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Scientific Article

Carbon Ion Beam Radiation Therapy as Part of a Trimodal Therapy for Non-small Cell Superior Sulcus Tumors: The INKA Study

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Purpose: Superior sulcus tumors are frequently treated with neoadjuvant chemoradiation therapy (nCRT) followed by surgery via a trimodal approach. The INKA study evaluated the replacement of photon irradiation by carbon ion radiation therapy (C12-RT) in this regimen.

Methods and Materials: The prospective INKA study included patients with locally advanced non-small cell superior sulcus tumors (<cN3 cM0). Patients received 2 cycles of cisplatin and vinorelbine as per local standard. During the second cycle, 39 Gy(Relative biological effectiveness (RBE)) of hypofractionated C12-RT in 13 fractions were applied. Surgery following fludeoxyglucose F18 positron emission tomography−computed tomography restaging was performed 2 weeks later. The primary endpoint was feasibility and safety measured by the incidence of Common Terminology Criteria for Adverse Events (version 4.0) grade 3/4 toxicity and/or discontinuation because of any reason. Secondary endpoints included the morphologic (Response Evaluation Criteria in Solid Tumors 1.0), metabolic (Positron Emission Tomography Response Criteria in Solid Tumors 1.0), and histopathologic response after nCRT as well as quality of life measurement (QLQ-C30/LC13).

Results: Between 2015 and 2020, 14 patients were included and received nCRT. No grade 3/4 toxicity occurred, with no discontinuation because of toxicity. Before surgery, 8 patients (57%) showed a partial response on computed tomography scan. Thirteen patients showed a metabolic response (metabolic complete remission (mCR), 1; metabolic partial remission (mPR), 12). Three patients (21%) were deemed inoperable after nCRT. In patients with resection, a pathologic Complete remission (CR) was seen in 2 patients (19%) and near-complete remission (<10% vital tumor cells) in 6 patients (55%). Pain score was more than half of that at baseline (mean, 69.2 ± 26.2 vs 30.6 ± 29.1; $P = .005$) after completion of nCRT and before surgery.

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Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

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Conclusions: The INKA trial is the first study to evaluate nCRT with C12-RT and showed excellent response, low toxicity, and rapid pain relief.

Background and Purpose

Although lung cancer is one of the most common tumor entities in the world, superior sulcus tumors only represent approximately 3% to 5% of these cases.[1] However, superior sulcus tumors in particular are difficult to treat and were regarded as inevitably fatal until the 1950s, when induction radiation therapy and en bloc resection were introduced.[2] Shaw et al[3] established the sequence of neoadjuvant photon radiation therapy (30-35 Gy over 2 weeks) followed by surgery as the new standard of care, leading to 5-year overall survival (OS) rates of up to 30%. After simultaneous neoadjuvant chemotherapy was introduced in the 1990s, the current standard of care is a trimodal approach leading to 5-year OS rates of up to 40%.[4]

Carbon ion radiation therapy (C12-RT) is predominantly used for inherently radioresistant tumors with highly radiosensitive anatomic structures in close vicinity (eg, skull base chordoma or chondrosarcoma and adenoid-cystic carcinoma). Lung cancer is a rather infrequent indication for C12-RT and the respective study landscape is almost exclusively of Japanese origin. In the early 2000s, Miyamoto et al[5] successfully evaluated the feasibility of 52.8 Gy(Relative biological effectiveness (RBE)) and 60.0 Gy(RBE) C12-RT in 4 fractions for stage I non-small cell lung cancer (NSCLC). No toxicity higher than grade 3 was described.[5] Nonetheless, particle therapy in lung cancer is rather challenging because respiratory motion in combination with surrounding lung tissue hinders a reliable calculation of the dose distribution.[6] Superior sulcus tumors represent the ideal lung tumor entity for evaluation of C12-RT because of their anatomic localization. Per definition, superior sulcus tumors are located near radiosensitive structures, and at the same time, the lung apex is less prone to respiratory motion. We sought to evaluate the scientific utilization of carbon ions within the trimodal therapy of non-small cell superior sulcus tumors.

