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# Evaluation of different techniques in craniospinal irradiation with particular focus on bone marrow toxicity

Michal Devečka

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Vorsitzender: Prof. Dr. Jürgen Schlegel

Prüfer der Dissertation:

1. Prof. Dr. Stephanie E. Combs
2. Priv.-Doz. Dr. Marciana Nona Duma

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# Table of Contents

# List of Abbreviations

| | |
|---|---|
| 3DCRT | 3D conformal radiotherapy |
| ACTH | adrenocorticotrophic hormone |
| AFP | alpha-fetoprotein |
| ATRT | atypical theratoid rhabdoid tumor |
| BBB | blood brain barrier |
| BMTomo | Helical tomotherapy plan optimized for proliferating bone marrow sparing |
| CERR | computational environment for radiotherapy research |
| CI | conformity index |
| CN | conformation number |
| CNS | central nervous system |
| CSF | cerebrospinal fluid |
| CSI | craniospinal irradiation |
| CT | computed tomography |
| CTV | clinical target volume |
| CYT | cytarabine |
| DFS | disease-free survival |
| DTPA | diethylenetriaminepentaacetic acid |
| EFS | event-free survival |
| FLT | 3'-deoxy-3'[18F]-fluorothymidine |
| GH | growth hormone, |
| GTR | gross tumor resection |
| Hb | hemoglobin |
| HI | homogeneity index |
| HT | helical tomotherapy |
| IMPT | intensity modulated proton therapy |
| IMRT | intensity modulated radiotherapy |
| IQ | intelligence quotient |
| IT | intrathecal |
| KPS | Karnofsky performance status |

| | |
|---|---|
| LINAC | linear accelerator |
| LM | leptomeningeal metastasis |
| LS-CYT | liposomal cytarabine |
| MLC | multi-leaf collimator |
| MTX | methotrexate |
| MVCT | megavoltage-computed tomography |
| NCCN | National comprehensive cancer network |
| NGGCTs | non-germinomatous germ cell tumors |
| OARs | organs at risk |
| OS | overall survival |
| p-CSI | proton craniospinal irradiation |
| PET | positron emission tomography |
| PFS | progression-free survival |
| PNET | supratentorial primitive neuroectodermal tumors |
| PTV | planning target volume |
| RA | rapid arc |
| RT | radiotherapy |
| SSD | source skin distance |
| STR | subtotal tumor resection |
| TKIs | tyrosin-kinase inhibitors |
| Tomo | Helical tomotherapy plan not optimized for proliferating bone marrow sparing |
| TSH | thyroid-stimulation hormone |
| VMAT | Volumetric arc therapy |
| WBC | white blood cell count |
| WBRT | Whole brain radiotherapy |
| WBME | Weighted bone marrow exposure |
| WBMEx | Activity of proliferating bone marrow exposed to certain dose (x) in % |
| WHO | World health organization |
| WSI | whole spinal irradiation |
| β-HCG | beta-human chorionic gonadotropin |

# List of Figures

# List of Tables

# 1 Introduction

Craniospinal irradiation (CSI) is a special radiotherapy technique. It was first introduced in the treatment of medulloblastoma. Nowadays it is used in curative treatment in central nervous tumors with leptomeningeal spread (LM). Most common indications include medulloblastoma and supratentorial primitive neuroectodermal tumor (PNET), ependymoma, central nervous system germinoma and non-germinomatous germ cell tumors (NGGCTs). Less often it may be used for patients treated with hematological malignancies such as lymphoma or leukemia. For solid tumors with LM, the data on the use of CSI is scarce and CSI is not standardly recommended in such a condition.

The “specialty” of the CSI lies in the size of the irradiated volume i.e. planning target volume (PTV). As the PTV encompasses the whole liquor space multiple attached fields are necessary for the treatment. Different solutions have been proposed how to deal with field-junctions. Also, different radiotherapy techniques have found their way in treating patients with CSI, ranging from two-dimensional (2D) x-ray planned radiotherapy (RT) and CT-planned three-dimensional conformal radiotherapy (3D-CRT) to intensity-modulated radiotherapy (IMRT), volumetric arc therapy (VMAT), helical tomotherapy (HT) and protons (p-CSI).

Due to the size of the PTV, a number of organs at risk (OARs) need to be taken into account when CSI is applied. Hence several side effects are common. These can be acute or late. The late toxicities may include cognitive impairment, endocrinopathies, cardiac toxicity, secondary cancer and in children growth problems. As the most common acute side effects are dysphagia, odynophagia, anorexia, nausea and vomiting. Besides these, as vast parts of proliferating bone marrow are irradiated during CSI treatment, bone marrow suppression is also a common side effect, which sometimes lead to treatment breaks and prolongation, potentially having adverse effects on the healing rate and in palliative cases can even cause treatment termination. Hence, this thesis deals with following subjects:

1. It examines and compares the bone marrow toxicity in patients treated with HT and 2D CSI.
2. To better understand this, a dosimetric study of nine selected patients is done to compare various treatment techniques or their optimization (3D-CRT, original HT (Tomo), optimized HT with bone marrow sparing (BMTomo) and p-CSI) with a special focus on bone marrow. Herein novel parameters such as dose activity histogram (DAH) and weighted bone marrow exposure (WBME) are introduced

based on functional imaging in order to better assess the dose to bone marrow than the traditional dose volume histogram (DVH).

3. The dose to OARs for other acute toxicities is compared among the different techniques in the dosimetric study. Minimizing acute toxicities is relevant for patients treated with CSI.
4. As the data on CSI as a palliative treatment are scarce, survival data of the patients treated in a single academic institution are provided. Moreover, an easy scoring system is proposed for possible patients' selection for CSI in palliative intention. Also, survival data for the curatively treated patients is provided.

# 2 Background

## 2.1 Indications for CSI

### 2.1.1 Diseases treated with CSI in curative intention

#### 2.1.1.1 Medulloblastoma and supratentorial PNET

Cranial PNETs are embryonal tumors with a heterogeneous differentiation. According to the location, they can be divided to the infratentorial medulloblastoma and supratentorial PNETs. PNETs are further subdivided based on their histologic differentiation and consist of cerebral neuroblastoma, pinealoblastoma, ependymoblastoma, medulloepithelioma and retinoblastoma and esthesioneuroblastoma. Together they are the most common malignant brain tumors of childhood but account only for 1.8% of all brain tumors with an overall incidence of 0.26 per 100.000 person-years (Surawicz 1999). In adults, they are considered very rare(Louis 2007).

The primary workup for patients with medulloblastoma and other PNETs includes brain and spinal MRI due to their propensity to cerebrospinal fluid spread and metastatic seeding. For the same reason, a liquor examination is mandatory. Based on these findings patients are grouped to different stages according to modified Chang classification, see Table 1 (Packer 2003). Herein the patients are grouped to standard or high-risk groups based on M-stage, residual tumor mass, and age. All patients with cranial PNET are standardly considered of high-risk.

| **Standard (Average) Risk** | **High Risk** |
|---|---|
| >3 years old | <3 years old |
| <1.5 $cm^2$ residual disease after resection | Subtotal resection, >1.5 $cm^2$ residual tumor |
| M0 by craniospinal MRI and CSF | M+; leptomeningeal seeding |
| Classic or desmoplastic histology | Location outside of posterior fossa (PNET) excluding esthesioneuroblastoma |
| | Large cell/anaplastic medulloblastoma |

*Table 1 Risk stratification according to the modified Chang classification (Packer 2003)*

For medulloblastoma, the general treatment recommendations are based on the data obtained mostly from pediatric studies although there are also a limited number of studies

regarding adults.(Hubbard 1989, Ferrante 1991, Prados 1995, Kramer 1997, Abacioglu 2002, Herrlinger 2005, Brandes 2015)

Optimal treatment includes maximal safe resection followed by CSI with sequential boost irradiation to the primary tumor site as well as to macroscopic metastatic disease sites. The prescribed dose, as well as the use of additional sequential chemotherapy, is based on the risk-group. In case of inoperability, patients are treated with definitive RT with or without chemotherapy according to the risk-group. However, patients who underwent complete or subtotal resection fare better than those with biopsy only. In the studies of Hughes and del Charco, it was shown that five-year actuarial OS was 69% resp. 78% for patients with total or subtotal resection versus 40% resp. 43% for patients who underwent biopsy only. Also, local control was impaired dropping from 80-90% to only 27% with biopsy alone. This demonstrates the value of surgery in the multimodal treatment of medulloblastoma (Hughes 1988).

After surgery, patients proceed to CSI. CSI doses vary according to the risk-group (see risk stratification above.) For average-risk disease, CSI with a total dose of 23.4Gy if chemotherapy is given, otherwise higher doses as for high-risk patients, i.e. 36Gy are prescribed. The primary tumor bed receives a boost to a total dose of 54-55.8Gy. Daily single doses of 1.6 to 1.8Gy are used (Berry 1981, Hubbard 1989, Fukunaga-Johnson 1998, Taylor 2003, Wolden 2003). In high-risk patients, the use of adjuvant chemotherapy is recommended. Patients with metastatic spread should receive an additional boost irradiation up to 45-50Gy to the spine metastatic sites and 50-54Gy to the cranial metastases. Some authors suggest increasing the total dose of CSI to 39.6Gy in case of disseminated spinal disease (Brandes 2015). RT should start within the fifth postoperative week and should be completed within 50 days as this was shown to have a prognostic impact on prognosis (Hubbard 1989, Ferrante 1991, Abacioglu 2002, Taylor 2003). The role of adjuvant chemotherapy in children is well established and lead to decreasing the delivered dose in CSI from 36 to 24Gy in the standard-risk medulloblastoma and improvement in survival for the high-risk group (Packer 2006). Furthermore, chemotherapy in children is used to avoid or delay CSI in patients under three years old where CSI could be associated with major neurocognitive complications. There is less data for adults and the use of chemotherapy but Herrlinger et al.(Herrlinger 2005) showed a trend to prolonged survival with adjuvant chemotherapy. However, this was not significant perhaps due to small sample size of 34 patients with medulloblastoma and 2 with PNET out of which 20 received adjuvant chemotherapy. Call et al. (Call 2014) showed only a benefit for adjuvant

chemotherapy in high-risk adult patients with classic histology though also only in a retrospective study with most patients receiving a dose of 36Gy for CSI. Other studies (Brandes 2003, Padovani 2007) were also inconclusive regarding the benefit of adjuvant chemotherapy and possibly reducing the dose in average-risk patients as is the case in children.

In summary, currently, the NCCN guidelines recommend either 30-36Gy for CSI in adult average-risk medulloblastoma patients with or without adjuvant chemotherapy. Alternatively, a reduced dose CSI with 23.4Gy may be used in young adults when adjuvant chemotherapy is used. For high-risk patients, 36Gy CSI and adjuvant chemotherapy are considered the preferred treatment. In all cases, CSI is followed by a boost to primary tumor location of up to 54Gy – 55.8Gy and in cases of macroscopic metastases, these also receive sequential boost irradiation of up to 45Gy for spinal and 54Gy for brain lesions respectively.

The recommendations for supratentorial PNETs excluding esthesioneuroblastoma and retinoblastoma follow that of high-risk medulloblastoma although the number of studies for these tumors is limited. Pinealoblastomas are considered highly aggressive embryonal tumors that arise mostly in childhood with a leptomeningeal spread in up to 50% of cases. The 5-year OS for patients treated with multimodal therapy including CSI is approximately 50-70% whereas the OS for the remaining PNETs ranges between 30 to 50% (NCCN 2017).

#### 2.1.1.2 Ependymoma

Ependymomas are glial tumors mostly located at the ependymal lining of the brain ventricles. However, they may also arise in the brain parenchyma or along the spinal cord. They account for approximately 4% and 10% of adult and pediatric CNS tumors respectively. As for location, they make less than 10% of tumors arising in the brain and 25% of the primary tumors in the spinal cord. In children, most of the tumors are located in the brain whereas approximately 75% of adult ependymomas are located along the spinal cord. Ependymomas infiltrate mostly locally, yet approximately 10% of tumors disseminate into the cerebrospinal fluid and cause metastases. Supratentorial ependymomas metastasize only in 1.6% whereas the incidence of CSF spread for infratentorial ependymomas is approximately 9% (Goldwein 1991, Vanuytsel 1991, Timmermann 2000, Merchant 2002, Chamberlain 2003, Grill 2003).

The World Health Organization (WHO) classifies ependymal tumors into four major subtypes: myxopapillary ependymoma (WHO grade I), subependymoma (WHO grade I),

classic ependymoma (WHO grade II), and anaplastic ependymoma (WHO grade III). Formerly also ependymoblastomas were considered a highly malignant variant of ependymoma. These tumors are now however classified as PNET(Louis 2007).

Similar to medulloblastoma the work up includes an MRI of the craniospinal axis and a lumbar puncture to assess the primary tumor and to stage for possible metastatic disease. The finding of metastatic disease has a prognostic and therapeutic impact. It is well mentioned at this place that as much as one-third of patients will have negative findings on the spinal MRI with positive liquor cytology (Moreno 2010).

As for the majority of brain tumors, surgery is the initial treatment modality also in ependymoma. Maximal safe resection should be performed. Although there are no randomized trials on the extent of surgery, there is a wide consensus based on retrospective data that patients in whom a total resection was performed fare better than those in whom only partial resection was performed. WHO grade I ependymomas are non-infiltrative and thus curable by resection alone (Healey 1991, Duffner 1998, Robertson 1998, Timmermann 2000, Metellus 2007, Rodriguez 2009, Amirian 2012, Aizer 2013).

Adjuvant RT in ependymoma remains a controversial issue to a certain extent. Till now, no randomized trials exist to support its use. Most of the data support its use only in incompletely resected tumors. Historically, wider radiation fields were used such as craniospinal irradiation, whole brain irradiation or posterior fossa irradiation for infratentorial tumors. However, most relapses are local and greater RT volumes were not associated with improved survival. Hence, a focal RT to the tumor bed with some safety margin to account for microscopical tumor spread and positioning uncertainties is acknowledged to be sufficient (Goldwein 1991, Paulino 2002, Combs 2006).

The use of CSI in a prophylactic fashion when imaging studies and liquor cytology are negative is not indicated based on the data of Vanuytsel et al (Vanuytsel 1991), where the incidence of spinal seeding was greater in patients who underwent prophylactic CSI. These findings were similar for both classical and anaplastic ependymoma (For high-grade tumors the incidence was 9.4% (5/53) with spinal irradiation and 6.7% (2/30) without prophylactic treatment; for low-grade tumors, the respective values were 9.3% (4/43) and 2.2% (2/89)).

In summary, no prospective, randomized trials comparing adjuvant RT with observation exist. Also, there are no studies comparing the use of CSI in patients with positive CSF with other treatment modalities e.g. chemotherapy. Gross tumor resection (GTR) is recommended for all tumors when achievable. WHO grade I ependymomas can be cured

by surgery alone. NCCN guidelines recommend the use of adjuvant local RT for all cases of anaplastic ependymoma and for all incompletely resected tumors. As already mentioned adjuvant local RT for completely resected classical ependymoma remains to some extent a controversial issue such as the NCCN recommends to consider adjuvant RT but states that observation is also possible for supratentorial tumors. CSI is reserved for metastatic ependymomas (positive CSF or macroscopic lesions) and its use in prophylactic fashion cannot be recommended (see above). The prescription doses for CSI are 36Gy with a focal boost up to 54-59.4Gy for cranial tumor manifestations and 45-50,4Gy for spinal cord manifestations, although even higher total dose (e.g. 59.4Gy) may be used in the region of cauda equine (same high doses as used for boost are used when only local radiotherapy is indicated). Normally the daily dose is 1.8Gy per fraction (NCCN 2017).

#### 2.1.1.3 CNS Germinoma and Nongerminomateous germ cell tumors

Germ cell tumors most frequently arise in the testes or ovaries. However, they can be found also in extragonadal sites, typically located in the midline (e.g. mediastinum, retroperitoneum). In the CNS, they originate mostly in pineal or suprasellar regions. Histologically they comprise a heterogeneous group of tumors and can be divided into germinoma, embryonal carcinoma, yolk-sac tumor also known as endodermal sinus tumor, choriocarcinoma, teratoma (which can be further subdivided into mature teratoma, immature teratoma, and teratoma with malignant transformation) and mixed germ cell tumor. Together all these tumors excluding germinoma can be termed as dysgerminoma. Germinomas are usually located suprasellar while dysgerminomas are found mostly in the pineal region. Japanese prognostic classification divides these tumors according to prognosis (Table 2).

| Good prognosis | Intermediate prognosis | Poor prognosis |
|---|---|---|
| • Pure germinoma<br>• Mature teratoma | • Germinoma with syncytiotrophoblastic giant cells<br>• Immature teratoma<br>• Teratoma with malignant transformation<br>• Mixed tumors mainly composed of germinoma or teratoma | • Choriocarcinoma<br>• Yolk sac tumor<br>• Embryonal carcinoma<br>• Mixed tumors mainly composed of choriocarcinoma, yolk sac tumor, or embryonal carcinoma |

*Table 2 Japanese prognostic classification for germ cell tumors (Fujimaki 2009)*

Germ cell tumors of the CNS are relatively rare and account for 0.5 to 3% of pediatric CNS tumors. However, this applies only to Europe and North America, while the incidence of these tumors is much higher in Asia where they represent approximately 11% of the pediatric CNS tumors (Echevarria 2008).

Intracranial germ cell tumors are mostly diagnosed in the children or adolescent age with the highest incidence in the second decade of life. Therefore, most data available comes from pediatric studies.

The work-up for CNS germ cell tumors include MRI of the brain and spine and lumbar puncture whenever possible. As germ cell tumors can be generally divided into secreting and non-secreting serum and CSF tumor markers have to be examined. While an elevation of alpha-fetoprotein (AFP) is diagnostic for NGGCTs, some germinomas may have elevated beta-human chorionic gonadotropin (β-HCG). A biopsy is mandatory in all tumors without elevated serum and CSF markers to distinguish germinoma from mature teratoma or other tumors. In case of elevated AFP, a biopsy should still be performed to ascertain the histological subtype, however, it is no more deemed mandatory.

#### *2.1.1.3.1 Germinoma*

Germinoma is a very radiosensitive tumor, therefore historically the treatment consisted of CSI. Several studies argued that in case of localized disease CSI could be omitted as less than 10% of the recurrences were located along the spine. Instead, whole-ventricular irradiation was suggested as sufficient treatment (Linstadt 1988, Dattoli 1990, Haddock 1997, Matsutani 1997, Aoyama 1998, Haas-Kogan 2003, Shikama 2005).

