Clinical and Translational Radiation Oncology 2 (2017) 59–62

Contents lists available at ScienceDirect

Clinical and Translational Radiation Oncology

journal homepage: www.elsevier.com/locate/ctro

Case Report

Simultaneous integrated prophylactic cranial irradiation in sino-nasal cancer

Kenneth Jensen [a,*], Maja Bendtsen Sharma [a], Simon Lenler-Eriksen [b], Per Friis [c], Anne Ivalu Sander Holm [d]

[a] Department of Oncology, Aarhus University Hospital, Denmark
[b] Department of Pathology, Aarhus University Hospital, Denmark
[c] Department of Otorhinolaryngology, Head and Neck Surgery, Aarhus University Hospital, Denmark
[d] Medical Physics, Aarhus University Hospital, Denmark

ARTICLE INFO

Article history:
Received 2 December 2016
Revised 20 January 2017
Accepted 20 January 2017
Available online 20 February 2017

Keywords:
Sino nasal cancer
Small cell neoplasm
Neuroendocrine neoplasm
Radiotherapy
Prophylactic craniel irradiation

ABSTRACT

Therapy for small cell cancer and high grade neuroendocrine tumours of the paranasal sinuses is extrapolated from the treatment of small cell lung cancer and paranasal cancer of different histologies. Prophylactic cranial irradiation has proven survival benefit in small cell lung cancer.

Two patients with aggressive cancer of the paranasal sinuses received radiotherapy with simultaneous integrated prophylactic brain irradiation, using two sequential plans. Chemotherapy was given before, during and after radiotherapy.

None of the patients had intracranial recurrence. One patient experienced severe, but transient encephalitis-like symptoms that could only be attributed to radiotherapy. No long term side effects in the CNS were observed.

The treatment was feasible, but with possible severe, but transient side effects. It should be considered in cases with head and neck cancer, with a high risk of intracerebral metastasis, as well as a significant overlap between the primary irradiated volume and the brain.

Introduction

Sinonasal cancers are infrequent cancers with a grave prognosis. The cancers pose great challenges for both the surgical and radio-therapeutic management, due to the abundance of adjacent organs at risk. Small cell and high grade neuroendocrine cancer of the sinonasal area are rare entities [1] with an even poorer prognosis [2], including a high risk of intracranial expansion as well as haematogenous metastases to the brain. For small cell lung cancer (SCLC) the addition of prophylactic cranial irradiation (PCI) to the treatment leads to both a significant risk reduction of brain metastases and prolonged survival [3]. The risk of haematogenous metastases from small cell head and neck cancer is lower than that of SCLC, yet still significant, and PCI has been recommended for selected cases of small cell head and neck cancer [2,4–7]. Adding PCI after radiotherapy for sinonasal cancer is sub-optimal from a dosimetric point of view, as some areas of the brain already received a radiation dose from the primary tumour irradiation, that may cause late side effects, and probably has a low effect on tumour cells, as the dose per fraction is very low. Furthermore, studies on SCLC indicates, that PCI given during chemotherapy, has superior effect compared to delayed PCI [8]. In two cases we chose to use an integrated PCI during primary radiotherapy to the tumour areas. A description of the cases is given below with emphasis on the technique and results of the PCI.

Case 1

Male, 56 years, no significant comorbidity, but well controlled type II diabetes and hypertension. Two months prior to diagnosis he noticed a slight facial pain and nasal discharge.

MRI and FDG-PET-CT showed a primary tumour of the left maxillary sinus with extension to anterior and posterior wall, gingiva and to the ipsilateral nasal cavity, ethmoid sinuses, orbital content and retromaxillary space. There were regional metastases to parapharyngeal-, retrostyloid- as well as level 1B and 2 lymph nodes. No distant metastasis, ie. T4aN2cM0

Pathology: The tumour was composed of irregular sheets of relatively small, rounded cells with prominent, hyperchromatic nuclei. Immunohistochemical analysis for CD45, S-100 and desmin

* Corresponding author at: Department of Oncology, Aarhus University Hospital, Noerrebrogade 44, 8000 Aarhus C, Denmark.
E-mail address: kennethjensen@dadlnet.dk (K. Jensen).

http://dx.doi.org/10.1016/j.ctro.2017.01.007

were negative. Positive reactions were seen for cytokeratin (AE1/AE3 and KL-1), p16, CD56, and the neuroendocrine markers chromogranin A and synaptophysin. The tumour was negative for CK5/6 and p63. Proliferation index using Ki-67, was high (70%). The tumour was diagnosed as a small cell neuroendocrine carcinoma.