Methods and Materials

The INKA study was a monocentric phase 2 pilot study evaluating the safety and feasibility of neoadjuvant hypofractionated C12-RT in patients with non-small cell superior sulcus tumors (T3-4 N0-2 M0). The detailed study protocol has been published earlier (https://bmccancer.biomedcentral.com/articles/10.1186/s12885-015-1163-7). Eligible patients were aged between 18 and 75 years and amenable to standard of care concurrent cisplatin/vinorelbine chemotherapy (Karnofsky Performance Score ≥70, no decompensated medical disease). The initial fludeoxyglucose F18 (FDG) positron emission tomography (PET)−computed tomography (CT) scan was not allowed to be older than 6 weeks. No previous thoracic radiation therapy or active medical devices without approval for particle therapy (eg, cardiac pacemakers) were allowed.

Treatment characteristics

Except for the use of hypofractionated carbon ion instead of photon radiation therapy, treatment corresponded to local standard of care. Neoadjuvant chemoradiation therapy (nCRT) included 2 cycles of chemotherapy (day 1, cisplatin 80 mg/m^2 and vinorelbine 25 mg/m^2; day 8, vinorelbine 25 mg/m^2). Concurrently with the second cycle, C12-RT was applied (39 Gy[RBE]) in 13 fractions using active raster scanning). Vinorelbine dose was reduced to 15 mg/m^2 during the second, concurrent cycle. Two weeks after completion of radiation therapy and an FDG-PET-CT restaging, surgery was performed (including systemic mediastinal lymphatic node dissection).

Target volumes were delineated as follows: the gross tumor volume (GTV) comprised the macroscopic visible primary tumor and the PET-positive lymph nodes if present. The clinical target volume was defined as the GTV with a safety margin of 6 mm. Based on the 4-dimensional planning CT, an internal target volume was generated. During treatment planning, 95% of the internal target volume should receive 39 Gy(RBE) in 13 fractions (5-6 fractions a week), leading to an equivalent dose at 2 Gy (α-to-β ratio, 10Gy) of 42.3 Gy. The esophagus, lungs, brachial plexus, and spinal cord were contoured as organs at risk. The local effect model 1 was used for calculation of the biological dose of the carbon ion irradiation.[7] During the local effect model 1 calculation, an α-to-β ratio of 10 Gy was assumed for the GTV and an α-to-β ratio of 2 Gy was assumed for organs at risk.

Study endpoints

The primary endpoint was safety and feasibility, characterized by the incidence of grade 3/4 toxicities (Common Terminology Criteria for Adverse Events, version 4.0) excluding hematologic toxicities or treatment-related interruptions (grade 1-4). The secondary endpoints included the morphologic response (Response Evaluation Criteria in Solid Tumors 1.0) based on CT scan, the metabolic