Rogers et al. (Rogers 2005) reviewed publications since 1988 and found that the recurrence rate after whole-brain or whole-ventricular RT plus boost was 7.6% compared with 3.8% after CSI, with no predilection for isolated spinal relapses (2.9% *vs* 1.2%). In a study by Ogawa et al. (Ogawa 2008) 165 patients with CNS germinoma who did not receive CSI were analyzed. Fifteen patients (9.1%) suffered from a spinal recurrence. Large intracranial disease (≥4cm) and multifocal intracranial disease were risk factors for spinal recurrence in patients with intracranial germinoma with no evidence of spinal metastases at diagnosis. Interestingly radiation field, total radiation dose, and the use of chemotherapy did not affect the occurrence of spinal recurrences. Patients with isolated spinal relapse who were received salvage therapy with spinal RT and chemotherapy fared much better than those who had either intracranial recurrence or were salvaged by RT only. The disease-free survival (DFS) at 3 years was 100% for the former group and only 17% for the latter. Approximately 5-10% of the patients present with tumors both in pineal and suprasellar

regions. Weksberg et al. (Weksberg 2012) analyzed patients with bifocal tumors with (group I) or without positive CSF (group II). For both groups, CSI resulted in 100% disease control whereas treatment with limited fields without chemotherapy resulted in spinal recurrences in ca. 11.7% in group I and the one and only patient treated with limited fields RT without chemotherapy suffered from both spinal and intracerebral recurrence. When chemotherapy and limited field RT were given the spinal relapses occurred in 4.3% and 30.7% for group I and II respectively.

Efforts were made to further decrease the volume of radiation fields in order to possibly minimize the cognitive impairment as a side effect of RT as the most of the patients are of a very young age. As in other pediatric tumors, chemotherapy was used as a partial or total substitute RT. Extra-CNS germinomas are very sensitive to chemotherapy and can be cured by chemotherapy alone. However, studies in CNS germinomas with chemotherapy as a sole treatment modality didn't show promising results. In a study by Kellie et al. (Kellie 2004) cisplatin, cyclophosphamide, etoposide, and bleomycin followed by carboplatin, etoposide, and bleomycin were used to treat 19 patients. Results were well below the normal results for patients treated with RT with a 5-years event-free survival (EFS) and OS of 47% and 68% respectively. Other groups reported also inferior results when compared to RT alone (Balmaceda 1996).

Chemotherapy was incorporated also in multimodal protocols with RT testing the hypothesis whether the chemotherapy could reduce the extension of the treatment fields. Biggest European trial SIOP CNS GCT 96 (Calaminus 2013) evaluated in a prospective non-randomized way CSI against chemotherapy followed by local RT only. Though the OS didn't differ among the treatment groups. PFS was better for patients who received CSI (97% vs. 88%). The problem with focal RT was that patients recurred in the ventricular zone. Therefore, the new SIOP trial design aims at comparing CSI with whole ventricular radiotherapy preceded by chemotherapy (Calaminus 2012). The SIOP CNS GCT 96 also demonstrated that the dose of CSI could be reduced to 24Gy CSI followed by a 16Gy boost in 1.6 daily fractions. Aoyama et al. (Aoyama 2002) reported similar results with 100% overall survival and 86% relapse-free survival for patients with pure germinomas after chemotherapy with etoposide and cisplatin followed by focal radiotherapy with 24Gy in 12 fractions. Interestingly this study has a comparable PFS with SIOP CNS GCT 96 chemotherapy group but used a much lower radiation dose, more similar to the dose prescribed in the treatment of gonadal germinomas. Another interesting finding of the study is that patients with β-HCG secreting germinomas fared worse even though more intensive

chemotherapy was used (Ifosfamide, etoposide, cisplatin). Their OS and relapse-free survival was only 75% and 44% respectively. Other studies suggest that there is no significant difference among these patients when larger radiation fields are used (Shibamoto 1997, Sawamura 1998, Ogino 2005).

Alapetite et al. (Alapetite 2010) reviewed germinoma patients treated with chemotherapy and focal radiotherapy and found a PFS of 83.4%. Of the 10 patients experiencing recurrences, one had a local recurrence, eight patients had a recurrence in the periventricular zone and only one patient had a spinal LM. This suggests that most of the recurrences could have been avoided if whole ventricular radiotherapy had been deployed.

With regard to the available data it seems reasonable to treat CNS germinoma patients without metastatic disease with whole ventricular radiotherapy as a sole modality with a prescribed dose of 24Gy in 1.6Gy daily fraction followed by boost to the primary site (or sites in case of bifocal germinomas) up to a cumulative dose of 40Gy using the same fractionation regimen. Some studies suggested even lower doses albeit used in the context of CSI (Cho 2009).

Whether the dose can be further reduced with the addition of chemotherapy is to be clarified in the ongoing studies (University Hospital Muenster 2015, Children's Oncology Group 2017). As for germinoma with spread along the CNS (either positive CSF cytology or macroscopic disease), there is much less controversy and the current standard therapy remains CSI with excellent results (Murray 2015).

#### *2.1.1.3.2 Nongerminomateous germ cell tumors (NGGCTs)*

The NGGCTs comprise a heterogeneous group, thus the interpretation of the available data is much more difficult. Generally, NGGCTs are considered less radiosensitive as demonstrated on patients treated with CSI and focal boost without the use of chemotherapy. The overall survival of these patients ranged from 20 to 40% compared to cure rates nearing 100% in the germinoma counterparts. Patients receiving chemotherapy only fared a little better achieving survival rates of some 40 to 60%. Most commonly used regimens use etoposide, cisplatin or carboplatin sometimes combined with further agents (Motzer 1993, Balmaceda 1996, Kellie 2004).

The best results are obtained when using multimodality treatment. With the use of upfront chemotherapy followed by second-look surgery and in case of non-responders by high-dose chemotherapy with autologous stem cell rescue before receiving CSI, Goldman et al. demonstrated an excellent 5-year EFS and OS of 84 and 93% respectively (Goldman 2015).

The need for radiotherapy as a part of the treatment was also documented by others. Baranzelli et al. (Baranzelli 1998) treated 18 patients with 6 cycles of chemotherapy (vinblastine bleomycin - carboplatin or etoposide - carboplatin/ifosfamide - etoposide). However, eventually the vast number of patients relapsed and at the end, RT was used as a part of salvage treatment. Hence, the authors conclude that: “Although survival rate is noteworthy (66%), these tumors were not curable with this conventional chemotherapy alone and focal radiotherapy should be part of the treatment.” The need for multimodality approach was also documented by other groups (Matsutani 1998, Ogawa 2003, Kretschmar 2007) although with results worse than that reported by Goldman et al. (see above).

Currently the trial by Children’s oncology group (COG) ACNS1123: Phase 2 Trial of Response-Based Radiation Therapy for Patients with Localized Central Nervous System Germ Cell Tumors is building up upon the excellent previous results (see Goldman above) and will shed more light on the question whether whole ventricular irradiation will be as sufficient as CSI. Also, the ongoing Prospective Trial for the Diagnosis and Treatment of Intracranial Germ Cell Tumors (SIOPCNSGCTII) trial evaluates patients with NGGCTs. However, herein patients without metastatic spread receive only focal radiotherapy. Hence it will be interesting to compare the results of these two trials and also with the historical controls of the previous Goldman et al. data to see which kind of RT is necessary for the treatment of NGGCTs.

Another debated issue is the extent of surgery. Patients with residual mass post-chemotherapy or sequential chemotherapy fare worse than their counterparts with complete response. In the quoted phase II study by Goldman patients with no residual tumors had a 5-year PFS and OS of 100%. However, those who harbored residual tumor mass had a 5-year PFS and OS of 81 and 92% respectively (Goldman 2015). Thus, some authors argued that gross total resection may improve survival although no clear data regarding this issue are currently available (Ushio 1999, Kochi 2003, Ogawa 2003, Calaminus 2005). Despite the lack of definitive data, second look surgery can be considered in patients with residual tumors (Souweidane 2010). Another reason for surgery might be the growing teratoma syndrome which is an enlarging tumor with normal or declining serum markers which is found to be a mature teratoma upon resection. Growing teratoma syndrome is however quite rare with an incidence below 10 percent (Rustin 1986, Lee 1995, O'Callaghan 1997). The state of the art treatment for mature teratoma is surgical resection as mature teratomas are unresponsive to chemotherapy and radiation.

To sum it up, for NGGCT the backbone of the treatment is the chemotherapy mostly including either cis- or carboplatin and etoposide with other agents. RT is also deemed a necessary part of treatment as many patients relapsed when chemotherapy alone was used. Controversies exist regarding the volume of radiotherapy (Murray 2015).

Best results were achieved in the study by Goldman where CSI was used. Outside of the clinical trial, a minimum of whole-ventricular radiotherapy is indicated as mixed histology can occur and unsatisfactory relapses occurred in pure germinoma with focal radiotherapy only. There is hope that the aforementioned studies will ultimately resolve the question of the proper RT volume in localized CNS NGGCT. In an NGGCT with leptomeningeal spread, CSI preceded by chemotherapy represent the state of the art therapy. A further role of surgery has also to be elucidated in the setting of prospective trials.

### 2.1.2 CSI in palliative setting: leptomeningeal carcinomatosis from solid tumors

Solid tumor spread to leptomeninges poses a serious condition which results in fatal outcome mostly in a brief course of time. It is estimated that leptomeningeal carcinomatosis can present in as many as 70% of patients with progressive metastatic cancer and 5-10% of patients even as a first manifestation (Leal 2011). Sometimes, leptomeningeal carcinomatosis can be present also without any evidence of another systemic disease. Pathophysiologically, the spread of solid tumors to leptomeninges is achieved via hematogenous spread or direct tumor extension from bony metastases or along the cranial nerves. The most common tumors that present with leptomeningeal carcinomatosis are breast cancer, NSCLC, and melanoma (Wasserstrom 1982, Gleissner 2006).

The diagnosis of leptomeningeal carcinomatosis (LM) is achieved either by lumbar puncture or by MRI. The treatment options available are systemic chemotherapy, intrathecal chemotherapy, and radiotherapy. Due to the existence of blood-brain barrier (BBB) systemic chemotherapy was deemed not to be as effective as in the treatment of extra-CNS metastatic sites. Yet in case of progressive systemic disease outside of CNS intravenously applied chemotherapy can also be used to treat leptomeningeal carcinomatosis. In fact, Boogerd et al.(Boogerd 2004) showed in a randomized trial that the addition of intrathecal chemotherapy to systemic chemotherapy and focal radiation didn’t provide any additional survival benefit and lead to increased toxicity. Also in the retrospective study by Oechsle et al. (Oechsle 2010) systemic chemotherapy resulted in significantly improved OS as compared to patients treated only with intrathecal chemotherapy, radiotherapy or both. This can be explained due to the fact that the larger leptomeningeal metastases may have good

vasculature or disrupted BBB thus being amenable to treatment with systemic therapies. A number of other reports show the efficacy of systemic agents (e.g. temozolomide, capecitabine) for which responses in some cases even durable were shown (Herrlinger 2004, Rogers 2004, Tham 2006, Ekenel 2007, Rudnicka 2007).

To avoid the problem with the BBB and when the metastatic disease outside of CNS doesn't pose an urgent threat the therapy normally consists of intrathecal methotrexate and radiotherapy to bulky sites. However, intrathecal chemotherapy doesn't affect macrometastatic sites and it is dependent on normal CSF flow.

Other intrathecal agents include thiotepa, cytarabine (Ara-C) and sustained-release cytarabine (Depocyte). In one randomized control trial (Glantz 1999) comparing Depocyte with methotrexate, "DepoCyte produced a response rate comparable to that of methotrexate and significantly increased the time to neurological progression while offering the benefit of a less demanding dose schedule." Depocyte offers a better dosing schedule over methotrexate in that it needs to be applied only once in two weeks whereas methotrexate is normally given twice a week (Jaeckle 2002, Rueda Dominguez 2005).

When considering treatment with intrathecal chemotherapy it is advised that radionuclide studies ($^{111}$In- or $^{99m}$Tc-DTPA ventriculography) are done to assess the CSF flow. LM may cause a block in CNS flow and hence compromise the efficacy and potentially also increase the toxicity of the applied intrathecal chemotherapy. If such blocks are found focal radiotherapy to this sites may alleviate this problem (Chamberlain 1998).

The data on intrathecal chemotherapy is probably best-regarding treatment of LM as there is a number of randomized clinical trials. They are shown in Table 3.

RT remains a backbone of treatment of patients with LM even though its effect on survival can be questioned (Rudnicka 2007). Focal RT for treatment of cranium and bulky spinal sites are deemed a golden standard. Such therapy is easy to apply and has little acute toxicity and can provide alleviation of pain and in individual cases improve the neurological symptoms. The use of craniospinal irradiation is much more controversial. There is a small study by Hermann et al. (Hermann 2001) who studied 16 patients with LM from various solid tumors treated with 36Gy CSI (à 1.6-2.0Gy) and 10 treated with CSI plus IT MTX. Median OS was 8 weeks for the CSI alone and 16 weeks for the combined treatment, although the number of patients was too small to draw any final conclusion. In the previous study by Oechsle et al. (Oechsle 2010) patients who got systemic chemotherapy had a median survival of 5.6-5.8 months. However, in their study, solid tumors accounted only for

54% and the rest were hematological malignancies. Patients with LM due to breast cancer in the study of Boogerd et al. (Boogerd 2004) had a similar survival.

In summary, current NCCN guidelines recommend treatment as follows: Patients with good performance status (KPS≥60) without major neurological deficits, minimal systemic disease, and reasonable systemic options should be treated with induction intrathecal chemotherapy and in case of breast cancer primary high dose methotrexate can be used. CSI is not stated as an option for LM from solid tumors. Whole brain radiotherapy (WBRT) and RT to bulky sites are indicated (NCCN 2017). In Germany, the guidelines recommend the use of extended WBRT with the inclusion of the upper two cervical vertebrae and focal radiotherapy for bulky disease sites. CSI is also not routinely recommended. Multiple factors need to be assessed as to what treatment (IT or systemic chemotherapy or radiotherapy) should be used such as the extent of extracranial disease, and of the LM itself (whether is microscopic or macroscopic), patient's symptoms, KPS, and tumor histology (Weller 2014).

| Trial | Design | Outcome |
|---|---|---|
| **Grossman et al.** | IT MTX versus thiotepa (59 patients; solid tumors and lymphoma) | OS, 15.9 (MTX) versus 14.1 weeks (thiotepa) |
| **Hitchins et al.** | IT MTX versus MTX + CYT (44 patients; solid tumors and lymphoma) | OS, 12 (MTX) versus 7 weeks (MTX+CYT) |
| **Glantz et al.** | LS-CYT versus MTX (61 patients; solid tumors) | OS, 105 (LS-CYT) versus 78 days (MTX), difference not significant |
| **Glantz et al.** | LS-CYT versus CYT (28 patients; lymphoma) | OS, 99.5 (LS-CYT) versus 63 days (CYT), difference not significant. Cytologic response rate 71% (LS-CYT) versus 15% |
| **Boogerd et al.** | IT versus no IT therapy, but systemic therapy and RT were given in both arms (35 patients; breast cancer) | OS, 18.3 (IT) versus 30.3 weeks (no IT) |

| | | |
|---|---|---|
| **Shapiro et al.** | Lymphoma (25 patients) | LS-CYT versus all MTX and CYT-treated patients combined: PFS 35 versus 43 days (not significant) |
| | | LS-CYT versus MTX: PFS 35 versus 37.5 days (not significant) |
| | Solid tumors (103 patients), LS-CYT versus MTX | LS-CYT versus CYT: PFS 34 versus 50 days, cytologic remission rate 33.3% versus 16.7% (both not significant) |

*Table 3 Trials on intrathecal chemotherapy in LM*

*(Leal 2011) Abbreviations: IT, intrathecal; LM, leptomeningeal metastasis; MTX, methotrexate; CYT, cytarabine; LS-CYT, liposomal cytarabine; PFS, progression-free survival; RT, radiotherapy.*

There are and probably will never be any more randomized control studies comparing different treatment modalities or their combinations as such studies would require large numbers of patients with well-balanced characteristics. Yet this is not possible as patients with LM differ greatly in their demographics, primary histology, numbers of systemic treatments received with different agents etc. Therefore, retrospective data and registries (http://site.meningeosis.net/) are very important to further evaluate the treatment options for this group of patients.

### 2.1.3 Hematological malignancies and the use of CSI

The data on the use of CSI in hematological malignancies is scarce. Most of it comes from the series of pediatric patients with acute lymphoblastic leukemia (ALL). Historically patients with ALL suffered from a high rate of CNS relapses which prompted interest in prophylactic CNS treatment. Based on the studies V and VI from St. Jude's Children hospital a CSI with 24Gy delivered in 15 to 16 fractions dramatically decreased the CNS relapse from 67% to 4% (Aur 1973, Dahl 1978). A lower dose of 12Gy was inferior in preventing a CNS relapse. In the following study, VII CSI was compared to cranial radiation in combination with intrathecal MTX. The results showed that both regimens were comparable in their efficacy of preventing a CNS relapse with ca. 8% of patients developing it (Simone 1981). Another trial from Children's Cancer Study Group (Nesbit 1982) compared 24Gy of CSI combined with irradiation of liver, spleen, and gonads vs. 24Gy of CSI alone vs. 24Gy of whole brain radiotherapy combined with intrathecal MTX vs. intrathecal MTX alone. The former three

arms of the study resulted in equivalent results which were superior to the sole intrathecal therapy. In high-risk leukemia patients defined as WBC at diagnosis >50 000/ul the regimen consisting of WBRT with intrathecal MTX was found to be superior to CSI. Further studies have questioned even the use of WBRT and suggested that aggressive systemic chemotherapy combined with intrathecal chemotherapy may be sufficient (Clarke 2003).

In case of the diagnosis of meningeal leukemia, CSI was also used. In Children's Cancer Study Group studies doses of 24Gy for the cranium and 12Gy for spine were used originally. In subsequent studies in the late 1980s, the spinal dose was lowered to 6Gy only. When patients treated on these historical protocols were compared their 5-year EFS was 69% for the patients treated more recently and 67% for the ones treated on older protocols. However, patients receiving only 6Gy for spine got more intensive chemotherapy (Cherlow 1996). In comparison, protocols such as ALL-BFM 90 and ALL-BFM 95 didn't use CSI in patients with meningeal leukemia. Only WBRT was used. The 6-year EFS was 48% and 57,7% for the patients with meningeal leukemia treated in the former and latter protocol respectively (Schrappe 2000). These numbers are inferior to those of the Children's Cancer Study Group.

