapy • Cumulative cisplatin dose • Radiotherapy completion rate • Chemotherapy completion rate
Study Design	Multinational, multicenter, retrospective, observational study
Statistics	Patient demographics and treatment parameter will be described using descriptive statistics. Overall survival (OS) will be calculated from the beginning of (chemo)radiotherapy until death, while progression-free survival (PFS) is defined as time interval between start of (chemo)radiotherapy until death, local/locoregional or distant progression. The Kaplan-Meier method will be used to calculate OS and PFS, and groups will be compared using log-rank tests. Both uni- and multivariate Cox proportional hazard regression analyses will be performed to analyze the prognostic role of several patient- und treatment-related parameters including chemotherapy administration on survival. In order to control for potential confounder variables, both propensity score matching and inverse probability weighting approaches are aimed to conduct.
Enrollment	1400 anticipated
Study Completion	March 2025

3. PIs – Funding

Senior-PI: Prof. Dr. Dr. Nils H. Nicolay, M.D., Ph.D.
Junior-PI: Dr. Alexander Rühle, M.D., MHBA
Funding: No external funding

4. Brief Summary

The number of elderly head-and-neck squamous cell carcinoma (HNSCC) patients is increasing (1); however, the evidence regarding the ideal treatment for this often vulnerable and frail patient cohort is limited (2, 3). Although the benefit of concomitant chemotherapy has been reported to decrease in elderly HNSCC patients based on the MACH-NC meta-analysis (4), it remains unknown whether state-of-the art radiotherapy techniques such as intensity-modulated radiotherapy (IMRT), modern supportive treatments and alternative chemotherapy fractionation (e.g., cisplatin weekly) may have altered this observation (5-7). The objective of this retrospective multinational multicenter study is to determine the oncological outcomes of elderly patients (≥65 years) with locally advanced HNSCCs undergoing definitive (chemo-)radiation and to investigate the influence of concomitant

chemotherapy on overall survival and progression-free survival after adjusting for potential confounder variables such as age, performance status and comorbidity burden.

5. Aim

Multinational multicenter retrospective analysis to reveal the role of concomitant chemotherapy in elderly patients with locally advanced head-and-neck squamous cell carcinoma (HNSCC) undergoing definitive (chemo)radiotherapy

6. Outcome Measures:

Primary Outcome Measure:

- Overall survival (OS)

Secondary Outcome Measures:

- Progression-free survival (PFS)
- Locoregional control (LRC)
- Patterns-of-care regarding chemotherapy administration and radiotherapy

7. Study Population and Methods

All Elderly (≥65 years) head-and-neck squamous cell carcinoma (HNSCC) patients undergoing definitive (chemo)radiotherapy with curative intention between 2005 and 2019 at a tertiary cancer center will be included and analyzed in terms of overall survival and the potential benefit of concomitant chemotherapy administration.

Methods

The SENIOR study is an investigator-initiated multinational multicenter retrospective observational study aiming to elucidate the value of concomitant chemotherapy in elderly patients with locally advanced HNSCCs undergoing definitive (chemo)radiotherapy with curative intention. About 1000 patients that received a definitive (chemo)radiotherapy between 2005 and 2019 at 13 tertiary cancer centers in Germany, Switzerland, Cyprus, and the USA will be included.

Patient and treatment data will be collected retrospectively using patient charts. The following criteria will be collected:

- Date of radiotherapy initation
- Patient age at start of radiation
- Gender
- Site of cancer
- T Stage
- N Stage
- HPV status
- Grading
- Tobacco History
- Pack Year history
- Active Smoking During Radiation