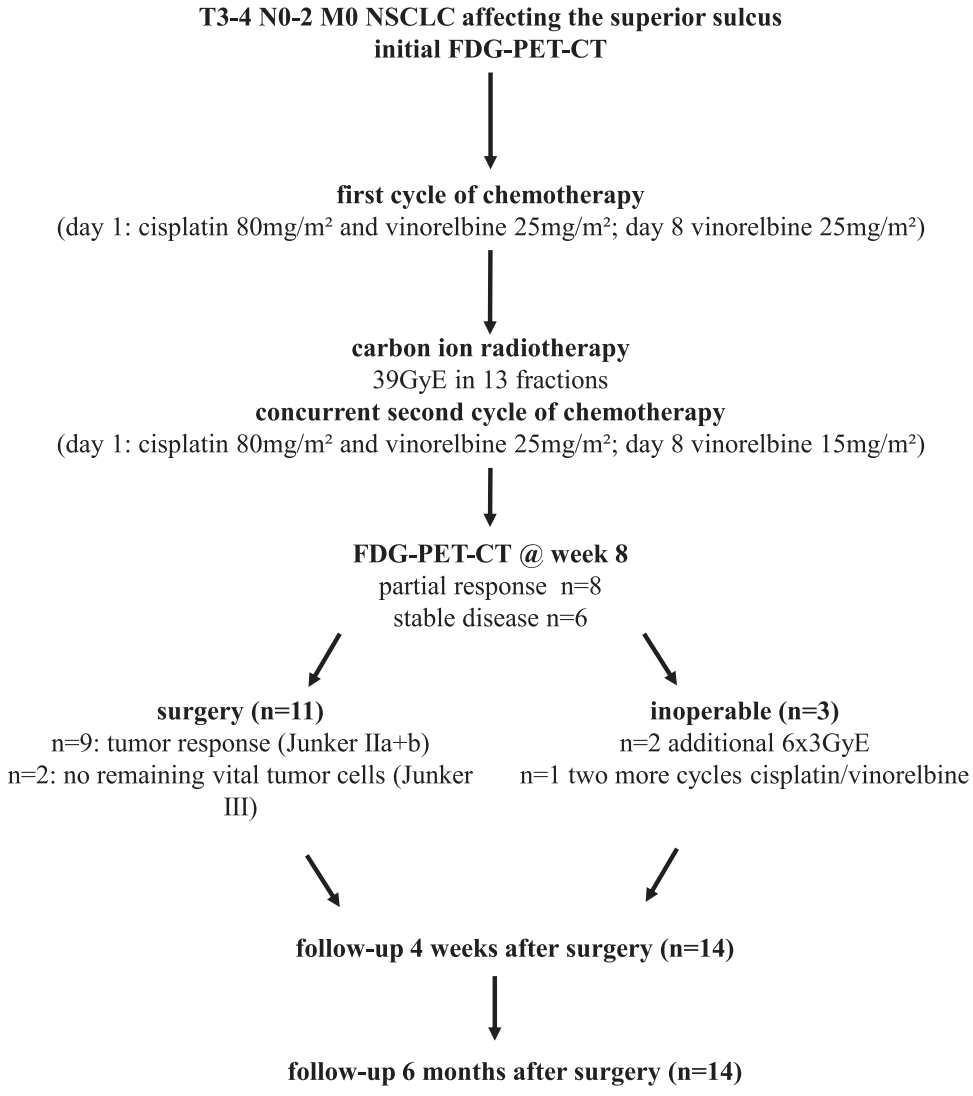

Figure 1 Scheme of the INKA trial, including the number of patients treated at each treatment step and response assessment.
Abbreviations: CT = computed tomography; FDG = fludeoxyglucose F18; NSCLC = non-small cell lung cancer; PET = positron emission tomography.

response (Positron Emission Tomography Response Criteria in Solid Tumors 1.0) described by Wahl et al[8] based on FDG-PET, the histopathologic tumor regression according to the Junker classification (grade 1, no or only slight tumor regression; grade 2a, >10% vital tumor cells; grade 2b, <10% vital tumor cells; grade 3, complete tumor regression),[9] and health-related quality of life based on the European Organisation for Research and Treatment of Cancer (EORTC) questionnaires QLQ-C30 and QLQ-LC13. In a post hoc analysis local control (LC), distant control (DC) progression-free survival (PFS), and OS were calculated, starting from the first day of irradiation.

Statistical methods

EORTC questionnaires QLQ-C30 and QLQ-LC13 as well as toxicity assessment were completed at baseline, at the beginning of radiation therapy, 2 weeks post radiation therapy as well as 3 and 6 months after surgery.[10,11] The obtained raw item data from the EORTC questionnaires were linearly transformed to a standardized range of 0 to 100 as described in the third edition of the EORTC QLQ-C30 Scoring Manual.[12] Higher scores represent a higher level of functioning. However, regarding the symptom burden, higher scores represent a higher degree of symptoms. The Wilcoxon rank sum test was used to compare the calculated means. Additionally, a comparison with a German norm population was performed.[13] LC, DC, PFS, and OS (beginning on the first day of radiation therapy) were estimated with the Kaplan-Meier method. Each was calculated and assessed with the log-rank test. A *P* value less than .05 was considered statistically significant. All statistical analyses were performed with SPSS software (IBM SPSS version 28.0).

The INKA study was approved by the ethics committee of (https://bmccancer.biomedcentral.com/articles/

Table 1 Demographic data, tumor stage, and radiation therapy details

Age (y)	56 (47-69)
Karnofsky performance index	90% (70%-100%)
Female	3 (21%)
Male	11 (79%)
Adenocarcinoma	5 (36%)
Squamous cell carcinoma	3 (22%)
NOS	4 (28%)
Other	2 (14%)
n = 1 pleomorphic; n = 1 sarcomatoid	
T3	10 (71%)
T4	4 (29%)
N0	12 (86%)
N1	1 (7%)
N2	1 (7%)
Primary tumor diameter (cm)	5.8 (4.6-8.5)
CTV volume (mL)	218 (88-449)
Plexus brachialis Dmax (Gy)	40 (29-42)
Spinal cord Dmax (Gy)	28 (0-34)
Esophagus Dmean (Gy)	8 (0-16)
Ipsilateral lung Dmean (Gy)	4 (0-14)
Contralateral lung Dmean (Gy)	0 (0-4)

Data are reported as median (range) or n (%).
Abbreviations: CTV = clinical target volume; NOS = not otherwise specified.