Nowadays CSI in leukemia is mostly used as individual salvage treatment in recurrent leukemia with CNS involvement. There are historical data advocating the use CSI rather than WBRT only (Land 1985, Winick 1993, Kumar 1995, Ribeiro 1995, Ritchey 1999, Schrappe 2000). In many cases, however, the prognosis of such patients is dismal as CNS manifestation is often only a prelude to a systemic recurrence.

The data on the use of CSI in the treatment of either primary or secondary CNS lymphoma is limited to a few case reports. Recent papers regarding treatment of CNS lymphoma are mostly addressing the use of novel therapeutical agents such as temozolomide, rituximab, nedaplatin, pemetrexed and the use of high-dose chemotherapy with autologous stem cell rescue (Wang 2013, Zhang 2013, Lee 2015, Glass 2016, Oh 2016).

Even from the past, no larger studies regarding the use of CSI in the treatment of lymphoma were found. This is interesting as lymphomas are generally viewed as radiosensitive tumors. WBRT was historically the mainstay of treatment of PCNSL. Nowadays the backbone of the treatment is high dose MTX. WBRT is used mostly as consolidation or as salvage therapy, due to its potential neurotoxicity (Kasenda 2015).

According to the published literature as many as 7 – 29% of cerebral lymphomas present with meningeal dissemination on their initial presentation. In one study with repeated CSF studies and meningeal biopsy involvement of leptomeninges was found in 42% of the patients (Balmaceda 1995, Korfel 2012). As lymphomas are considered exquisitely radiosensitive perhaps a low dose CSI could be used as a consolidation therapy after completing chemotherapy.

In conclusion, CSI is not nowadays routinely used in the treatment of leukemia or lymphoma. However, its use in special cases may be considered as also suggested by current NCCN guidelines (NCCN 2017).

## 2.2 CSI Techniques

### 2.2.1 Standard 2D and 3D-conformal RT in CSI

Whereas 2D radiotherapy uses only conventional radiographs for the treatment planning, 3D treatment planning is CT-based. The clinical target volume (CTV) is composed of entire CNS and CSF space. CT based treatment can result in better target definition of problem areas such as the cribrose plate. Additionally, MRI should be used to determine the caudal border of the thecal sac. Nerves exiting the spine should be included in the CTV until the spinal ganglion to include the lateral meningeal extension. Further care is needed to include the CSF space along the II. and the VIII. cranial nerve.

Due to its great volume when treating CSI on a standard linear accelerator multiple adjacent fields have to be used. Normally, the patient is treated in the prone position and two opposed lateral fields (depending on the height of the patient) are applied to treat the brain and one or two posterior fields are used to treat the spine. Caution is needed due to the junction of the fields in order not to overdose the spinal cord or underdose the PTV. The prone position is better for visualization of the treatment fields; however, it is less comfortable and thus potentially susceptible to more intrafraction movement. Also, when treating very young children with the need of sedation or anesthesia supine position may be advantageous.

Different approaches exist to deal with the field junctions. One can either form the field in a fashion that the beam edges intersect anterior to the spinal cord, thus resulting in an under-dosing of the spinal cord and PTV (Figure 1). In the second approach, to avoid this, a half-beam technique is used. Herein the cranial dorsal field is junctioned to the opposed fields precisely without resulting in any over- or underdosing of the spinal cord and thus PTV (Figure 2). This is done by collimator angulation and couch rotation. Due to remaining uncertainty and dose inhomogeneity, the junctions of fields are moved (multiple e.g. 3 plans with different junction locations are used in the course of treatment).

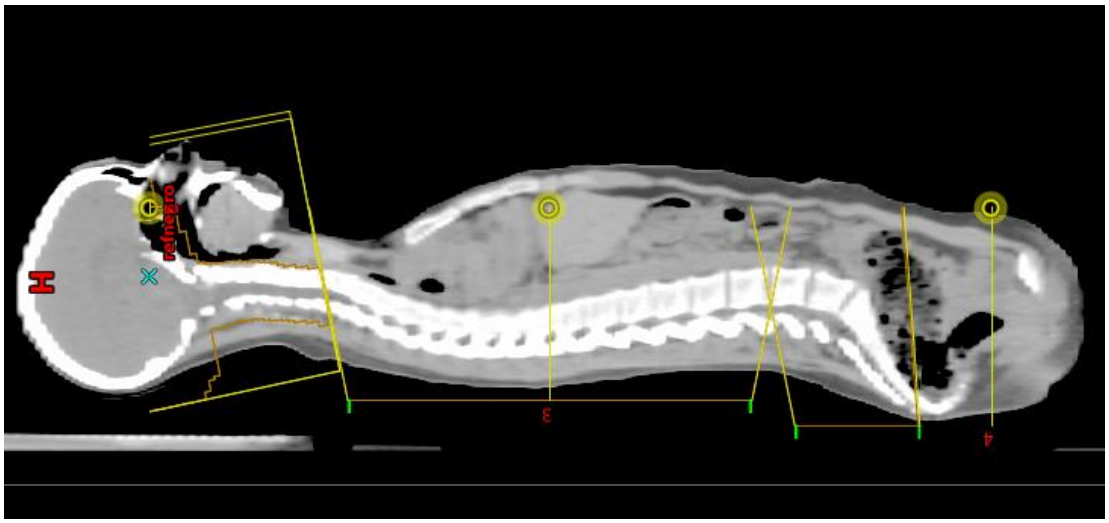


*Figure 1 Standard CSI field setup with beams intersection anterior to the spinal cord*

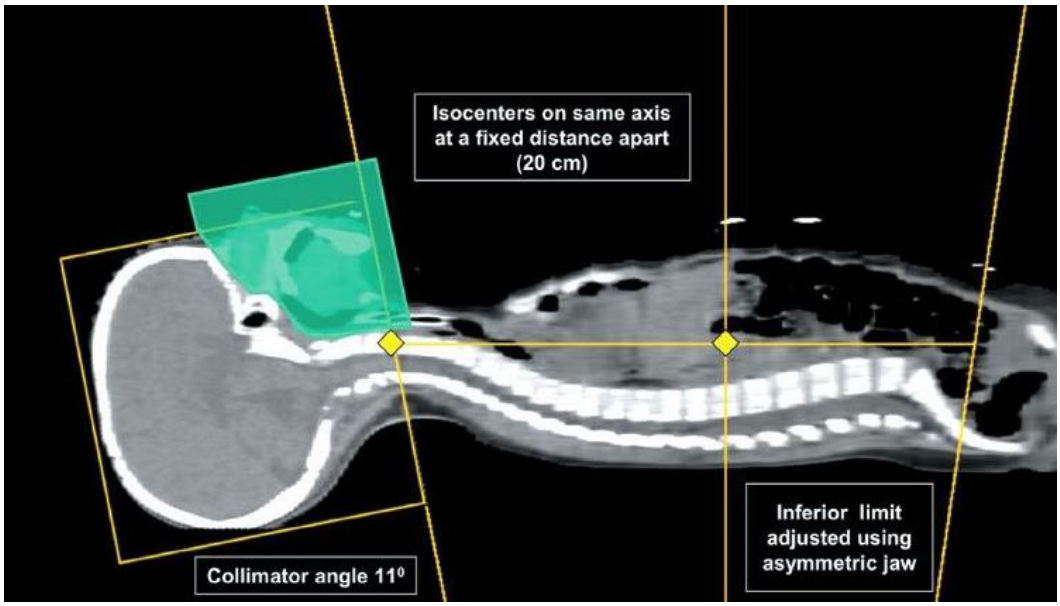



*Figure 2 Standard CSI field setup with half beam technique (Parker 2006)*

### 2.2.2 Intensity modulated techniques

Intensity-modulated radiotherapy (IMRT) differs from the standard 3D conformal RT (3DCRT) in respect to treatment planning and delivery. In 3DCRT the planner (e.g. dosimetrist or physicist) sets the number of fields with their parameters: Gantry and collimator angle, MLC shape, wedges and the weight of each field. In contrast in IMRT, the fields are further subdivided and weighted by the optimization algorithm. After the planner chose the gantry angles for the fields, he gives a number of constraints regarding the PTV coverage and OARs and the computer algorithm splits the fields into further subfields shaping the MLC and sets the monitor units automatically so that the dose distribution is

according to the desired constraints (if physically achievable). Like for 3DCRT, also for IMRT, a planning CT scan is always needed. IMRT generally provides a better dose conformity and homogeneity and most of the time results in longer treatment times, more monitor units used, a greater volume irradiated with lower dose and smaller volume irradiated with higher dose.

Technically IMRT can be done in many ways. The simplest is the “step and shoot” in which the MLC rearranges after each and every subfield was treated from a particular gantry angle. In the “dynamic leaf”, the MLC moves during the treatment from the specified gantry angle. Another IMRT Linac-based technique is the “volumetric arc therapy (VMAT)” sometimes also referred to as “rapid arc (RA)”. Herein the planner assigns the number of arcs, the start and stop gantry angle, as well as the collimator angle for each arc and the rest is done by the software algorithm according to the constraints as in standard IMRT. The standard IMRT normally uses 3-9 gantry angles for the treatment. In VMAT the treatment is done continuously during the gantry rotation from the selected start angle until the stop angle is reached (e.g. full rotation of 360°). The leaves of the MLC also adjust their position during the gantry rotation.

Helical tomotherapy (HT) is a radiotherapy treatment machine. HT works somehow similar to a CT scanner in that the patient is being moved inside to a gantry where the small 6MeV linear accelerator rotates during the treatment. HT uses a special form of the MLC. In a LINAC each leaf of the MLC has its own motor to move it continuously. In HT, the leaves of the MLC are moved with compressed air. This results in faster movement of the leaves (open-close time 20ms) with the effect that each leaf has only two positions, either completely closed or completely open. Therefore, this MLC is also referred to as a binary MLC. In HT treatment planning, the planner sets following parameters: field width, pitch, and modulation factor as well as the constraints. The field width can be set to 1cm, 2.5cm or 5cm and describes the beam aperture in patient’s longitudinal direction. Pitch is defined as a fraction of the beam width at the axis of rotation that the couch travels for a complete gantry rotation. Typical values of the pitch are 0.25-0.5. Modulation factor describes the ratio of maximum to the mean leaf opening time for all non-zero leaf opening values per projection. Altogether all these factors influence the quality of the treatment plan and the overall treatment time. Smaller field width and pitch, as well as greater modulation factor, results in more precise beam delivery to the target, possibly sparing critical OARs in the vicinity of the PTV. The trade-off for this is longer treatment time. Therefore, it is necessary

to weight out the possible benefits and the total treatment time needed to deliver a certain plan.

With these modern radiotherapy techniques, the problems with the junctions can also be minimized. Several methods have been described to deal with this problem, basically using overlapping fields with three isocenter optimizations and gradually increase/decrease in dose on the edges of the overlapping fields. Such techniques are much less prone to intra-fractional movement than compared to the 2D- or 3D- RT. And more importantly, no junctions shift and thus no additional treatment plans are needed. The unique ability of HT to treat fields up to 160 cm (as compared to ca. 40 cm of a standard LINAC) resolves the problem of junctions completely.

### 2.2.3 Proton therapy

The use of protons rather than photons for patients' treatment is not a new one. However, until the 21st century, only a few facilities offering such treatment were available worldwide. Nowadays there are ca. 60 centers across the globe offering treatment with protons and others are still under construction (Particle Therapy Co-Operative Group 2016).

Compared to photons, protons have different physical properties offering potential advantages in the treatment. The depth-dose curve differs significantly (Figure 3). Protons deposit their energy at a particular depth according to their energy referred to as Bragg peak and have almost no exit dose (Paganetti 2002).

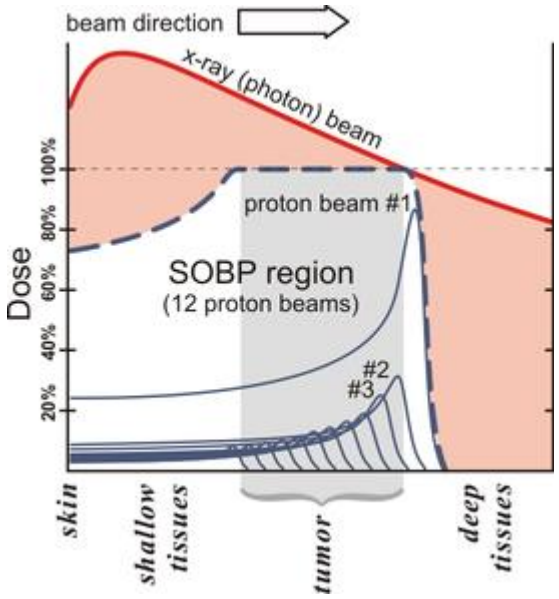



*Figure 3 Depth-dose curve comparison for photon and proton beam (Wikipedia 2017)*

This is the main advantage of protons as it enables further sparing of healthy tissues or gives potential to dose-escalation. There are two methods of proton treatment. One is called passive scattering and the other one is referred to as spot-scanning. In passive scattering, scatterers are used to broaden up the beam to the necessary treatment field size and range modulators or ridge filters together with patient-specific beam modifying devices are used to obtain the desired dose distribution inside the patient. These patient-specific beam modifying devices pose an additional financial burden and also can cause a delay in the treatment start as they need to be manufactured first. Additionally, when protons pass through the scatterers and beam modifiers undesired neutrons are generated increasing the integral radiation dose to the patient. Protons, unlike photons, have a charge, thus can be steered by a magnetic field. This is used in the spot- scanning proton beam delivery. Herein the tumor is scanned voxel-wise according to its relative depth (i.e water equivalent range) by the magnetically steered beam with a constant energy. Then the energy changes and next energy layer is treated and the whole process repeats until the whole tumor is scanned. With this technique, no additional devices are needed. This type of beam delivery also enables the most advanced form of proton therapy – intensity modulated proton therapy (IMPT), where proton beams from multiple directions are optimized together to create the desired dose distribution (Lomax 1999, Oelfke 2001, Paganetti 2002, Marc 2010).

Proton beam was also used in CSI. Both beam deliveries were used. When passive scattering is used the treatment resembles that with conventional 2D-/3D- CSI with a similar field geometry (two lateral fields for head and 2 dorsal fields for spine) and the need of junction and their movement in the course of treatment. In spot-scanning also attached dorsal fields only are possible. No junction-shifts are necessary if the overlapping wields with gradually increase/decrease in dose on the edges are used (Yuh 2004, Timmermann 2007, Yoon 2011, Barney 2014).

CSI with protons (p-CSI) was proved feasible and effective in children as well as in adults. P-CSI results in lower dose to structures anterior to the spinal canal, such as pharynx, esophagus, thyroid, heart, stomach, intestine, salivary glands and also lowers the integral dose thus reducing the acute side effects such as dysphagia/odynophagia, xerostomia and potentially allow for bone marrow sparing if only a part of the vertebra is included in the target volume (St Clair 2004, Yuh 2004, Yoon 2011, Brown 2013, Barney 2014, Giantsoudi 2017).

## 2.3 Toxicities of CSI

### 2.3.1 Acute toxicities

Hematologic toxicity is one of the most pronounced acute side effects. Due to the depletion of proliferating bone marrow during the treatment, this effect can potentially be even longer lasting and can jeopardize delivering of further therapy i.e. chemotherapy.

In 1961 Ellis described the distribution of proliferating bone marrow. His data were based on cadaver studies(Ellis 1961). Hayman and Campbell studied the distribution of proliferating bone marrow in adult cancer patients using 3'-deoxy-3'[(18)F]-fluorothymidine (FLT) - positron emission tomography (PET)/CT (Hayman 2011, Campbell 2015). Hayman studied 13 cancer patients and found out that “the mean percentage of proliferating bone marrow by anatomic site was 2.9%+/-2.1% at the skull, 1.9%+/-1.2% at the proximal humeri, 2.9%+/-1.3% at the sternum, 8.8%+/-4.7% at the ribs and clavicles, 3.8%+/-0.9% at the scapulas, 4.3%+/-1.6% at the cervical spine, 19.9%+/-2.6% at the thoracic spine, 16.6%+/-2.2% at the lumbar spine, 9.2%+/-2.3% at the sacrum, 25.3%+/-4.9% at the pelvis, and 4.5%+/-2.5% at the proximal femurs.” Campbell studied 51 patients with NSCLC. In his study mean percentage of proliferating bone marrow was as follows: “Skull (6.0%), cervical vertebrae bodies (3.7%), thoracic vertebrae bodies (17.7%), lumbar vertebrae bodies (14.8%), sacrum (7.2%), pelvis (22.8%), proximal humeri (3.5%), proximal femuri (5.7%), ribs, clavicles and scapulae (16.6%), sternum (2.0%).”

According to Hall and Giaccia, the TD50/5 (maximal tolerance dose – dose that results in 50% probability of normal tissue complication within a time interval of five years) for proliferating bone marrow is 4.5Gy (Hall 2012). Menda et al. evaluated patients treated with radio-chemotherapy in head and neck cancer using FLT-PET/CT. They found out that after one week of therapy (10Gy and one cycle of Cisplatin) the proliferating bone marrow proliferation reduced for an average of 76% (range 63 - 84%) in the irradiated part and that the areas of non-irradiated marrow behaved more variably. On average, according to their standard uptake value (SUV), they exhibited a decrease of 12% (range -52% - +16%). There was a correlation in the circulating platelet count and the FLT uptake in the lumbar bone marrow (Menda 2010). Cervical bone marrow didn’t have an impact on the overall blood count, due to its small percentage of the overall bone marrow activity (see above).

Thus, vast areas of proliferating bone marrow will be irradiated when treating a patient with CSI. This will deplete the bone marrow reserves causing a decrease in virtually all cell lines. At the biggest risk are patients who underwent a chemotherapy prior to CSI or patients who

are scheduled to receive further chemotherapy either during or after completing the CSI. Often protracted leuco- or thrombopenia results in long treatment breaks.(del Charco 1998, Paulino 2000).

The most common acute non-hematological toxicities are dysphagia or odynophagia due to the proximity of pharynx and esophagus to the PTV. These are however transient and can be relieved with NSAID in most cases. Also, nausea and vomiting can occur. Yet these also can be alleviated with antiemetics or if other signs of increased intracranial pressure are suspected (i.e. headache) by dexamethasone. Other possible side effects of the treatment are alopecia, radiodermatitis, and xerostomia.