Due to the advanced stage of the tumour nodes the patient was inoperable. Treatment with curative intent was initiated with chemotherapy: cisplatinum 75 mg/m2 i.v. day one and etoposide 120 mg/m2 i.v. day one to three every three weeks for a total of four series. Three weeks after initiation, he had grade 3 neutropenia (CTCAE 4.0) and the treatment was postponed one week. He subsequently received prophylactic G-CSF and received the remaining chemotherapy as planned without neutropenia. Ten days after initiation of chemotherapy he began radiotherapy.

The target was defined as gross tumour with a 5 mm margin for high dose clinical target given 66 Gy in 33 fractions. A further margin of 5 mm plus the remaining entire involved sinuses, was added for a high risk volume, treated with 60 Gy. No further elective volumes were included (Fig. 1). In addition, the entire brain was treated to 25.2 Gy for the last 14 fractions, as it was estimated, that at least 1.8 Gy per fraction was required to achieve a biological effect. No correction was made for fraction size to reach the biologic effect of 25 Gy in 10 fractions, which is standard at our institution for PCI with SCLC.

For the first part of the treatment, 5 planar and 5 non-coplanar fields were used in order to minimize the dose to the brain. For the last part, 6 coplanar and 2 non-coplanar fields were chosen (Fig. 2A and B). As the left part of the visual pathways was partly included in the target volumes, constraints for the organs at risk could not be met. Because of the non-coplanar fields the bilateral parotid glands received a higher dose than typically allowed. Fixed beam angles were chosen over arcs, due to their superior dose distribution in the low dose volume, ie. the majority of the brain volume. The PCI was planned for the last fractions in order to estimate side effects and response for the first part of radiotherapy and chemotherapy.

One month after initiation of radiotherapy, the patient was admitted 4 days due to dehydration, weight loss, pneumonia, oral candidiasis, mucositis and pain. He was treated with i.v. antibiotic, i.v. fluid and a nasogastric tube.

At the fourth series of chemotherapy, 14 days after cessation of radiotherapy, he had severe fatigue, but no neurological symptoms, still dependent on the nasogastric tube for sufficient nutrition, but the mucositis were healing as expected.

Three weeks later he was admitted to a local hospital with fever and increasing fatigue. No neurological symptoms, no neutropenia, low c-reactive protein. He was treated with oral antibiotics and discharged the same day. At home he experienced continuous fever with temperatures reaching to 39 °C.

Eleven days later he returned to the department of oncology for an acute evaluation due to intermittent fever 38–39 °C, insomnia, intense dreams, headache and neck pain. Objectively his general condition had deteriorated and he was confused and dehydrated. He had no focal neurological symptoms objective abnormalities. MRI of the head and neck and CT of the thorax and abdomen showed regression of the tumour, with no new tumour manifestations. C-reactive protein was continuously low. Cerebrospinal fluid contained increased mononuclear cells, elevated protein and normal level of glucose. The patient was rehydrated and received antibacterial and antiviral treatment as well as high dose steroids on the suspicion of meningitis. No positive microbiology or serology were present. ECG showed unspecific signs of encephalopathy but not consistent with herpetic encephalitis, and CSF-autoimmune encephalitis antibodies were all negative. The patient was discharged after 5 days and continued high dose steroids. The neurological symptoms slowly regressed over months, with no lasting deficits.