10.1186/s12885-015-1163-7). Written informed consent was obtained from all included patients. The trial is registered at (https://bmccancer.biomedcentral.com/articles/10.1186/s12885-015-1163-7).

Results

Fourteen patients were included in the INKA trial and were treated between February 2015 and September 2020. Figure 1 provides an overview including study visits and response assessment. Enrolment was prematurely closed in February 2022 because of slow accrual, after 14 of 20 initially planned patients were included and treated.

In terms of the primary endpoint, no grade 3/4 toxicities or treatment-related interruptions (grade 1-4) occurred. Demographic data, tumor stage, and radiation therapy details are shown in Table 1. Toxicity was low and is shown in Fig. 2 (additional details shown in Table E1). No patient developed grade 3 to 5 events at any time. Tumor response is shown in Table 2. The CT-graphic response was partial response in 8 patients (57%) and stable disease in 6 patients (43%) 2 weeks after completion of radiation therapy. The metabolic response was complete in 1 patient (7%), partial in 11 patients (79%), stable in 1 patient (7%), and not assessable in another patient (7%) because of lack of cross-calibration between the initial PET scan and restaging PET scan. The patient having had complete metabolic remission also showed complete tumor regression in the surgical specimen as shown in the case study (Fig. 3). Three patients were deemed inoperable after completion of the study

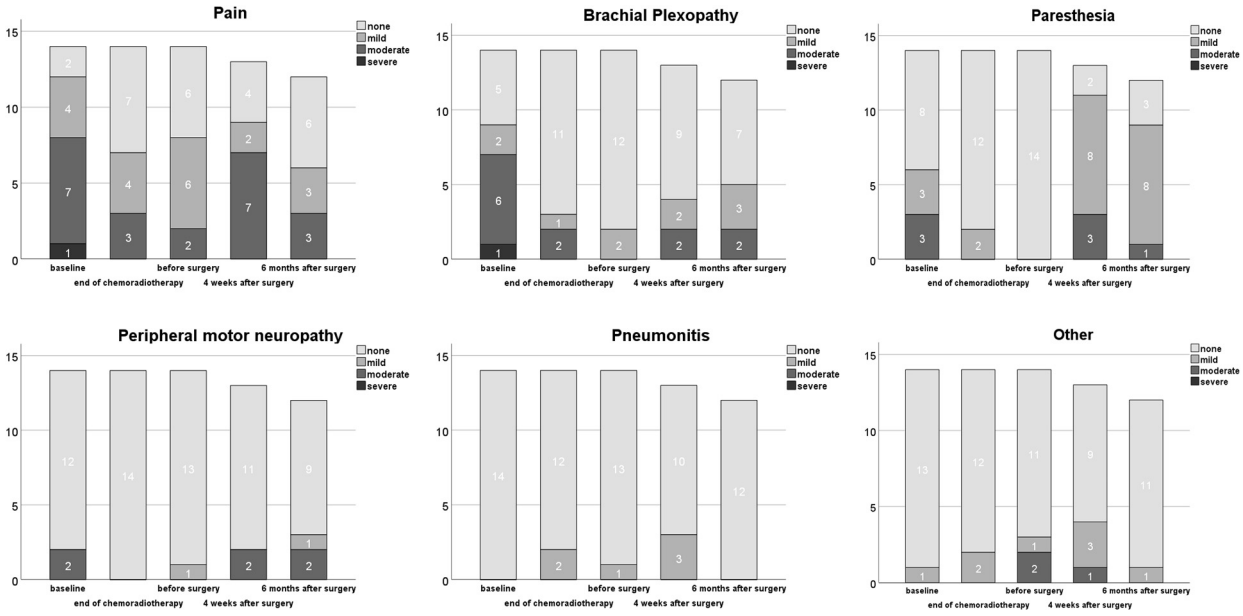

Figure 2 Toxicity according to Common Terminology Criteria for Adverse Events (version 4.0): grade 0 (none), grade 1 (mild), grade 2 (moderate), and grade 3 (severe).