### 2.3.2 Long-term side effects

The data on long-term side effects originate from children patients. One of the most feared side effects is neurocognitive impairment. It is age related (i.e. younger age = greater risk) and radiation volume and dose-related (Grill 1999). In a study of 194 pediatric CNS cancer patients younger than three years showed that children treated with CSI had significantly greater progressive impairment of intelligence quotient (IQ) compared to local RT or treatment without radiation (-1.3 versus -0.5 versus +0.9 IQ points per year, respectively) and also significantly higher incidence of severe impairment (IQ <70) than either local RT or treatment without RT (71 versus 24 versus 20 percent, respectively) (Fouladi 2005). As for the radiation dose, children with high-risk medulloblastoma receiving approx. 36Gy CSI were compared to children with average-risk medulloblastoma (i.e. receiving 23.4Gy), both followed by a boost to the macroscopic tumor with respect to their IQ and academic achievement. A decline in IQ as well as in reading, spelling, and mathematics was shown. This was more pronounced in the high-risk group. However, the most important risk factor for the impaired neurocognitive function was the young age at the time of diagnosis (Merchant 2014).

Ototoxicity is another frequent late sequel of CSI when treating patients with medulloblastoma, however, it is not a side effect of CSI per se. In CSI, normally the prescribed dose doesn't exceed 36Gy in 1.8Gy per fraction which is below the QUANTEC constraints for cochlea (Bentzen 2010, Jackson 2010). Historically in many diseases, the sequential boost was delivered to the whole posterior fossa thus further exposing cochleae to high dose radiation. Also in the treatment of some diseases where CSI is used (i.e. medulloblastoma, germinoma dysgerminoma) platinum chemotherapy is also prescribed which can further result in the deterioration of hearing function. With the use of IMRT or

protons, the dose to the cochlea can be further reduced as compared to the 2D/3D-CRT techniques thus potentially reducing this debilitating late toxicity. Vieira et al. reported on the use of IMRT for involved field boost in medulloblastoma patients and found out that "IMRT leads to a low rate of severe ototoxicity. Median radiation dose to auditory apparatus should be kept below 42Gy. Cisplatin doses should not exceed 375 mg/m$^2$"(Vieira 2014). Hence this supports the argument that normal CSI up to 36Gy doesn't pose a high risk for ototoxicity.

Patients treated with CSI can also suffer from a number of endocrinopathies. These can be disease related as in the case of germinomas (Dimitrakopouloua 2015) or result from the treatment (Constine 1993).

In a study by Laughton et al. endocrine abnormalities (growth hormone (GH), adrenocorticotrophic hormone (ACTH), and thyroid-stimulation hormone (TSH) deficiencies as well as primary hypothyroidism) in children after CSI were evaluated (Laughton 2008). He studied 88 children patients with embryonal brain tumors treated with CSI and high-dose chemotherapy. He found out that: "The cumulative incidence of GHD, thyroid-stimulating hormone (TSH) deficiency, adrenocorticotropic hormone deficiency, and primary hypothyroidism at 4 years from diagnosis was 93% ± 4%, 23% ± 8%, 38% ± 6%, and 65% ± 7%, respectively. Radiation dosimetry to the hypothalamic-pituitary axis was associated only with the development of TSH deficiency; the 4-year cumulative incidence was 44% ± 19% and 11% ± 8% (P = .014) for those receiving more or less than the median dose to the hypothalamus (≥ 42 v < 42Gy)." The study doesn't provide the reader with the dosimetric data on the thyroid in order to assess the correlation of the dose received by the thyroid and its function in time (Laughton 2008). Another study compared children patients treated with lower-dose (18Gy) CSI with their counterparts who received 23-39Gy. Authors concluded that endocrine morbidity was significantly reduced (Xu 2004).

Gurney et al. examined 1607 children brain cancer survivors in a case-control study with their siblings for late effects. He found that the survivors were at an increased risk of hypothyroidism, growth hormone deficiency, the need of medications to induce puberty and osteoporosis. Furthermore, an increase in cardiovascular events was also reported. "Overall the risk was small for patients treated with surgery only, consistently elevated for patients treated with surgery and radiotherapy and higher still for those who also received chemotherapy"(Gurney 2003). The limitations of this study are patients' self-reported outcomes and a small number of patients treated with CSI. Still, it provides interesting data

suggesting that patients with PNET/medulloblastoma are at risk not only for endocrinopathies but also for cardio-vascular events.

# 3 Material and methods

## 3.1 Patients

### 3.1.1 Treatment planning

Patients treated with CSI or WSI at our institution in 2001-2015 were eligible for the study. Patients treated before 2007 were simulated on a standard simulator. They were immobilized using a thermoplastic mask and vacuum cushion in prone position. Then a 2D treatment plan was calculated using 2 standard opposed fields for the brain with two attached dorsal fields for the spine. The field junctions are critical for over- and underdosing. To decrease the effect of uncertainty and dose inhomogeneity at the junctions of separate fields, the junctions were moved from day to day. So, the final treatment actually consisted of a sum of three plans, each with the junctions moved by 1 cm in cranial-caudal direction.

For patients treated with HT, a CT imaging was performed with 3-5mm slice thickness on a standard Siemens CT (Siemens Inc, Erlangen, Germany). Patients were immobilized in the supine position using a vacuum couch and a thermoplastic head mask (BRAINLAB, Munich, Germany). Then OARs and CTV and PTV were delineated according to institutional guidelines either in iPlan (BRAINLAB, Munich, Germany) or in Eclipse (Varian Medical Systems, Palo Alto, CA, USA). The CTV to PTV margin was as follows: For CTV Brain and cervical spinal canal 6mm-10mm in all directions, for CTV thoracic spinal canal it was 10mm antero-posterior and 10-15 mm lateral and for the remaining CTV it was again 10mm antero-posterior but 10-20mm lateral. The PTV to CTV margin used was rather big compared to the most publications available, however, as patients in this study were adults the whole vertebra was not included in CTV as it is the case of the children patients in order to ensure symmetric growth. In order to achieve a secure coverage of the PTV in its entire length, based on the institutional experience derived from the daily imaging using megavoltage-computed tomography (MVCT), this margin was deemed appropriate. PTV included whole liquor space or in 5 cases only the spinal liquor space. The treatment planning was performed with Tomotherapy Planning Station (Tomotherapy Inc, Madison, USA).

### 3.1.2 Clinical data assessment

In the clinical part, we retrospectively evaluated these patients. Data on demographic characteristics, diagnosis, and disease burden, treatment duration, delivered dose, dose per fraction, treatment technique, treatment interruption or abortion, as well as the use of chemotherapy with close temporal relation (three months) to the radiotherapy, were

obtained. To assess the efficacy and toxicity of the treatment, information on acute side effects, blood cell counts at the beginning of the radiotherapy and their nadir during or shortly after completion of the therapy and survival was gathered. Toxicity was graded according to CTCAE 4.03.

To obtain the information regarding the extent of systemic disease in patients treated in palliative intention, the last CT-scans before initiation of the CSI (or WSI) were reviewed. MRI findings and images were also reviewed in order to assess whether there was macroscopic or microscopic CNS disease.

## 3.2 Dosimetric study

In the dosimetric part of this thesis, 9 patients were analyzed. For each patient, four different treatment plans were evaluated. One was the original HT plan used for treatment (Tomo). The second treatment plan was calculated using standard 2D/3D treatment field setup, i.e. 2 opposed lateral fields for treatment of the neurocranium and the upper cervical myelon with 2 adjacent dorsal fields to cover the rest of the meningeal space (3DCRT). The third plan was again a HT one, optimized to better spare proliferating bone marrow and organs at high risk for acute side effects such as pharynx, esophagus and major salivary glands (BMTomo). The fourth plan used protons and used a single one beam dorsal setup for the treatment of neurocranium as well as the spine (p-CSI). All plans were standardized for a total delivery of 36Gy as used in high-risk medulloblastoma or as currently used at our institution to treat selected patients with LM.

### 3.2.1 Organs at risk (OARs)

In order to compare the treatment plans, further organs at risk were contoured by an experienced radiation oncologist. Dose to lenses, oral cavity, parotid and submandibular glands, pharynx, larynx, esophagus, heart, lungs, bowel, pancreas, thyroid and autochthone dorsal musculature were evaluated. Furthermore, proliferating bone marrow was contoured in its separate compartments (skull, the body of the cervical, thoracic and lumbar vertebrae, ribs and clavicles, sternum, sacrum, pelvic bones and proximal humeri and femuri) according to the study by Hayman et al (Hayman 2011).During the writing of this thesis the second study by Campbell et al (Campbell 2015) from the same group was published evaluating data of even more patients, hence our results were updated in respect with the most up-to-date data (Figure 4). All plans were evaluated with respect to the mean, minimal, maximal organ dose as well as V5 and V20 for the lungs and V25 for the heart and V26 for the thyroid.

### 3.2.2 Evaluation of proliferating bone marrow

For the evaluation of the dose in the proliferating bone marrow, two methods were used. For one, the proliferating bone marrow was considered as one organ with equal activity distribution in all of its parts. In the second case, we used the mean activity for the particular compartment as reported in the aforementioned publication and introduced weighted bone marrow exposure (WBME). We defined WBME as the sum of the product of the prespecified dose (mean, V5, V10, V15, V20, V25, V30, V35) to the particular bone marrow part and its mean activity (in percent) based on the FLT-PET/CT by Campbell et al (Campbell 2015). This allows comparing the standard dose volume histogram (DVH) where y-axis gives the volume of the specific structure in percent with dose activity histogram (DAH) where instead y-axis gives the activity of the bone marrow exposed to a certain dose.

- $WBME_{DMEAN}[Gy]=\sum$(Dmean of particular bone marrow part[Gy])x(its mean activity[%])
- $WBME_{Vx}[\%]=\sum$($V_x$ of particular bone marrow part[%])x(its mean activity[%])

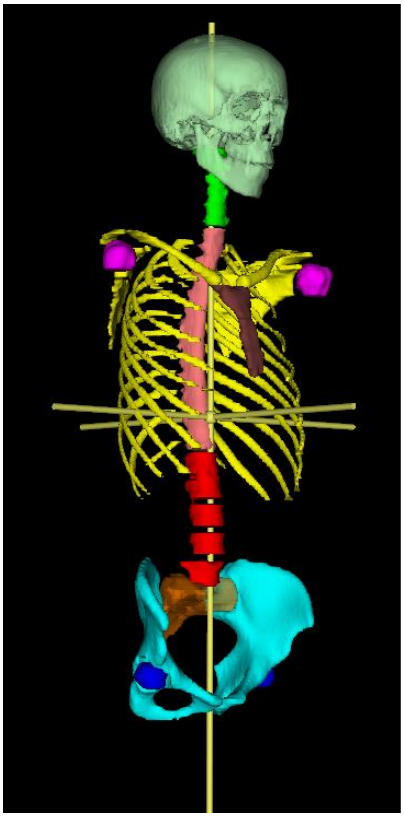


*Figure 4 An example of adult active bone marrow compartments contouring and the respective mean proportion of active bone marrow according to Campbell et al.*
*(Campbell 2015)*

*Light Green – Skull (6.0%)*
*Green – Cervical vertebrae bodies (3.7%)*
*Pink – Thoracic vertebrae bodies (17.7%)*
*Red – Lumbar vertebrae bodies (14.8%)*
*Orange – Sacrum (7.2%)*
*Cyan – Pelvis (22.8%)*
*Magenta – Prox. Humeri (3.5%)*
*Blue – Prox. Femuri (5.7%)*
*Yellow – Ribs, Clavicles and Scapulae (16.6%)*
*Brown – Sternum (2.0%)*

### 3.2.3 PTV Evaluation

All plans were also compared with respect to their PTV coverage. For this, following parameters were taken into account:

- Conformity index (CI) = $TV_{RI}/TV$;
- Homogeneity index (HI) = $(D_2 – D_{98})/D_{MEAN}$;
- Conformation number (CN) = $TV_{RI}^2/(TV \times V_{RI})$ ;

Where $TV_{RI}$ is the target volume covered by the 95% isodose, TV is target volume, $V_{RI}$ is the volume covered by the 95% isodose, and $D_{98}$ and $D_2$ refer to the dose received by the 98% and 2% of the PTV respectively (i.e. near maximum and near minimum dose). $D_{MEAN}$ gives the average dose to the PTV. CI can achieve values between 0 and 1, where 0 means no part of the PTV receives the desired dose (i.e. 95% of the prescribed dose) and 1 meaning that all of the PTV is irradiated to the 95% of the prescribed dose. Homogeneity index gives information on PTV homogeneity, where the lower its value the better the homogeneity (perfect homogeneously PTV coverage would mean HI=0). CN takes into account not only the PTV coverage but also healthy tissues exposed to the dose equal or exceeding the 95% of the prescribed dose. Hence, it is more accurate than CI. As CI it ranges from 0 to 1 with 1 also being its desired value (Feuvret 2006).

### 3.2.4 Delineation and treatment planning

The contouring of the further OARs required for this study was done in Eclipse. Treatment plans were calculated in Tomotherapy planning system for the first and third scenario. All HT plans were exported into Eclipse and the data readout was done out of Eclipse. If the initial HT treatment plan wasn't calculated for 36Gy the dose was set to 36Gy in Eclipse for comparison and evaluation. For the 3DCRT (second scenario) the planning system Eclipse (Varian) was used. Finally, to calculate proton plans an in-house developed software package for CERR (computational environment for radiotherapy research) was used with active scanning (spacing=0.5cm, FWHM=1). In comparison to Eclipse and Tomotherapy planning system, CERR is not available for clinical use. Yet, the results of the treatment planning can be used for a planning comparison study (Deasy 2003, Schell 2010). Due to CERR limits, creating multiple plans with smaller field size and junctioning them, as it would have been necessary for a real-life treatment, was omitted. Instead, the proton treatment plan used one dorsal field setup for the whole treatment length as this was deemed sufficient to evaluate the dosimetric differences. The used CT datasets had different

resolutions ranging from 128x128 to 512x512 pixels. For the patients with higher resolution, the images were downscaled in order to make the treatment plan calculation in CERR feasible.

## 3.3 Statistical methods

Descriptive statistics were used, to sum up the demographic and dosimetric information. Normally distributed data were assessed with t-test and not normally distributed data with Mann-Whitney U test. Fishers' exact test was used to test whether treatment technique or pre-treatment with chemotherapy have a significant effect on the occurrence of severe leukopenia or thrombopenia. For survival estimation, Kaplan-Meier method was used. Mantel-Cox method was used to test the equality of survival distribution according to treatment technique for the groups according to their treatment intention and for the subgroup analysis for patients with LM. Statistical calculations were done in SPSS 23.0 and MS Excel.

## 3.4 Compliance with ethical standards

All institutional guidelines were followed. Informed consent was obtained from all patients. Bavarian state law (Bayrisches Krankenhausgesetz §27 Abs. 4 Datenschutz) allows the use of patient data for research and publication, provided that any personal related data are kept anonymous. Nevertheless, this study was approved by the Ethics Committee of the School of Medicine of the Technical University of Munich on February 23rd, 2015 with the project number 84/15.

# 4 Results

In the clinical part of the thesis, 42 patients were evaluated. Patients were treated either by CSI (n=37) or by spinal irradiation only (n=5). Spinal irradiation was used after preceding whole brain radiotherapy or in one case for treatment of ependymoma without the manifest intracranial spread. The basic demographic characteristics are summarized in Table 4.

| | | |
|---|---|---|
| **Median Age at treatment (years)** | **36.7** | **(range 6-80)** |
| - Palliative | **57.8** | **(range 31-80)** |
| - Curative | **24.6** | **(range 6-60)** |
| **Treatment intention** | (n) | (percent) |
| - Palliative | 19 | 56 |
| - Curative | 23 | 44 |
| **Sex** | (n) | (percent) |
| - Male | 25 | 63 |
| - Female | 17 | 37 |
| **Median Age (years)** | 36.7 | (range 6-80) |
| - Palliative | 57.8 | (range 31-80) |
| - Curative | 24.6 | (range 6-60) |
| **Median Karnofsky performance index** | 80 | (range 30-100) |
| - Palliative | 70 | (range 40-90) |
| - Curative | 90 | (range 30-100) |

*Table 4 Basic characteristics of treated patients*

| **Primary Diagnosis according to treatment intention:** | **(n)** | **(percent)** |
|---|---|---|
| **Curative:** | **23** | **55** |
| - Choroid plexus carcinoma | 1 | 2 |
| - Ependymoma | 5 | 12 |
| - Germinoma | 6 | 14 |
| - Leukemia | 3 | 7 |
| - Medulloblastoma | 5 | 12 |
| - NGGCT | 1 | 2 |
| - Pinealoblastoma | 2 | 5 |
| **Palliative:** | **19** | **45** |
| - Adenocarcinoma of gastro-esophageal junction | 1 | 2 |
| - Astrocytoma WHO Grade III | 1 | 2 |
| - Breast cancer | 5 | 12 |
| - Malignant peripheral nerve sheath tumor | 1 | 2 |
| - non-CNS NGGCT | 1 | 2 |
| - Non-Hodgkin Lymphoma | 3 | 7 |
| - NSCLC | 5 | 12 |
| - Sarcomatoid CUP | 1 | 2 |
| - Gastric carcinoma | 1 | 2 |

*Table 5 Patients according to diagnosis and treatment indication*

23 patients were treated with curative intent and 19 patients received CSI for palliation (Table 5). The median follow-up was 14.6 (range 0-190) months. As of July 2016, 17 out of the 42 patients were still alive. In 18 from 19 patients treated in palliative intention, information on the extra-CNS disease was available. 11 patients had no macroscopic disease on their last CT scan, whereas one had stable disease, five patients suffered from a progressive systemic disease and in one patient, LM presented as the primary manifestation of the tumor. As for the CNS disease extension, this was classified as either microscopic with no evidence of meningeal tumor manifestation on MRI and only positive CSF cytology or as macroscopic when the MRI findings were positive. In 18 patients, the MRI findings were positive and in only one patient the diagnosis was made based only on positive CSF findings.

| Treatment intention | | CSI/WSI dose(Gy) | Total dose incl. boost (Gy) |
|---|---|---|---|
| **palliative** | N | 19 | 6 |
| | Mean | 27.9 | 28.7 |
| | Median | 30.6 | 33.0 |
| | Minimum | 3.0 | 6.0 |
| | Maximum | 36.0 | 54.0 |
| **curative** | N | 23 | 15 |
| | Mean | 29.1 | 46.9 |
| | Median | 25.6 | 54.0 |
| | Minimum | 12.8 | 30.0 |
| | Maximum | 40.0 | 55.0 |

*Table 6 Dose delivered according to treatment intention*

13 patients were irradiated using conventional 2D radiotherapy with standard field setup as previously described. Remaining 29 patients were treated on HT. The delivered dose is summarized in table 6. As for pretreatment characteristics, 3 patients received intrathecal and 13 patients systemic chemotherapy within 3 months before the onset of RT.