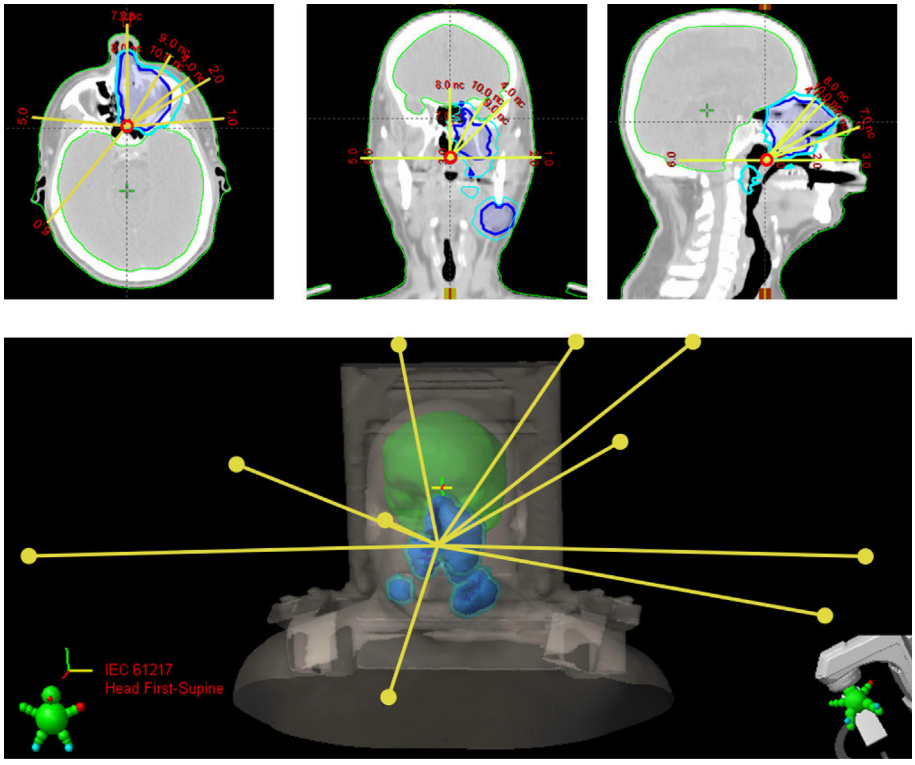

Fig. 1. Target and beam angle selection for part 1 of radiotherapy. Case 1. CTV1 (66 Gy): dark blue and CTV2 (60 Gy): light blue. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