Table 2 Tumor response

CT-graphic response (RECIST 1.0)	
Partial response	8 (57%)
Stable disease	6 (43%)
Metabolic response (PERCIST 1.0)	
Complete metabolic response	1 (7%)
Partial metabolic response	11 (79%
Stable metabolic disease	1 (7%)
Not assessable	1 (7%)
Surgery performed	11 (79%)
Complete resection (R0)	9 (82%)
Macroscopic complete resection (R1)	2 (18%)
Regression rate in specimen (Junker grade)	
1 (no change)	0 (0%)
2a (>10% vital tumor cells)	3 (27%)
2b (<10% vital tumor cells)	6 (55%)
3 (no vital tumor cells)	2 (18%)

Abbreviations: PERCIST = Positron Emission Tomography Response Criteria in Solid Tumors; RECIST = Response Evaluation Criteria in Solid Tumors.

treatment and were therefore not available for the histopathologic response endpoint. Histopathologic tumor regression according to the Junker classification was grade 2a (>10% vital cells) in 3 specimens (27%), grade 2b (<10% vital cells) in 6 specimens (54%), and grade 3 (pathologic complete remission) in 4 specimens (19%). Nine patients (82%) had complete resection (R0). Two patients (18%) had microscopic residual tumor (R1). One of these patients received additional 5 fractions of 2 Gy intensity modulated photon radiation therapy. The other patient refused additive treatment. Both patients did not show local recurrence during their latest follow-up of 12 and 42 months, respectively.

Table 3 shows the results of the health-related quality of life (an additional graphic visualization of significant items can be found in Fig. E1). Global health status was significantly reduced after the first cycle of chemotherapy and 4 weeks after surgery. After completion of nCRT, the mean pain score was less then half of that at baseline (69.2 ± 26.2 vs 30.6 ± 29.1; $P = .005$) and thus reached toward the mean value of the German general population (27.6 ± 30.9). A detailed comparison with the German general population can be found in Table E2. Four weeks after surgery, the mean pain score had relapsed nearly back to baseline (65.4 ± 25.8; $P = .667$), but significantly declined again 6 months after surgery (39.4 ± 27.1; $P = .022$). The dyspnea symptom burden was significantly higher 4 weeks after surgery (56.4 ± 28.5; $P = .023$) and persisted 6 months after surgery with a trend of improvement (48.5 ± 27.3; $P = .080$).

Three patients were deemed inoperable after neoadjuvant therapy. Two patients had a tumor response; however, they persisted to be technically inoperable after neoadjuvant treatment. One patient had a worsened pulmonary condition, which was not associated with an adverse event during neoadjuvant treatment. The 3 inoperable patients received additional therapies instead of surgery. Two patients received additional C12-RT with 6 fractions of 3 Gy(RBE) without concurrent or sequential chemotherapy. One patient received 2 additional cycles of cisplatin/vinorelbine without further irradiation. These 3 patients are also included in the long-term follow-up evaluation.

LC, DC, PFS, and OS were 93%, 86%, 79%, and 86% after a median follow-up of 42 months (Fig. E2). One patient had local recurrence in a right upper paratracheal node (station 2R) after 7 months. One patient developed brain metastases after 6 months. Another patient developed contralateral lung cancer after 46 months. Two patients died after 20 months and 23 months, respectively.

Discussion

Sulcus superior tumors are frequently painful, and curative treatment is particularly difficult because of the involvement of sensitive anatomic structures. The prospective phase 2 INKA trial sought to evaluate the feasibility of neoadjuvant hypofractionated C12-RT together with standard of care chemotherapy. Our study demonstrated excellent results with low toxicity, rapid pain mitigation after nCRT, and very good pathologic response already 2 weeks after the neoadjuvant treatment. No nonhematologic grade 3/4 toxicities or treatment-related interruptions occurred. The absence of pneumonitis grade 2 or higher in our study is not surprising given the fact that even high-dose C12-RT in a definitive-intent treatment led to pulmonary grade 3 toxicity of less than 4%.[14] The majority of patients showed at least partial morphologic and metabolic response before surgery (57% and 79%). Every surgical specimen showed at least partial tumor response. Pathologic complete remission was 19% in the presented study and, therefore, within the range of the 3 other prospective trials in the field that investigated comparable treatment schemes.[5,15,16] Complete pathologic response and near-complete response taken together were surprisingly high in the INKA trial (74%). Table E3 provides details regarding treatment schemes and response rates in comparison with the presented INKA study. One has to keep in mind the shorter interval in the INKA trial between completion of nCRT and surgery (2 weeks), leaving less time for the tumor to regress completely. Moreover, the INKA trial used hypofractionated radiation therapy (13 fractions instead of 25 fractions), which further decreased the time for the tumor to