## 4.1 Hematologic toxicity

Pretreatment blood counts are summarized in Figure 5 and Table 7. The nadir during or shortly after completion of treatment is depicted in Figure 6 and the Table 7. Hematologic toxicity according to CTCAE v4.03 is summarized in Figure 7. The relation of pretreatment blood cell counts to their respective nadirs is shown in Figure 8. Severe leukopenia ($<10^9$/l) was observed in 6 and severe thrombopenia ($<50x10^9$/l) in 13 patients. The dose distribution between the patients' groups according to treatment technique (2D and HT) was not significantly different. The nadir in blood cell count didn't significantly differ between 2D and HT treatment (p=0.803; p=0.178; p=0.334 for WBC, Hb, and thrombocytes -nadir respectively). Also, the differences in change ratio (nadir/baseline) were not significantly different for WBC and Hb. However, the thrombocytes change ratio (nadir/baseline) distribution was significantly different (p=0.028) (Figure 9). Chemotherapy within 3 months prior to initiation or during RT was associated with significantly lower thrombocytes nadir (p=0.005), while WBC and Hb nadirs were not significantly affected (Table 8).

| | Leukocytes (x10$^9$/l) | | Hemoglobin (g/dl) | | Thrombocytes (x10$^9$/l) | |
|---|---|---|---|---|---|---|
| | Baseline | Nadir | Baseline | Nadir | Baseline | Nadir |
| **Mean** | 7.9 | 2.3 | 13.1 | 11.3 | 273.1 | 81.7 |
| **Median** | 6.4 | 2.3 | 13.2 | 11.4 | 262.5 | 79.5 |
| **Minimum** | 2.2 | 0.2 | 7.9 | 8.2 | 69.0 | 7.0 |
| **Maximum** | 22.7 | 6.1 | 16.1 | 15.1 | 737.0 | 241.0 |

*Table 7 Baseline and nadir blood cell counts*

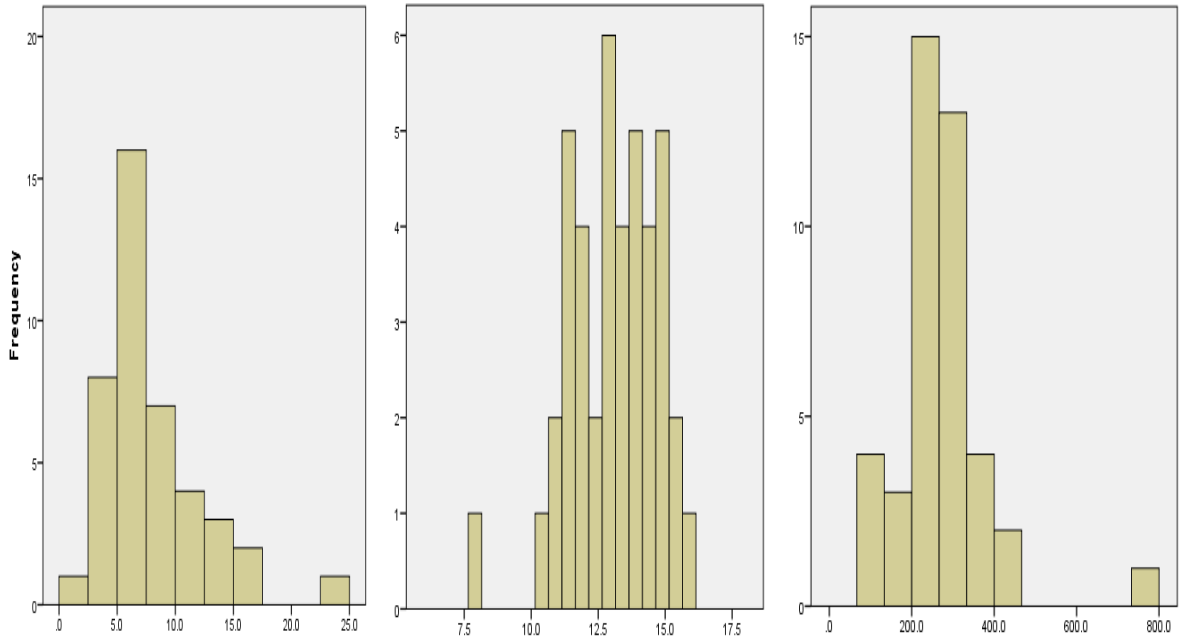



*Figure 5 Pretreatment blood cell counts (WBC, Hb and thrombocytes respectively)*

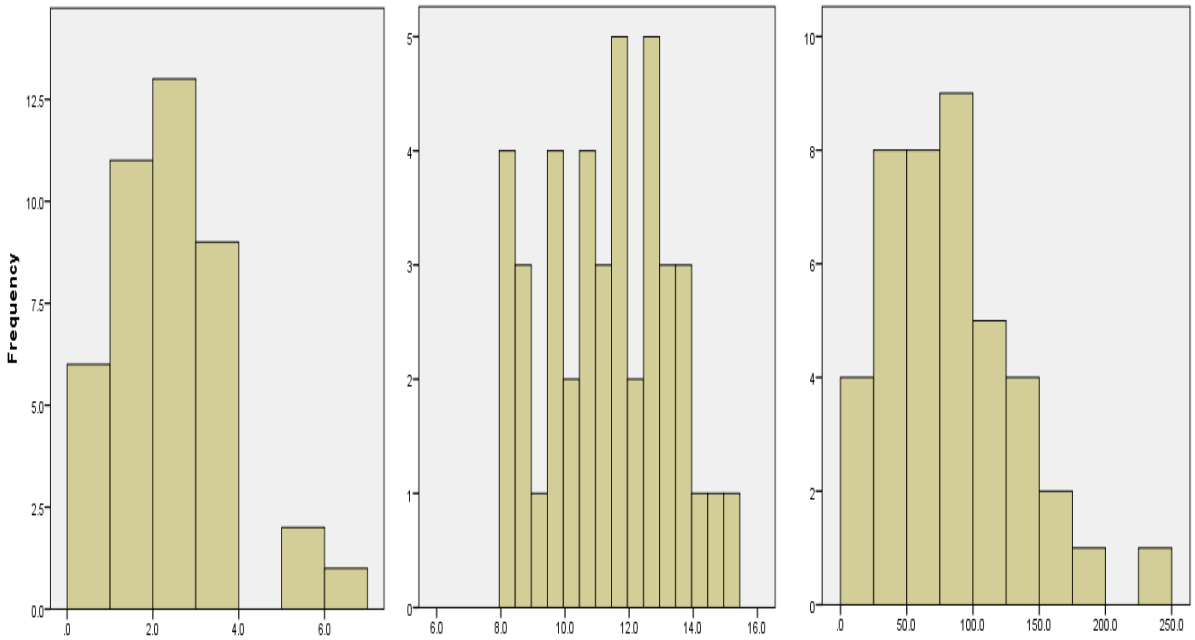



*Figure 6 Nadir blood cell counts (WBC, Hb and thrombocytes respectively)*

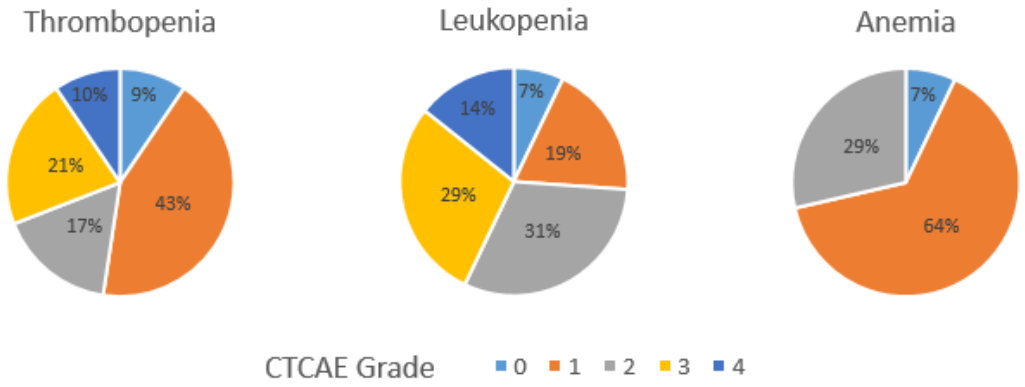



*Figure 7 Hematologic toxicity according to CTCAE 4.03.*

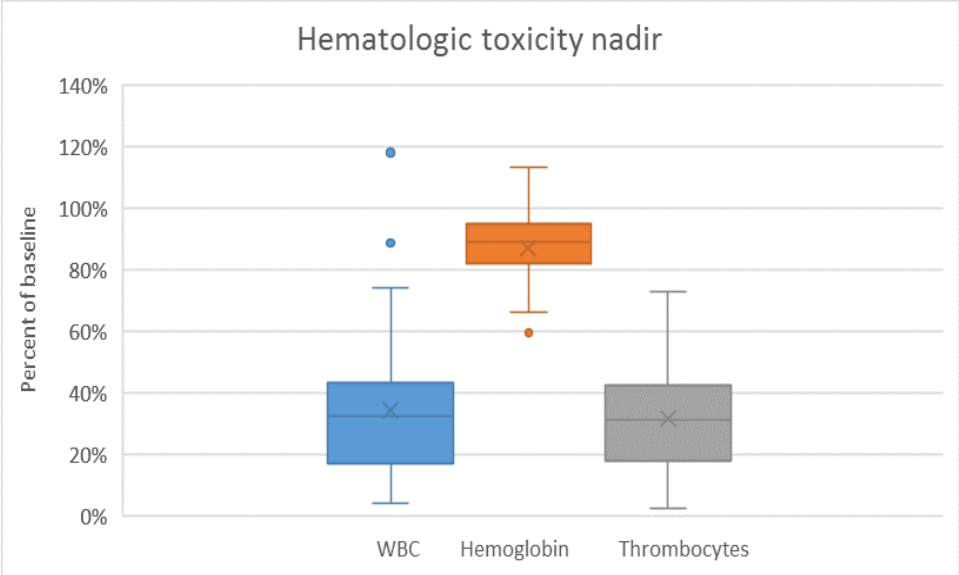



*Figure 8 Hematologic toxicity as percent of baseline*

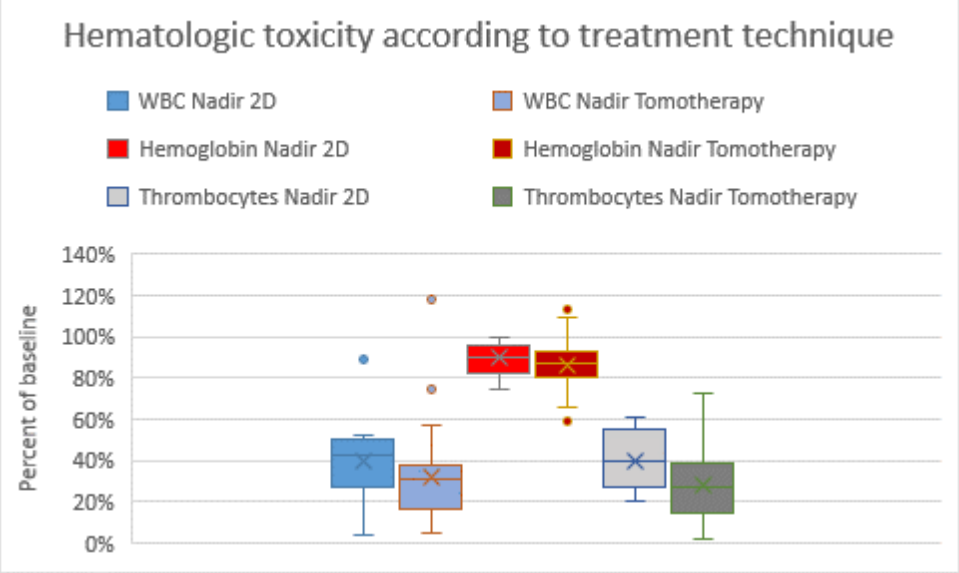



*Figure 9 Hematologic toxicity according to treatment technique*

| | Chemotherapy within 3 months before radiotherapy (0=no/1=yes) | N | Mean | Std. Deviation |
|---|---|---|---|---|
| **WBC Nadir (x10$^9$/l)** | 0 | 29 | 2.5 | 1.8 |
| | 1 | 13 | 1.9 | 1.5 |
| **Hb Nadir (g/l)** | 0 | 29 | 11.6 | 1.9 |
| | 1 | 13 | 10.8 | 1.8 |
| **Thrombocytes Nadir (x10$^9$/l)** | 0 | 29 | 95.9 | 50.8 |
| | 1 | 13 | 50.0 | 30.4 |
| **WBC difference (x10$^9$/l)** | 0 | 29 | 5.6 | 4.3 |
| | 1 | 13 | 5.6 | 4.5 |
| **Hb difference (g/l)** | 0 | 29 | 1.7 | 1.4 |
| | 1 | 13 | 1.8 | 1.8 |
| **Thrombocytes difference (x10$^9$/l)** | 0 | 29 | 178.9 | 59.4 |
| | 1 | 13 | 219.5 | 173.5 |

*Table 8 Blood cell counts' nadir according to chemotherapy use*

CTCAE grade 4 leukopenia (WBC <10$^9$/l) and grade 3 or 4 thrombopenia (Tro <50x10$^9$/l) were separately evaluated and classified as severe leukopenia or thrombopenia as blood cell counts below these levels may lead to treatment prolongation and potentially adversely affect treatment outcome. Treatment technique didn't significantly affect the grade of severe leukopenia or thrombopenia whereas chemotherapy applied within three months prior to RT did (p=0.023 for leukopenia and p=0.047 for thrombopenia). Growth factors or transfusions were given only in five patients. In 26 patients, treatment was performed without any interruption. Five patients had treatment breaks and finally, in 11 patients the treatment was discontinued. The reasons for treatment discontinuation were mostly major cytopenia not recovering after treatment break or general status deterioration with progressive disease in spite of the treatment.

The non-hematologic side effects experienced by patients were nausea (16 patients) with vomiting (5 patients), mucositis with resulting dysphagia (10 patients), alopecia (10 patients). Less common side effects included dysgeusia (5 patients), candida infection (4 patients) and xerostomia (3 patients). All side effects were CTCAE grade I-II, except in one patient experiencing nausea grade III and in two patients death occurred; in one treatment-related as a result of neutropenia and sepsis and in the other one as a result of a massive

thrombosis. Due to the retrospective nature of this study, some of the side effects may be underreported as they were not deemed to be the typical side effect expected (xerostomia, dysgeusia).

## 4.2 Survival

Survival according to treatment indication is shown in Figure 10. Median overall survival (OS) in the curative group was not reached. For the major diagnosis groups, the survival was as follows: Medulloblastoma (median OS=53 months), Pinealoblastoma (median OS=39 months), Ependymoma (median OS=not reached; all patients are alive), Germinoma (median OS=not reached; all patients are alive). In the palliative treatment group, median OS was 3.4 months. As for patients' subgroups, the median OS for patients with LM by breast cancer primary (n = 6) was 4.7 months and for NSCLC (n = 5) was 3.3 months. Despite these limited results, 11 out of 19 patients benefited from the treatment either for survival prolongation or for the improvement in pain or neurological deficits. There were four long-term survivors in patients treated for LM (two breast cancer patients surviving for a minimum of 11.3 (alive at last follow-up) and 13 months respectively, one patient with disseminated astrocytoma WHO grade II surviving 16 months (alive at last follow-up) and one patient with NSCLC surviving for more than 5 years (alive at last follow-up).