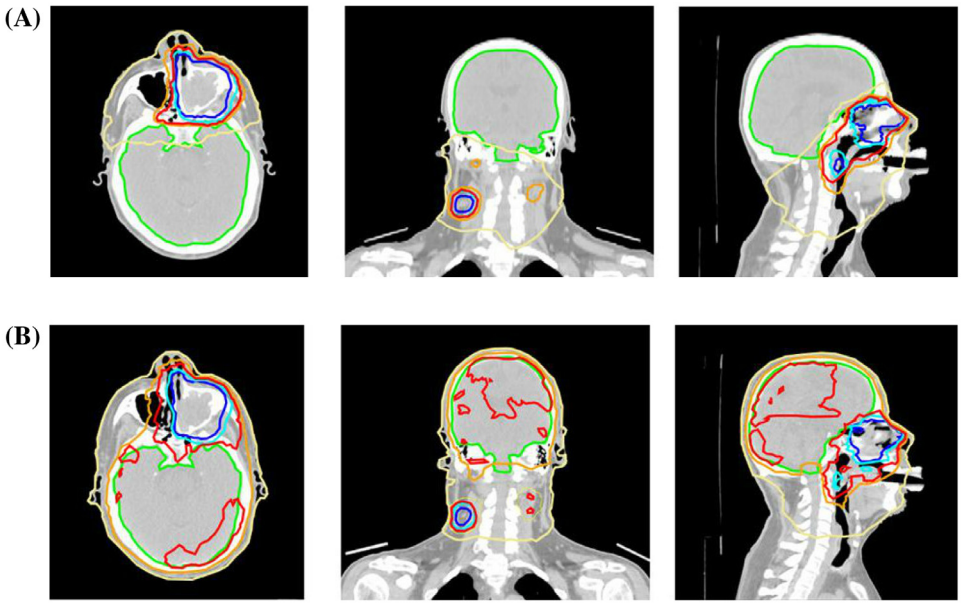

Fig. 2. (A) Treatment part 1. Brain sparing. Case 1. *Target:* CTV1 (66 Gy): dark blue and CTV2 (60 Gy) light blue *Isodosecurves:* Red: 36.1 Gy (95% PTV1). Orange: 32.8 Gy (95% PTV2). Yellow: 10 Gy. (B) Treatment part 2. Simultaneous integrated prophylactic cranial irradiation. Case 1. *Target:* CTV1 (66 Gy) dark blue and CTV2 (60 Gy): light blue. Brain: Green *Isodosecurves:* Red: 26.6 Gy (95% PTV1). Orange: 23.9 Gy (95% PTV Brain). Yellow: 10 Gy. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

The tumour evaluation with PET-CT and MRI performed 2 months after radiotherapy showed a partial response with diffuse oedema of the maxillary sinus and ethmoid cell but without excess FDG uptake. No nodal enlargement was observed, but one lymph node remained FDG avid. One month later a second evaluation PET-CT was performed, this time with no FDG positive changes.

After the first and second evaluation the patient was offered a maxillectomy with left orbital exenteration, neck dissection and reconstruction with free flaps. The patient still suffered from minor neurological deficits with intermittent confusion and fatigue and refused surgery. Six months after therapy the patient was well and without clinical symptoms nor neurological deficits.

Ten months after initiation of therapy the initial symptoms recurred. He had a biopsy proven recurrence in the maxilla with metastasis to the neck and mediastinal nodes, lung and liver. He was in excellent clinical condition and started chemotherapy with carboplatinum and etoposide, with an early and pronounced response, but succumbed to the disease 16 months after initiation of primary therapy.

Case 2

Male, 55 years old, referred with epistaxis, nasal occlusion and anosmia. He had no significant co-morbidity.

MRI and FDG-PET CT showed a FDG avid tumour in the right nasal cavity with extension to bilateral ethmoid and sphenoid cells and anterior fossa.

Pathology: The tumour was composed of densely packed medium sized to large tumour cells with pleomorphic nuclei, an increased mitotic rate and abnormal mitoses. There were widespread necrotic areas and interspersed were tumour areas with a tubular, intestinal adenocarcinoma appearance containing mucin. Immunohistochemistry showed positive reaction for cytokeratins (AE1/AE3, CK7, CK8, CK20), CDX-2, TTF-1, synaptophysin, CGA and CD56. Negative reaction for Vimentin, GFAP, TG, calcitonin and S-100. Proliferation index using Ki-67 was up to 80%. Histologically and immunophenotypically, the tumour was diagnosed as a poorly differentiated, non-small cell neuroendocrine carcinoma with differentiation towards an intestinal type adenocarcinoma (mixed adeno-neuroendocrine carcinoma, MANEC).

The patient was operated in one session with a dual approach: Initially the patient was operated with FESS technique where the nasal part of tumour was removed with a sphenoethmoidectomy to the scull base. The frontal sinuses were opened and tumour extension was removed. The area of tumour penetration through the scull base was localized. The neurosurgeons performed a bicoronal incision and removed the tumour extension to and through the dura, but no intra-cerebral extension was seen. The scull base was reconstructed with the fascia latae free flap. The postoperative period was uneventful. Due to dural invasion the disease was staged pT4bN0M0.

Fourteen days post operative the patient initiated chemotherapy with an identical schedule as case 1. Like patient 1, this patient had his second series postponed due to neutropenia (CTCAE 4.0 grade 2) and G-CSF was added for the remaining series.

The radiotherapy high risk CTV was defined as preoperative tumour extension plus 5 mm margin, treated with 60 Gy in 30 fractions. A moderate risk clinical target volume including the remaining, frontal, ethmoid, sphenoid and ipsilateral maxillary sinuses as well as ipsilateral nasal cavity was generated and treated to 54 Gy in 30 fractions. The entire brain was treated to 25.2 Gy for the last 14 fractions using an integrated volume. The treatment technique were comparable to case 1.