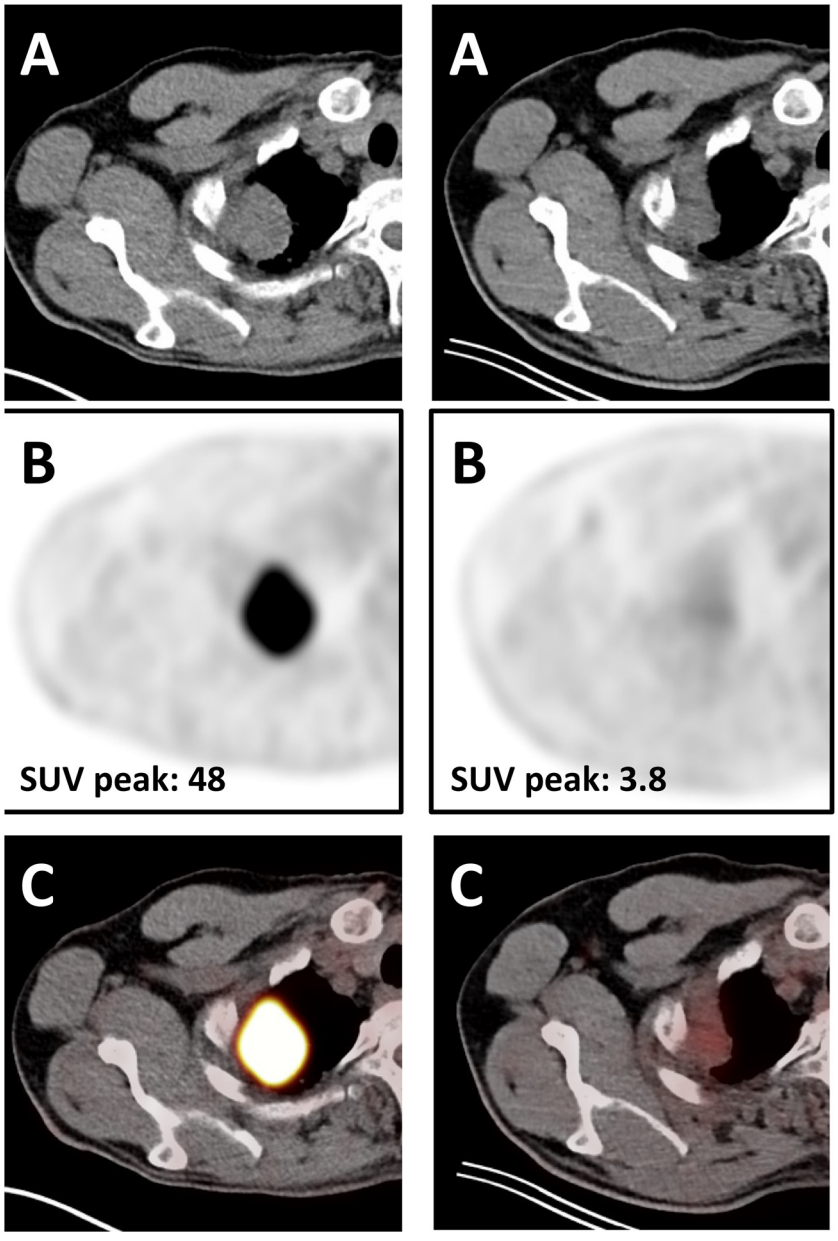

Figure 3 Case study: (A) computed tomography scan, (B) positron emission tomography scan, and (C) fused computed tomography/positron emission tomography images before (left column) and after (right column) chemoradiation therapy; the surgical specimen later revealed complete remission (Junker grade 3).
Abbreviations: SUV = standardized uptake value.