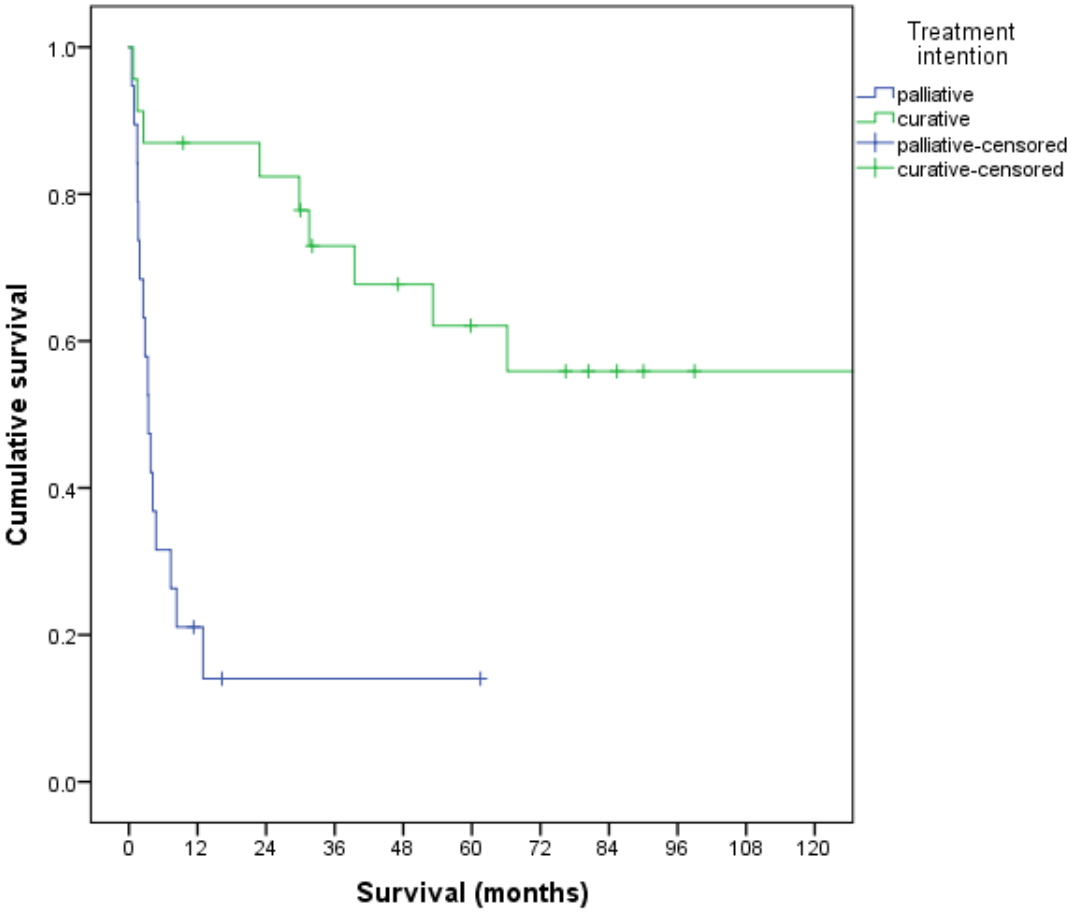



*Figure 10 Survival for curative and palliative treatment group*

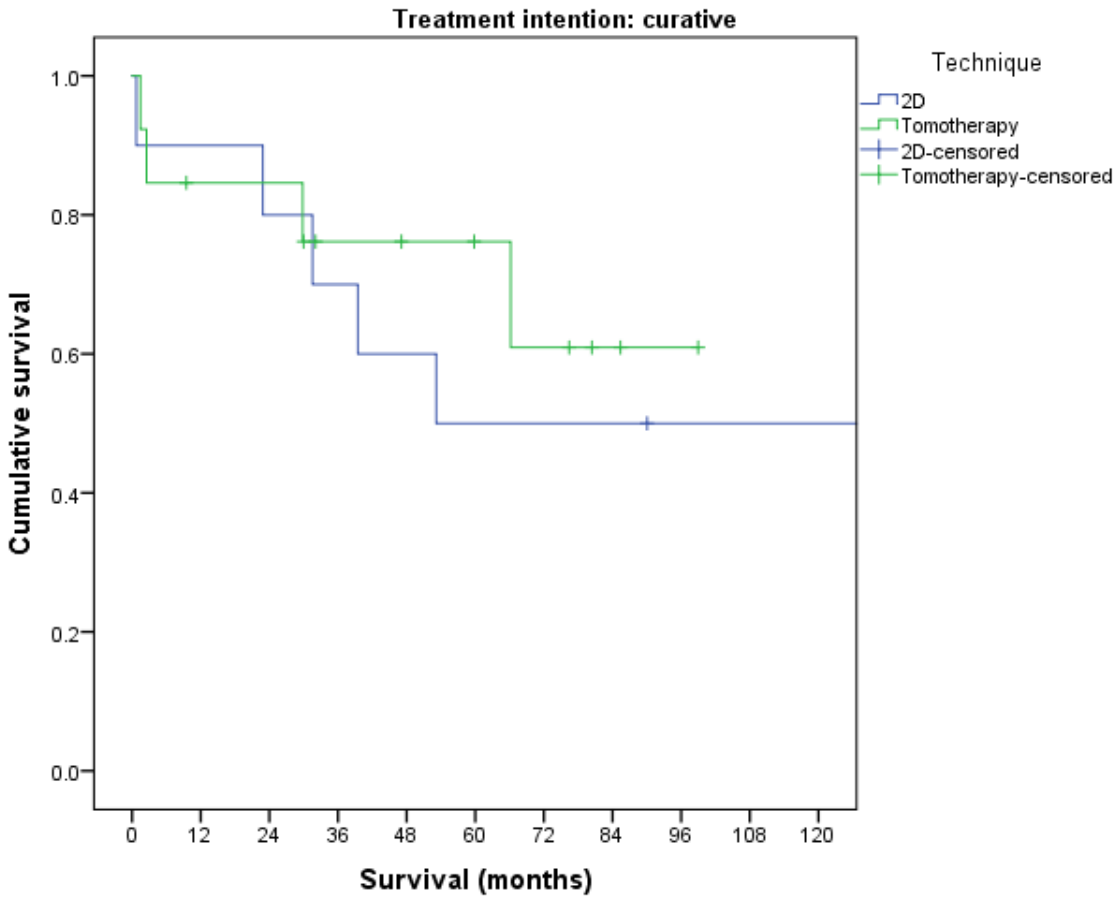



*Figure 11 Survival for patients treated in curative intention according to CSI-technique*

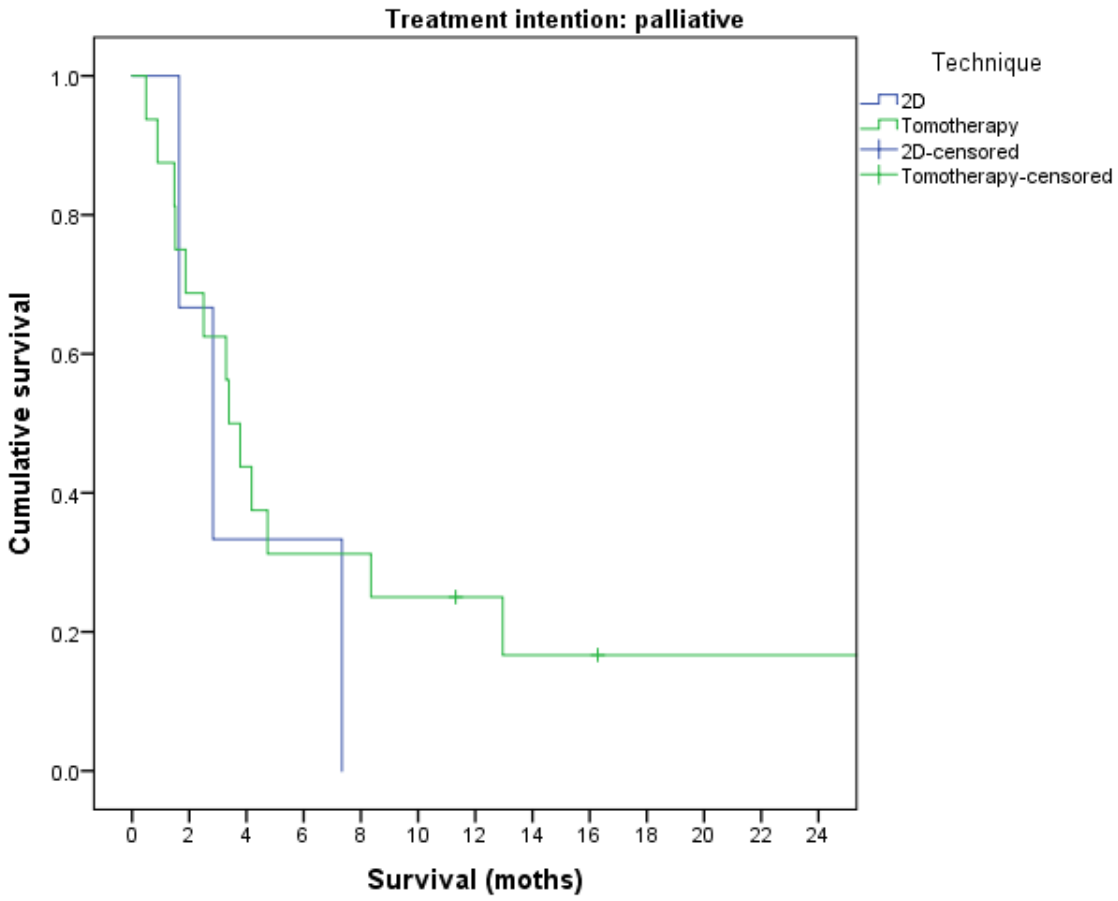



*Figure 12 Survival for patients treated in palliative intention according to CSI-technique*

Treatment technique didn't influence the survival when analyzed for curative and palliative group separately (Figure 11 and Figure 12). In the subgroup analysis (univariate and multivariate) of the palliative group, performance status and systemic disease were significantly associated with survival whereas the treatment technique wasn't (p=0.944). Patients with KPS ≥70 (p=0.018) and no systemic disease (p=0.032) fared much better than their counterparts (Figure 13 and Figure 14).

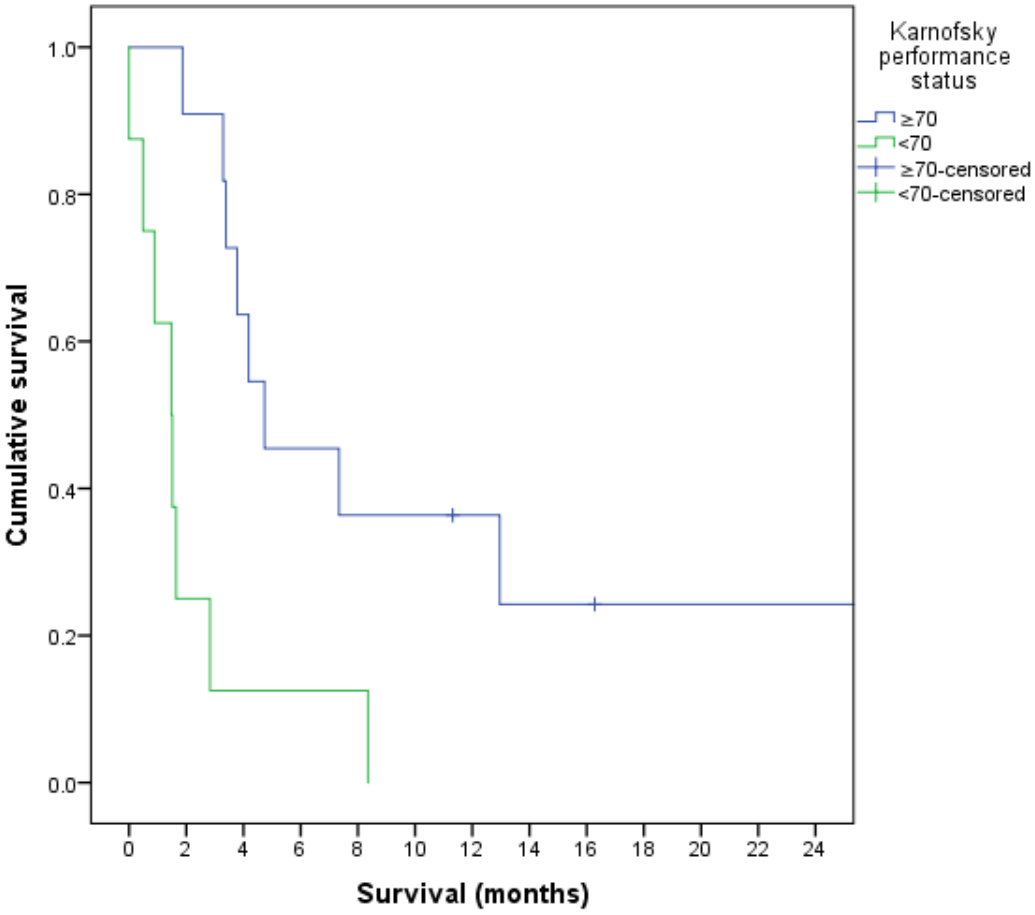



*Figure 13 Survival for palliative group according to KPS*

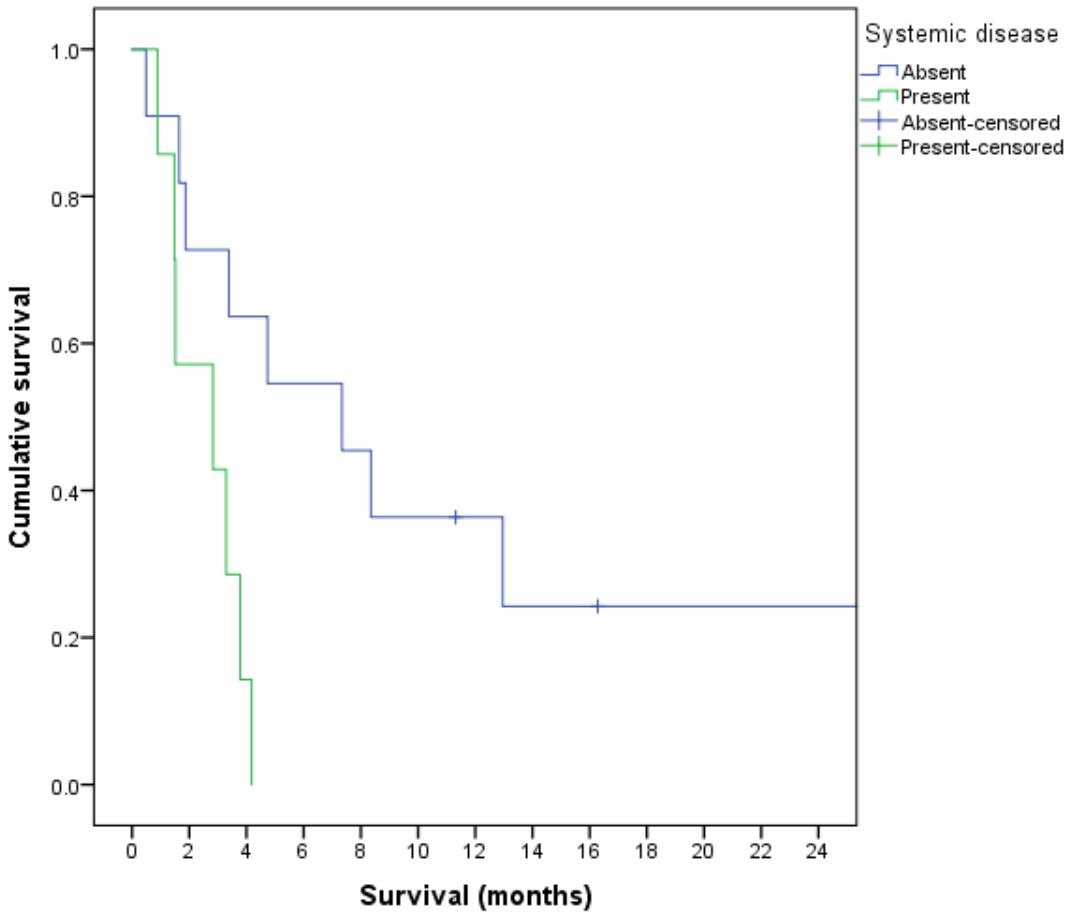



*Figure 14 Survival for palliative group according to presence of systemic disease*

Prognostic score combining these two factors was constructed (Table 9) and was highly significant (p=0.001) (Figure 15).

| **Score** | | **Median OS (months)** | **Median OS (weeks)** |
|---|---|---|---|
| **0** | No systemic disease a KPS≥70 | 7.3 | 31.9 |
| **1** | One of the two factors present | 3.3 | 14.3 |
| **2** | Systemic disease present and KPS<70 | 1.5 | 6.4 |

*Table 9 OS according to prognostic score based on KPS and presence of systemic disease*

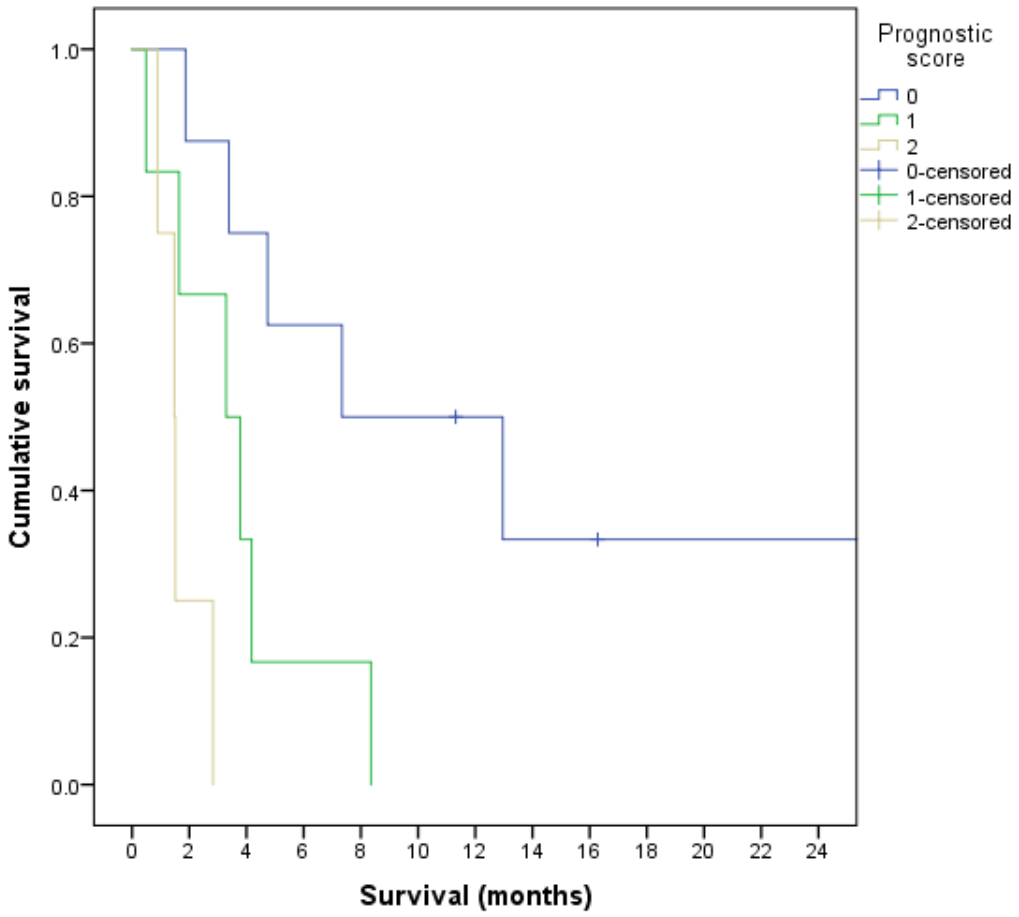



*Figure 15 Survival for the palliative group according to the prognostic score*

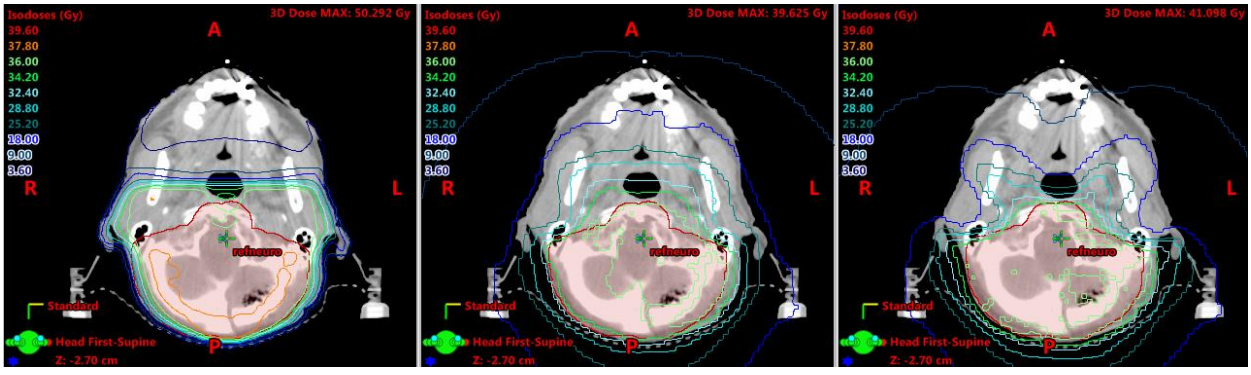
## 4.3 Dosimetric part – Proliferating bone marrow