- ECOG
- Age-adjusted Charlson Comorbidiity Index
- Hemoglobin at start
- Leukocytes at start
- CRP at start
- Creatinine at start
- GFR at start
- Weight at start
- Planned total radiotherapy dose
- Planned radiotherapy dose per fraction
- Planned number of fractions
- Planned total radiotherapy dose, EQD2
- Applied total radiotherapy dose
- Applied number of fractions
- Applied radiotherapy dose per fraction
- Applied total radiotherapy dose, EQD2
- Radiotherapy completed
- Chemotherapy received
- If chemotherapy, which type
- Cumulative cisplatin dose
- Chemotherapy completed
- Status locoregional control
- Locoregional control (months)
- Status progression-free survival
- Progression-free survival (months)
- Status overall survival
- Overall survival (months)

8. Statistics

Patient demographics and treatment parameter will be described using descriptive statistics. Overall survival (OS) will be calculated from the beginning of (chemo)radiotherapy until death, while progression-free survival (PFS) is defined as time interval between start of (chemo)radiotherapy until death, local/locoregional or distant progression. The Kaplan-Meier method will be used to calculate OS and PFS. Groups will be compared using log-rank tests. Both uni- and multivariate Cox proportional hazard regression analyses will be performed to analyze the prognostic role of several patient- und treatment-related parameters including chemotherapy administration on survival. In order to control for potential confounder variables, propensity score matching and inverse probability weighting approaches are aimed to conduct. The statistical analyses will be performed in collaboration with the Institute of Medical Biometry and Statistics (IMBI) Freiburg.

9. Publication and Authorship Rules

Results of the study will be published in peer-reviewed journals. Decisions regarding the inclusion of co-authors and determination of the author order will be performed by the PIs following the Guidelines for Good Scientific Practice of the DFG (German Research Foundation).

10. Data Management and Data Protection

Data collection will be conducted at the respective center. Prior to data transfer to the primary center Freiburg, patient data will be pseudonymized (e.g., FR-001). Patient-related data such as name and date of birth will not be shared with the primary center. The list with the assignment between patient name and pseudonymization-code (e.g., FR-001) will be securely stored at the participating center. Due to the number of patients per center (approximately 100 per center), backtracking of individual patients is not possible for the leading center Freiburg.

We have created a Data Protection Concept for our study.

Following the rules of good scientific practice, analyzed data sets will be stored for at least 10 years in institutional databases. There is no disclosure of personal data to third parties.

11. Participating Centers

- Department of Radiation Oncology, University Medical Center Freiburg, Freiburg, Germany
- Department of Radiooncology, Charité - Universitätsmedizin Berlin, Berlin, Germany
- Department of Radiotherapy and Oncology, J. W. Goethe University, Frankfurt am Main, Germany
- Department of Radiation Oncology, University of Würzburg, Würzburg, Germany
- Department of Radiation Oncology, University Hospital Schleswig-Holstein, Kiel, Germany
- Department of Radiation Oncology, University Medical Center, Johannes Gutenberg University, Mainz, Germany
- Department of Radiation Oncology, University Hospital LMU Munich, Munich, Germany
- Department of Radiation Oncology, Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Germany
- Department of Radiation Oncology, University Hospital Zurich, Zurich, Switzerland
- Department of Radiation Oncology, German Oncology Center, Limassol, Cyprus
- Department of Radiation Oncology, Case Western Reserve University, Cleveland, USA
- Department of Radiation Oncology, Icahn School of Medicine at Mount Sinai, New York, USA
- Division of Radiation Oncology, The Ohio State University Wexner, Columbus, USA
- Department of Radiation Oncology and Molecular Radiation Sciences, Johns Hopkins University School of Medicine, Baltimore, USA
- Department of Radiation Oncology, University Medical Center Leipzig, Leipzig, Germany
- Department of Radiotherapy and Radiation Oncology, Jena University Hospital, Jena, Germany
- Department of Radiation Oncology, Giessen-Marburg University Hospital, Giessen, Germany
- Department of Radiation Oncology, Masaryk Memorial Cancer Institute, Brno, Czechia
- Department of Radiation Oncology, University Hospital Halle (Saale), Halle (Saale), Germany

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13. Signatures

Prof. Dr. Dr. Nils Nicolay

PD Dr. Alexander Rühle