regress completely by more than 2 weeks. None of the aforementioned prospective studies investigated patient-reported outcome measures. Thus, the presented study provides unique insights. Shortly after completion of nCRT, pain was drastically reduced, but recurred after surgery. Patients who did not undergo surgery had better quality of life and less toxicity. However, there were not enough data available to perform statistical comparison, and thus, no definitive conclusion can be drawn. Moreover, the significant differences in quality of life after surgery in terms of pain and dyspnea might originate from other factors, which were not controlled for. There was no pain medication surveillance and no monitoring of underlying pulmonary diseases and their respective therapy. None of the 3 patients who did not undergo surgery died or had any recurrence during their follow-up (Fig. E2). However, their median follow-up was less mature (26 vs 46 months). The main limitation of the INKA trial is its prematurely closure because of slow patient accrual, with 14 instead of 20 patients available for final analysis. However, difficulties with accruing patients in this rare NSCLC subset were not unexpected, as described by Kernstine et al,[17] who stated that it required 76 surgeons from all over North America in order to accrue

Table 3 EORTC QLQ-C30 quality of life/symptom scale and EORTC QLQ-LC13 symptom scale scores at baseline, before radiation therapy, before surgery, 4 weeks after surgery, and 6 months after surgery

	Baseline		Before radiation therapy			Before surgery			Four weeks after surgery			Six months after surgery		
	n	Mean ± SD	n	Mean ± SD	*P*	n	Mean ± SD	*P*	n	Mean ± SD	*P*	n	Mean ± SD	*P*
EORTC QLQ-C30														
Global health status	13	65.4 ± 9.5	13	50.6 ± 19.1	**.036**	12	64.6 ± 23.1	.671	12	52.8 ± 19.9	**.029**	10	62.5 ± 18.1	.310
Functional scales														
Physical functioning	13	75.4 ± 22.5	14	81.0 ± 16.9	.192	12	80.0 ± 17.3	.344	13	62.6 ± 28.1	.265	11	73.9 ± 21.6	.944
Role functioning	12	51.3 ± 37.6	14	73.8 ± 23.3	**.011**	12	68.1 ± 27.9	.151	13	38.5 ± 31.4	.301	11	56.1 ± 30.1	.288
Emotional functioning	12	55.1 ± 26.0	14	63.1 ± 31.1	.212	12	67.4 ± 61.2	.050	13	63.5 ± 31.5	.181	11	66.7 ± 19.8	.123
Cognitive functioning	13	78.2 ± 24.9	14	84.5 ± 20.1	.272	12	86.1 ± 17.1	.306	13	80.8 ± 21.3	.679	11	78.8 ± 24.9	1.000
Social functioning	13	58.9 ± 37.6	14	53.6 ± 26.2	.833	12	66.7 ± 30.9	.724	13	50.0 ± 36.6	.164	11	56.0 ± 29.1	.717
Symptom scales														
Fatigue	13	35.9 ± 18.8	14	39.7 ± 25.3	.671	12	33.3 ± 21.7	.765	13	50.4 ± 24.7	.105	11	27.3 ± 25.9	.125
Nausea/vomiting	13	3.8 ± 10.0	14	3.6 ± 7.0	1.000	12	6.9 ± 15.0	.680	13	9.0 ± 23.0	.680	11	3.0 ± 10.1	.785
Pain	13	69.2 ± 26.2	14	51.2 ± 31.7	**.049**	12	30.6 ± 29.1	**.005**	13	65.4 ± 25.8	.667	11	39.4 ± 27.1	**.022**
Dyspnea	13	25.6 ± 24.7	14	19.1 ± 21.5	.257	12	30.6 ± 30.0	.783	13	56.4 ± 28.5	**.023**	11	48.5 ± 27.3	**.080**
Insomnia	13	41.1 ± 33.7	14	38.1 ± 36.6	.366	12	30.6 ± 26.4	.131	13	48.7 ± 32.2	.796	11	36.4 ± 34.9	.431
Appetite loss	13	0 ± 0	14	14.3 ± 31.2	.180	12	8.3 ± 15.0	.083	13	23.1 ± 31.6	**.024**	11	3.3 ± 10.1	.317
Constipation	13	10.3 ± 21.0	14	31.0 ± 33.2	**.038**	12	13.9 ± 26.4	.655	13	12.8 ± 21.7	.793	11	6.1 ± 23.1	.414
Diarrhea	13	2.6 ± 9.2	14	4.8 ± 12.1	.317	12	2.8 ± 9.6	1.000	13	7.7 ± 19.9	.414	11	3.1 ± 10.05	1.000
Financial difficulties	13	20.5 ± 21.7	14	21.4 ± 28.0	.562	12	13.9 ± 22.9	.564	13	35.9 ± 34.4	.083	11	33.3 ± 36.5	.160
EORTC QLQ-LC13														
Symptom scales														
Dyspnea	13	11.1 ± 12.8	14	17.3 ± 21,6	.102	12	14.4 ± 16.5	.244	13	39.3 ± 27.0	**.005**	11	31.3 ± 19.1	**.009**
Coughing	13	33.3 ± 30.4	14	30.9 ± 30.6	.414	12	33.3 ± 25.9	.480	13	30.8 ± 9.2	.480	11	39.4 ± 13.4	1.000
Hemoptysis	13	2.6 ± 9.2	14	2.4 ± 8.9	1.000	12	0 ± 0	.317	13	0 ± 0	.317	11	0 ± 0	.317
Sore mouth	13	10.3 ± 16.0	14	7.1 ± 14.2	.317	12	3.0 ± 10.1	.317	13	2.6 ± 9.2	.083	11	3.0 ± 10.1	.157
Dysphagia	13	2.6 ± 9.2	14	4.8 ± 12.1	.317	12	9.1 ± 15.6	.157	13	0 ± 0	.317	11	3.0 ± 10.1	.317
Peripheral neuropathy	13	20.5 ± 29.0	14	16.7 ± 21.7	.564	12	15.2 ± 22.9	.680	13	33.3 ± 27.2	.426	11	30.3 ± 37.9	.550
Alopecia	13	2.6 ± 9.2	14	19.0 ± 36.3	.102	12	21.2 ± 34.2	.066	13	15.4 ± 32.2	.180	11	6.1 ± 13.4	.157