The main focus of this thesis was to compare the different treatments in respect to proliferating bone marrow exposure as a possible surrogate for the hematologic toxicity. On average, the original HT plans (Tomo) delivered a higher dose to the proliferating bone marrow than the standard 3DCRT. This is true when considering only the volumetric information as well as when considering the different activity of the particular bone marrow compartments i.e. $WBME_{DMEAN}$. However, the difference between the two techniques was slightly lower when considering the $WBME_{DMEAN}$. The optimized HT plans (BMTomo) resulted on average in a slightly higher mean dose to the bone marrow considering the traditional DVH, but when $WBME_{DMEAN}$ is taken into account the BMTomo resulted into lower average exposure to the proliferating bone marrow. Lastly, p-CSI spares best proliferating bone marrow, where $WBME_{DMEAN}$ resulted in further dose reduction as compared to the standard volumetric based model (Table 10). A sample of treatment plans is provided in Figure 16 and 17.

| | 3DCRT | Tomo | BMTomo | p-CSI |
|---|---|---|---|---|
| **$WBME_{DMEAN}$ (Gy)** | 17.3 | 19.2 | 16.2 | 10.9 |
| **Bone Marrow $D_{MEAN}$ (Gy)** | 16.0 | 18.8 | 16.7 | 12.0 |
| **Absolute Difference (Gy)** | 1.3 | 0.4 | -0.5 | -1.0 |
| **Relative Difference (%)** | 8.4 | 1.9 | -3.0 | -8.7 |

*Table 10 Average dose to proliferating bone marrow.*
*All values are the mean of nine patients*

To further examine the dose distribution to bone marrow, not only DMEAN and $WBME_{DMEAN}$ was evaluated, but other dosimetric parameters (V5-V35 and $WBME_{V5-V35}$) to describe it in more detail. A simplified DVH across the average value of all nine patients as well as a dose-activity histogram (DAH), if considering $WBME_{V5-V35}$, shows the differences among the different treatment techniques (Figure 18, Table 12). Herein, the original tomotherapy (Tomo) had a dose bath which resulted in ca. 73% of proliferating bone marrow being irradiated with 5Gy. The break-even point between the Tomo and the standard 2D/3DCRT at ca. 25Gy when considering the volume and 20Gy when considering activity. The optimized tomotherapy (BMTomo) had on average slightly reduced low dose bath with ca. 64% of the proliferating bone marrow receiving ≥5Gy. And the curves cross the respective 2D/3DCRT curves between 10 and 15Gy. Thus, in the region ≤10Gy the 2D/3DCRT is superior to HT (both Tomo and BMTomo). Except for the very high dose ≥35Gy (measured in volume or activity) where BMTomo resulted in less exposure, the protons were superior in all aspects. It is also apparent that traditional DVH may underestimate the damage done to proliferating bone marrow when using traditional 2D/3DCRT CSI and overestimate it when using protons. For HT and probably also other IMRT techniques no general statement can be made as different field setup and different constraints can lead to different results. The average dosimetric parameters for each bone marrow compartment are reported in Table 11.



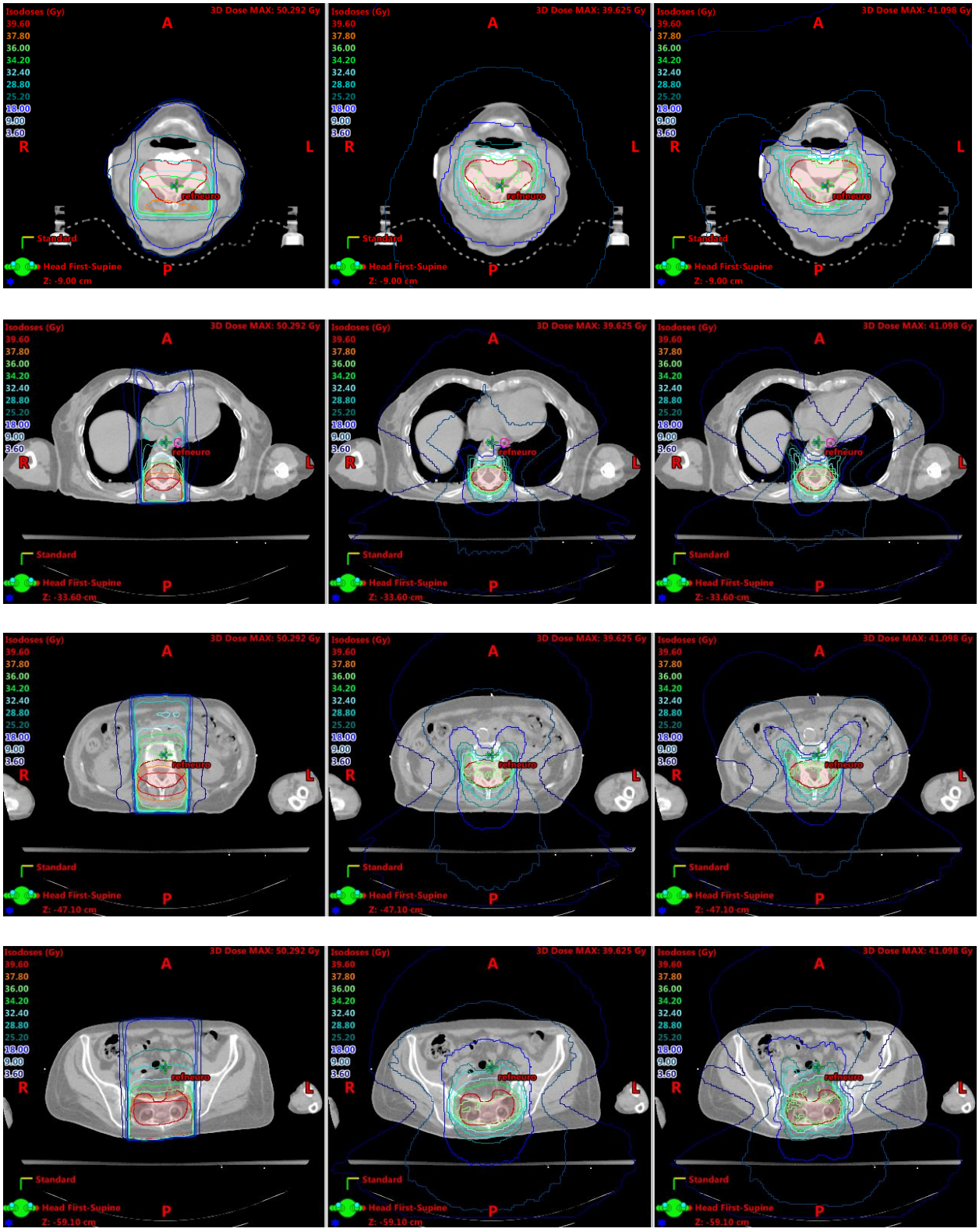



*Figure 16 An example of dose distribution for a single patient for the 3D-CRT, Original HT (Tomo) and Optimized HT (BMTomo), from left to right.*

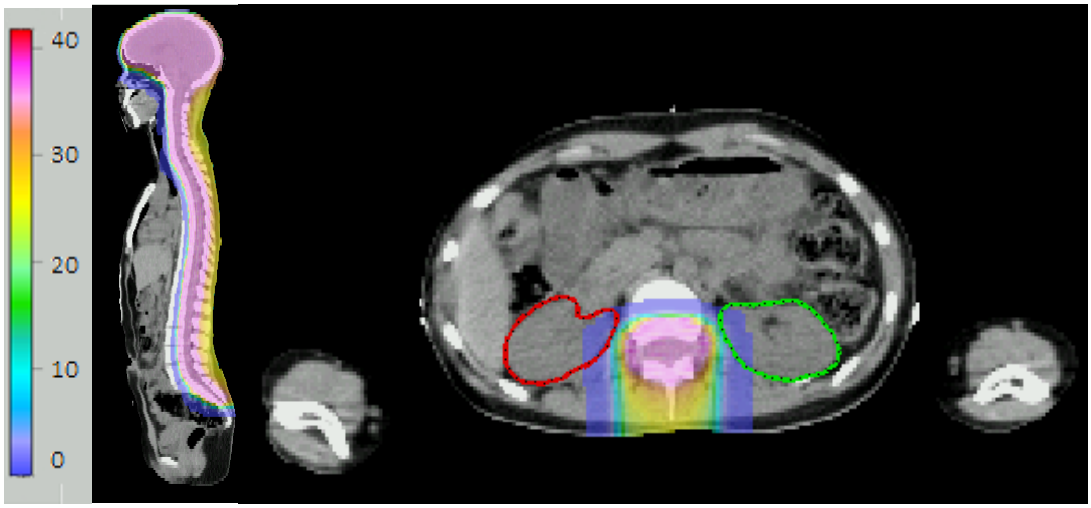



*Figure 17 An example of dose distribution (inGy) for a single patient for the p-CSI (sagittal and axial plane)*

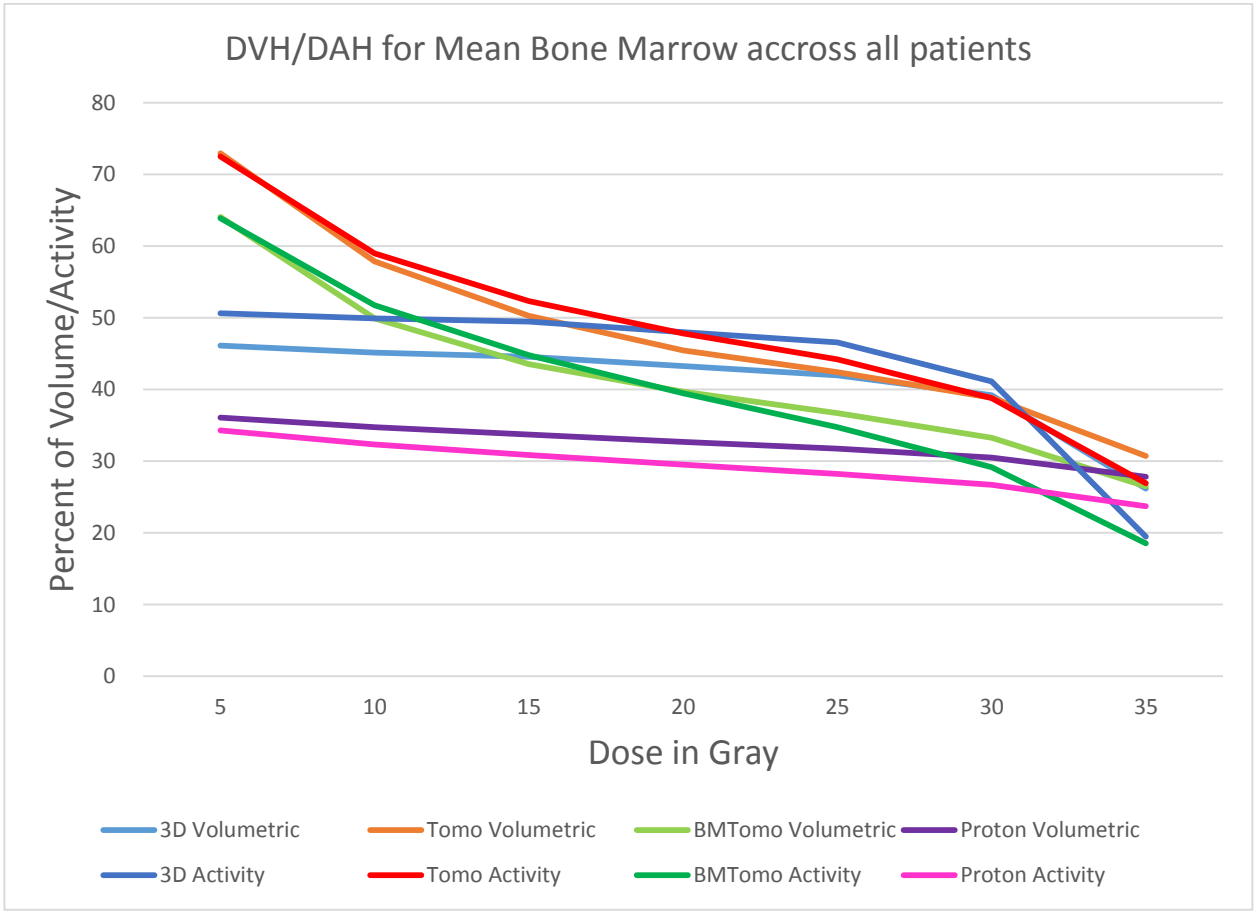



*Figure 18 An average DVH and DAH for proliferating bone marrow.*

*All values are the mean of nine patients*

| Bone marrow compartments | | 3DCRT | Tomo | BMTomo | p-CSI |
|---|---|---|---|---|---|
| **Skull** | Min Dose [Gy] | 3.2 | 6.5 | 3.2 | 0.0 |
| | Max Dose [Gy] | 39.9 | 40.9 | 40.3 | 38.7 |
| | Mean Dose [Gy] | 31.5 | 33.0 | 32.5 | 29.6 |
| | Median Dose [Gy] | 36.0 | 35.8 | 35.9 | 35.9 |
| | $V_5$ [%] | 87.9 | 99.9 | 97.9 | 84.3 |
| | $V_{10}$ [%] | 87.0 | 97.2 | 93.8 | 83.7 |
| | $V_{15}$ [%] | 86.6 | 93.3 | 90.4 | 83.1 |
| | $V_{20}$ [%] | 86.2 | 89.5 | 88.2 | 82.2 |
| | $V_{25}$ [%] | 85.8 | 87.2 | 86.4 | 81.4 |
| | $V_{30}$ [%] | 84.8 | 85.0 | 84.3 | 80.0 |
| | $V_{35}$ [%] | 70.7 | 76.1 | 78.4 | 75.0 |
| **Cervical Vertebrae** | Min Dose [Gy] | 20.4 | 26.6 | 14.9 | 0.6 |
| | Max Dose [Gy] | 38.7 | 37.1 | 38.3 | 38.2 |
| | Mean Dose [Gy] | 34.7 | 35.7 | 34.4 | 31.9 |
| | Median Dose [Gy] | 35.6 | 36.0 | 35.3 | 35.8 |
| | $V_5$ [%] | 100.0 | 100.0 | 100.0 | 95.7 |
| | $V_{10}$ [%] | 100.0 | 100.0 | 100.0 | 93.0 |
| | $V_{15}$ [%] | 99.9 | 100.0 | 99.8 | 90.5 |
| | $V_{20}$ [%] | 99.6 | 100.0 | 99.1 | 88.0 |
| | $V_{25}$ [%] | 97.6 | 99.8 | 97.0 | 85.1 |
| | $V_{30}$ [%] | 84.7 | 98.7 | 92.1 | 81.5 |
| | $V_{35}$ [%] | 68.3 | 89.9 | 63.3 | 74.4 |
| **Thoracic Vertebrae** | Min Dose [Gy] | 27.3 | 18.7 | 5.7 | 4.7 |
| | Max Dose [Gy] | 39.8 | 37.5 | 38.3 | 35.1 |
| | Mean Dose [Gy] | 33.7 | 33.3 | 28.0 | 21.6 |
| | Median Dose [Gy] | 33.7 | 34.9 | 31.4 | 28.4 |
| | $V_5$ [%] | 100.0 | 100.0 | 100.0 | 68.3 |
| | $V_{10}$ [%] | 100.0 | 100.0 | 95.6 | 64.1 |
| | $V_{15}$ [%] | 100.0 | 99.9 | 87.0 | 61.1 |
| | $V_{20}$ [%] | 100.0 | 97.8 | 78.2 | 58.4 |
| | $V_{25}$ [%] | 100.0 | 94.4 | 68.8 | 55.7 |
| | $V_{30}$ [%] | 91.8 | 83.5 | 55.6 | 52.5 |

| | | | | | |
|---|---|---|---|---|---|
| | $V_{35}$ [%] | 28.4 | 53.0 | 30.7 | 45.4 |
| **Lumbal Vertebrae** | Min Dose [Gy] | 24.7 | 20.8 | 9.5 | 0.0 |
| | Max Dose [Gy] | 42.2 | 37.1 | 38.2 | 38.5 |
| | Mean Dose [Gy] | 33.1 | 31.8 | 26.7 | 16.9 |
| | Median Dose [Gy] | 32.6 | 33.2 | 28.4 | 12.6 |
| | $V_5$ [%] | 100.0 | 100.0 | 100.0 | 54.0 |
| | $V_{10}$ [%] | 100.0 | 100.0 | 98.2 | 50.2 |
| | $V_{15}$ [%] | 100.0 | 99.9 | 87.1 | 47.7 |
| | $V_{20}$ [%] | 100.0 | 95.7 | 73.1 | 45.3 |
| | $V_{25}$ [%] | 99.0 | 87.0 | 59.9 | 43.0 |
| | $V_{30}$ [%] | 79.2 | 71.4 | 45.4 | 40.2 |
| | $V_{35}$ [%] | 27.9 | 43.7 | 22.5 | 36.3 |
| **Sacral bone** | Min Dose [Gy] | 0.2 | 1.8 | 1.1 | 0.0 |
| | Max Dose [Gy] | 48.1 | 36.9 | 37.7 | 38.9 |
| | Mean Dose [Gy] | 26.2 | 29.3 | 25.2 | 19.2 |
| | Median Dose [Gy] | 31.0 | 33.2 | 29.4 | 21.2 |
| | $V_5$ [%] | 74.9 | 95.6 | 93.3 | 62.0 |
| | $V_{10}$ [%] | 71.4 | 85.4 | 83.1 | 58.3 |
| | $V_{15}$ [%] | 69.2 | 79.0 | 74.8 | 54.6 |
| | $V_{20}$ [%] | 67.3 | 72.3 | 67.6 | 51.1 |
| | $V_{25}$ [%] | 65.2 | 64.9 | 59.5 | 48.5 |
| | $V_{30}$ [%] | 60.3 | 56.7 | 51.0 | 44.9 |
| | $V_{35}$ [%] | 43.4 | 40.4 | 33.6 | 38.7 |
| **Remaining Pelvis** | Min Dose [Gy] | 0.0 | 0.4 | 0.3 | 0.0 |
| | Max Dose [Gy] | 39.3 | 34.6 | 31.1 | 25.7 |
| | Mean Dose [Gy] | 2.4 | 7.0 | 3.6 | 0.2 |
| | Median Dose [Gy] | 0.5 | 5.7 | 2.1 | 0.0 |
| | $V_5$ [%] | 1.8 | 52.4 | 23.4 | 1.1 |
| | $V_{10}$ [%] | 1.2 | 28.2 | 7.2 | 0.7 |
| | $V_{15}$ [%] | 0.9 | 12.5 | 2.8 | 0.5 |
| | $V_{20}$ [%] | 0.7 | 4.8 | 1.1 | 0.3 |
| | $V_{25}$ [%] | 0.6 | 1.8 | 0.3 | 0.2 |
| | $V_{30}$ [%] | 0.5 | 0.7 | 0.1 | 0.1 |
| | $V_{35}$ [%] | 0.3 | 0.1 | 0.0 | 0.0 |