The patient had only moderate, expected side effects, including nausea during chemotherapy and a slight headache that responded to endoscopic cleansing of the sinuses post therapy. No lasting neurological deficits. There is no sign of relapse 24 months after therapy.

Discussion

Aggressive neuroendocrine sino-nasal tumours are very prone to recurrence both loco-regionally and distant, and should be treated with multimodality treatment whenever possible. Despite intense treatment, the prognosis is poor. The presented cases illus-

trates that even with intense treatment, loco-regional failure may occur. Intracerebral metastases poses a severe threat to the patient's quality of life as well as survival. Based on retrospective data from head and neck cancer [4] as well as high level evidence extrapolated from SCLC, PCI will probably reduce that risk. From a dosimetric point of view, an integrated PCI in the primary radiotherapy treatment, may reduce the risk of late side effects due to superior conformity and homogeneity. As survival and late quality of life is the argument for PCI, we chose a very aggressive approach with chemotherapy given before, during and after radiotherapy and PCI integrated into the primary radiotherapy. This resulted in severe side effects, as one patient developed sign of radiotherapy induced encephalopathy that slowly but completely regressed during months. The acute side effects were, on the other hand, not unexpectedly high, taking the radiotherapy high-dose-target alone into consideration. None of the patients had an intracranial recurrence and simultaneous integrated PCI should be considered for head and neck cancer patients with a high risk for intracerebral metastasis from haematogenous spread, but only in cases with a significant dose overlap between the radiotherapy for the initial tumour manifestations and the brain.

Acknowledgments

Thomas Ravnkilde for contributions with the dose plans.

References

[1] Bell D, Hanna EY, Weber RS, DeMonte F, Triantafyllou A, Lewis Jr JS, et al. Neuroendocrine neoplasms of the sinonasal region. Head Neck 2016;38(Suppl. 1):E2259–66. http://dx.doi.org/10.1002/hed.24152. Epub;%2015 Jul 18.:E2259-E2266..

[2] Rosenthal DI, Barker Jr JL, El-Naggar AK, Glisson BS, Kies MS, Diaz Jr EM, et al. Sinonasal malignancies with neuroendocrine differentiation: patterns of failure according to histologic phenotype. Cancer 2004;101(11):2567–73.

[3] Zhang W, Jiang W, Luan L, Wang L, Zheng X, Wang G. Prophylactic cranial irradiation for patients with small-cell lung cancer: a systematic review of the literature with meta-analysis. BMC Cancer 2014;14:793. http://dx.doi.org/10.1186/1471-2407-14-793.:793-14.

[4] De Felice F, Lei M, Guerrero Urbano T. Controversies in small cell carcinoma of the head and neck: prophylactic cranial irradiation (PCI) after primary complete initial remission. Cancer Treat Rev 2015;41(8):725–8.

[5] Takahashi S, Miyashita T, Hoshikawa H, Haba R, Togami T, Shibata T. Accelerated hyperfractionated radiotherapy for small cell carcinoma of the nasopharynx. Head Neck 2015;37(5):E63–5.

[6] Yazici O, Ozdemir NY, Sendur MA, Aksoy S, Zengin N. Current approaches for prophylactic cranial irradiation in extrapulmonary small cell carcinoma. Curr Med Res Opin 2014;30(7):1327–36.

[7] Franco P, Numico G, Migliaccio F, Catuzzo P, Cante D, Ceroni P, et al. Head and neck region consolidation radiotherapy and prophylactic cranial irradiation with hippocampal avoidance delivered with helical tomotherapy after induction chemotherapy for non-sinonasal neuroendocrine carcinoma of the upper airways. Radiat Oncol 2012;7(21):21–7. http://dx.doi.org/10.1186/1748-717X-7-21.

[8] Sas-Korczynska B, Korzeniowski S, Wojcik E. Comparison of the effectiveness of "late" and "early" prophylactic cranial irradiation in patients with limited-stage small cell lung cancer. Strahlenther Onkol 2010;186(6):315–9.