(*continued on next page*)

Table 3 (*Continued*)

	Baseline			Before radiation therapy		Before surgery			Four weeks after surgery			Six months after surgery		
	n	Mean ± SD	n	Mean ± SD	*P*	n	Mean ± SD	*P*	n	Mean ± SD	*P*	n	Mean ± SD	*P*
Pain in chest	13	46.2 ± 28.9	14	31.0 ± 24.3	.084	12	21.2 ± 22.5	.054	13	38.9 ± 27.8	.414	11	27.3 ± 35.9	.256
Pain in arm or shoulder	13	66.7 ± 36.0	14	42.9 ± 40.1	**.034**	12	24.2 ± 26.2	**.011**	13	51.3 ± 32.2	.321	11	42.4 ± 42.4	**.048**
Pain in other parts	13	16.7 ± 33.3	14	23.9 ± 33.1	.546	12	3.3 ± 10.1	.197	13	35.9 ± 39.5	.436	11	24.2 ± 42.4	.671

Abbreviation: EORTC = European Organisation for Research and Treatment of Cancer; QLQ = Quality of Life Questionnaire.
Bold = statistically signifcant.

110 superior sulcus tumor patients for the SWOG 9416 study. The currently ongoing JCOG 1807C study (DEEP OCEAN) evaluates cisplatin-based polychemotherapy together with photon radiation therapy (66 Gy/2 Gy, including 22 Gy/2 Gy sequential boost prescribed to the clinical target volume). Two cycles of durvalumab are given sequentially after nCRT and again after surgery for approximately 1 year.[15] Given the excellent results with durvalumab consolidation after definitive chemoradiation therapy in patients with NSCLC in the PACIFIC trial, the DEEP OCEAN protocol seems to be promising.[18] Nonetheless, 66 Gy appears to be a dose escalation compared with the current standard of 45 Gy for neoadjuvant photon radiation therapy. Assuming an α-to-β ratio of 10 Gy for superior sulcus tumor cells, the 39 Gy(RBE) prescribed in our INKA trial corresponds to a 42.3 Gy equivalent dose at 2Gy. This dose is even slightly below the current standard of practice and still achieved excellent results including low toxicity, which could be attributed to the superior biological effect of C12-RT. Of note, this higher biological effect still allowed for simultaneous administration of chemotherapy without unexpected or aggravated toxicity.

Conclusions

The INKA trial is the first study in its field and showed excellent histopathologic response and low toxicity after neoadjuvant chemotherapy with concurrent C12-RT. These encouraging results should lead to further investigations, and multicentric efforts should be made to evaluate this regimen in further trials in the future.

Disclosures

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In loving memory of Renate Haselmann, our long-term study nurse. Fabian Weykamp was responsible for statistical analysis.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.adro.2024.101573.

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