| | | | | | |
|---|---|---|---|---|---|
| **Ribs, Scapulae and Clavicles** | Min Dose [Gy] | 0.1 | 1.6 | 1.3 | 0.0 |
| | Max Dose [Gy] | 43.0 | 37.6 | 37.8 | 38.3 |
| | Mean Dose [Gy] | 2.8 | 7.1 | 7.4 | 1.3 |
| | Median Dose [Gy] | 0.7 | 4.9 | 5.8 | 0.0 |
| | $V_5$ [%] | 8.3 | 56.3 | 57.2 | 5.3 |
| | $V_{10}$ [%] | 6.8 | 18.9 | 20.0 | 4.3 |
| | $V_{15}$ [%] | 6.0 | 9.4 | 8.1 | 3.7 |
| | $V_{20}$ [%] | 5.4 | 5.3 | 4.4 | 3.2 |
| | $V_{25}$ [%] | 3.6 | 3.7 | 3.5 | 2.7 |
| | $V_{30}$ [%] | 2.9 | 2.8 | 2.8 | 2.3 |
| | $V_{35}$ [%] | 2.0 | 1.8 | 1.7 | 1.6 |
| **Sternum** | Min Dose [Gy] | 11.6 | 6.5 | 1.6 | 0.0 |
| | Max Dose [Gy] | 25.0 | 19.2 | 10.0 | 0.0 |
| | Mean Dose [Gy] | 19.1 | 11.8 | 3.1 | 0.0 |
| | Median Dose [Gy] | 18.7 | 11.6 | 2.6 | 0.0 |
| | $V_5$ [%] | 100.0 | 97.5 | 11.3 | 0.0 |
| | $V_{10}$ [%] | 99.9 | 61.9 | 0.4 | 0.0 |
| | $V_{15}$ [%] | 95.7 | 24.2 | 0.0 | 0.0 |
| | $V_{20}$ [%] | 38.1 | 4.2 | 0.0 | 0.0 |
| | $V_{25}$ [%] | 2.3 | 0.0 | 0.0 | 0.0 |
| | $V_{30}$ [%] | 0.0 | 0.0 | 0.0 | 0.0 |
| | $V_{35}$ [%] | 0.0 | 0.0 | 0.0 | 0.0 |
| **Proximal Humeri** | Min Dose [Gy] | 0.0 | 1.1 | 1.2 | 0.0 |
| | Max Dose [Gy] | 0.8 | 4.5 | 5.0 | 0.0 |
| | Mean Dose [Gy] | 0.2 | 2.6 | 2.5 | 0.0 |
| | Median Dose [Gy] | 0.2 | 2.7 | 2.4 | 0.0 |
| | $V_5$ [%] | 0.0 | 5.2 | 0.9 | 0.0 |
| | $V_{10}$ [%] | 0.0 | 0.0 | 0.0 | 0.0 |
| | $V_{15}$ [%] | 0.0 | 0.0 | 0.0 | 0.0 |
| | $V_{20}$ [%] | 0.0 | 0.0 | 0.0 | 0.0 |
| | $V_{25}$ [%] | 0.0 | 0.0 | 0.0 | 0.0 |
| | $V_{30}$ [%] | 0.0 | 0.0 | 0.0 | 0.0 |
| | $V_{35}$ [%] | 0.0 | 0.0 | 0.0 | 0.0 |
| | Min Dose [Gy] | 0.1 | 0.5 | 0.4 | 0.0 |

| | | | | | |
|---|---|---|---|---|---|
| **Proximal Femuri** | Max Dose [Gy] | 0.4 | 1.8 | 0.9 | 0.0 |
| | Mean Dose [Gy] | 0.2 | 0.8 | 0.6 | 0.0 |
| | Median Dose [Gy] | 0.2 | 0.7 | 0.6 | 0.0 |
| | $V_5$ [%] | 0.0 | 0.0 | 0.0 | 0.0 |
| | $V_{10}$ [%] | 0.0 | 0.0 | 0.0 | 0.0 |
| | $V_{15}$ [%] | 0.0 | 0.0 | 0.0 | 0.0 |
| | $V_{20}$ [%] | 0.0 | 0.0 | 0.0 | 0.0 |
| | $V_{25}$ [%] | 0.0 | 0.0 | 0.0 | 0.0 |
| | $V_{30}$ [%] | 0.0 | 0.0 | 0.0 | 0.0 |
| | $V_{35}$ [%] | 0.0 | 0.0 | 0.0 | 0.0 |
| **Entire Bone Marrow** | Min Dose [Gy] | 0.0 | 0.4 | 0.3 | 0.0 |
| | Max Dose [Gy] | 48.1 | 40.9 | 40.3 | 40.0 |
| | Mean Dose [Gy] | 16.0 | 18.8 | 16.7 | 12.0 |
| | Median Dose [Gy] | 4.5 | 16.0 | 10.4 | 0.0 |
| | $V_5$ [%] | 46.1 | 73.0 | 64.1 | 36.1 |
| | $V_{10}$ [%] | 45.1 | 57.9 | 49.9 | 34.8 |
| | $V_{15}$ [%] | 44.6 | 50.3 | 43.6 | 33.7 |
| | $V_{20}$ [%] | 43.3 | 45.5 | 39.7 | 32.7 |
| | $V_{25}$ [%] | 42.0 | 42.4 | 36.7 | 31.7 |
| | $V_{30}$ [%] | 39.2 | 38.9 | 33.3 | 30.5 |
| | $V_{35}$ [%] | 26.2 | 30.7 | 26.5 | 27.8 |

*Table 11 Dosimetric parameters of proliferating bone marrow compartments. All values are the mean of nine patients.*

| Dose [Gy] | 3DCRT [%] | | Tomo [%] | | BMTomo [%] | | p-CSI [%] | |
|---|---|---|---|---|---|---|---|---|
| **X** | Vx | WBMEx | Vx | WBMEx | Vx | WBMEx | Vx | WBMEx |
| **5** | 46.1 | 50.7 | 73.0 | 72.5 | 64.1 | 63.9 | 36.1 | 34.3 |
| **10** | 45.1 | 49.9 | 57.9 | 59.0 | 49.9 | 51.7 | 34.8 | 32.3 |
| **15** | 44.6 | 49.5 | 50.3 | 52.3 | 43.6 | 44.8 | 33.7 | 30.9 |
| **20** | 43.3 | 48.0 | 45.5 | 47.8 | 39.7 | 39.5 | 32.7 | 29.5 |
| **25** | 42.0 | 46.6 | 42.4 | 44.2 | 36.7 | 34.8 | 31.7 | 28.2 |
| **30** | 39.2 | 41.1 | 38.9 | 38.8 | 33.3 | 29.2 | 30.5 | 26.7 |
| **35** | 26.2 | 19.5 | 30.7 | 27.0 | 26.5 | 18.5 | 27.8 | 23.7 |

*Table 12 Volumes (Vx) or Activity (WBMEx) exposed to certain dose for the entire bone marrow.*

*All values are the mean of nine patients.*

## 4.4 Dosimetric part – other OARs

| OAR | | 3DCRT | Tomo | BMTomo | p-CSI |
|---|---|---|---|---|---|
| **Autochtone dorsal muscles** | Min Dose [Gy] | 0.7 | 6.1 | 5.5 | 0.0 |
| | Max Dose [Gy] | 49.9 | 37.7 | 37.6 | 37.9 |
| | Mean Dose [Gy] | 26.2 | 25.0 | 24.2 | 16.8 |
| | Median Dose [Gy] | 32.1 | 25.1 | 24.5 | 20.2 |
| **Body** | Min Dose [Gy] | 0.0 | 0.1 | 0.1 | 4.7 |
| | Max Dose [Gy] | 51.3 | 40.9 | 40.4 | 36.3 |
| | Mean Dose [Gy] | 8.0 | 10.5 | 9.8 | 3.9 |
| | Median Dose [Gy] | 1.1 | 6.9 | 6.2 | 0.0 |
| **Body outside of the PTV** | Min Dose [Gy] | 0.0 | 0.1 | 0.1 | 0.0 |
| | Max Dose [Gy] | 51.3 | 40.9 | 40.3 | 39.0 |
| | Mean Dose [Gy] | 5.9 | 8.5 | 7.7 | 1.4 |
| | Median Dose [Gy] | 0.9 | 6.3 | 5.5 | 0.0 |
| **Bowel** | Min Dose [Gy] | 0.2 | 0.8 | 0.6 | 0.0 |
| | Max Dose [Gy] | 41.2 | 33.5 | 29.7 | 17.0 |
| | Mean Dose [Gy] | 7.8 | 10.7 | 9.1 | 0.1 |

| | | | | | |
|---|---|---|---|---|---|
| | Median Dose [Gy] | 2.5 | 10.2 | 8.8 | 0.0 |
| **Bulbus Left** | Min Dose [Gy] | 4.4 | 4.6 | 4.1 | 0.0 |
| | Max Dose [Gy] | 4139.2 | 33.7 | 33.4 | 35.0 |
| | Mean Dose [Gy] | 25.9 | 16.0 | 14.8 | 9.8 |
| | Median Dose [Gy] | 28.4 | 14.9 | 13.3 | 4.9 |
| **Bulbus Right** | Min Dose [Gy] | 5.2 | 533.5 | 4.0 | 1.1 |
| | Max Dose [Gy] | 36.8 | 34.2 | 34.6 | 34.8 |
| | Mean Dose [Gy] | 26.2 | 15.9 | 15.1 | 10.0 |
| | Median Dose [Gy] | 28.5 | 15.1 | 14.0 | 5.3 |
| **Cochlea Left** | Min Dose [Gy] | 36.1 | 35.2 | 35.4 | 35.7 |
| | Max Dose [Gy] | 37.3 | 36.7 | 37.2 | 36.3 |
| | Mean Dose [Gy] | 36.7 | 36.0 | 36.4 | 36.0 |
| | Median Dose [Gy] | 36.7 | 36.0 | 36.4 | 36.0 |
| **Cochlea Right** | Min Dose [Gy] | 36.2 | 35.4 | 34.9 | 33.9 |
| | Max Dose [Gy] | 37.3 | 36.8 | 37.3 | 36.3 |
| | Mean Dose [Gy] | 36.7 | 36.0 | 36.2 | 35.8 |
| | Median Dose [Gy] | 36.7 | 36.0 | 36.3 | 36.0 |
| **Esophaghus** | Min Dose [Gy] | 8.1 | 9.5 | 3.6 | 0.0 |
| | Max Dose [Gy] | 32.7 | 34.8 | 28.8 | 7.4 |
| | Mean Dose [Gy] | 28.7 | 23.5 | 8.6 | 0.1 |
| | Median Dose [Gy] | 28.9 | 23.1 | 6.9 | 0.0 |
| **Heart** | Min Dose [Gy] | 1.2 | 5.1 | 1.9 | 0.0 |
| | Max Dose [Gy] | 30.7 | 23.5 | 22.6 | 0.0 |
| | Mean Dose [Gy] | 15.1 | 11.5 | 5.8 | 0.0 |
| | Median Dose [Gy] | 16.1 | 11.1 | 5.0 | 0.0 |
| | $V_{25}$ [%] | 17.8 | 0.5 | 0.1 | 0.0 |
| **Kidney left** | Min Dose [Gy] | 0.9 | 3.6 | 3.5 | 0.0 |
| | Max Dose [Gy] | 29.8 | 30.4 | 33.1 | 19.8 |
| | Mean Dose [Gy] | 3.6 | 9.5 | 9.9 | 0.4 |
| | Median Dose [Gy] | 2.2 | 8.2 | 7.8 | 0.0 |
| **Kidney right** | Min Dose [Gy] | 0.8 | 4.0 | 3.5 | 0.0 |
| | Max Dose [Gy] | 29.0 | 29.7 | 33.4 | 15.4 |
| | Mean Dose [Gy] | 3.0 | 9.2 | 9.6 | 0.3 |
| | Median Dose [Gy] | 2.0 | 8.2 | 7.8 | 0.0 |

| | | | | | |
|---|---|---|---|---|---|
| **Larynx** | Min Dose [Gy] | 9.9 | 11.4 | 3.8 | 0.0 |
| | Max Dose [Gy] | 27.7 | 30.4 | 25.7 | 2.7 |
| | Mean Dose [Gy] | 19.7 | 18.8 | 7.6 | 0.0 |
| | Median Dose [Gy] | 19.8 | 18.3 | 6.5 | 0.0 |
| **Lens left** | Min Dose [Gy] | 8.9 | 4.7 | 4.1 | 0.2 |
| | Max Dose [Gy] | 23.7 | 8.9 | 7.8 | 3.4 |
| | Mean Dose [Gy] | 15.6 | 5.8 | 5.0 | 1.1 |
| | Median Dose [Gy] | 15.4 | 5.7 | 4.9 | 0.8 |
| **Lens right** | Min Dose [Gy] | 9.0 | 4.6 | 4.0 | 0.1 |
| | Max Dose [Gy] | 22.9 | 7.5 | 6.8 | 3.2 |
| | Mean Dose [Gy] | 14.4 | 5.3 | 4.6 | 1.0 |
| | Median Dose [Gy] | 14.0 | 5.2 | 4.5 | 0.7 |
| **Liver** | Min Dose [Gy] | 0.4 | 2.7 | 1.8 | 0.0 |
| | Max Dose [Gy] | 34.3 | 33.4 | 34.9 | 21.4 |
| | Mean Dose [Gy] | 5.9 | 8.9 | 8.5 | 0.1 |
| | Median Dose [Gy] | 1.7 | 8.2 | 7.7 | 0.0 |
| **Lungs** | Min Dose [Gy] | 0.5 | 2.4 | 1.9 | 0.0 |
| | Max Dose [Gy] | 36.5 | 37.1 | 37.6 | 38.1 |
| | Mean Dose [Gy] | 5.0 | 9.1 | 11.4 | 0.6 |
| | Median Dose [Gy] | 2.0 | 7.4 | 9.7 | 0.0 |
| | $V_5$ [%] | 18.5 | 77.4 | 85.2 | 2.7 |
| | $V_{20}$ [%] | 9.4 | 8.8 | 12.0 | 0.9 |
| **Oral cavity** | Min Dose [Gy] | 3.5 | 9.2 | 4.3 | 0.0 |
| | Max Dose [Gy] | 15.2 | 27.7 | 21.4 | 0.3 |
| | Mean Dose [Gy] | 5.7 | 16.1 | 8.6 | 0.0 |
| | Median Dose [Gy] | 5.5 | 15.6 | 8.0 | 0.0 |
| **Pancreas** | Min Dose [Gy] | 1.6 | 8.2 | 4.4 | 0.0 |
| | Max Dose [Gy] | 27.9 | 20.7 | 25.0 | 0.0 |
| | Mean Dose [Gy] | 16.1 | 14.1 | 11.4 | 0.0 |
| | Median Dose [Gy] | 20.6 | 14.1 | 10.5 | 0.0 |
| **Parotid gland left** | Min Dose [Gy] | 8.6 | 12.9 | 6.6 | 0.0 |
| | Max Dose [Gy] | 37.6 | 34.2 | 27.9 | 16.4 |
| | Mean Dose [Gy] | 28.9 | 23.2 | 12.4 | 0.5 |
| | Median Dose [Gy] | 30.8 | 23.3 | 11.4 | 0.0 |

| | | | | | |
|---|---|---|---|---|---|
| **Parotid gland right** | Min Dose [Gy] | 7.9 | 13.3 | 8.1 | 0.0 |
| | Max Dose [Gy] | 37.5 | 35.0 | 30.3 | 16.8 |
| | Mean Dose [Gy] | 30.3 | 23.8 | 14.8 | 0.6 |
| | Median Dose [Gy] | 33.4 | 23.9 | 13.7 | 0.0 |
| **Pharynx** | Min Dose [Gy] | 3.7 | 13.2 | 5.0 | 0.0 |
| | Max Dose [Gy] | 36.4 | 36.2 | 35.4 | 32.5 |
| | Mean Dose [Gy] | 15.9 | 25.9 | 16.3 | 2.4 |
| | Median Dose [Gy] | 12.6 | 25.9 | 15.0 | 0.1 |
| **Spleen** | Min Dose [Gy] | 0.5 | 2.5 | 2.2 | NA* |
| | Max Dose [Gy] | 10.8 | 19.2 | 22.1 | NA* |
| | Mean Dose [Gy] | 1.1 | 6.0 | 6.2 | NA* |
| | Median Dose [Gy] | 0.8 | 5.4 | 5.6 | NA* |
| **Submandi-bular gland right** | Min Dose [Gy] | 3.6 | 12.8 | 5.0 | 0.0 |
| | Max Dose [Gy] | 19.5 | 22.1 | 21.8 | 0.5 |
| | Mean Dose [Gy] | 6.9 | 16.9 | 10.5 | 0.0 |
| | Median Dose [Gy] | 5.9 | 16.8 | 9.9 | 0.0 |
| **Submandi-bular gland left** | Min Dose [Gy] | 5.0 | 12.6 | 5.6 | 0.0 |
| | Max Dose [Gy] | 20.0 | 22.2 | 19.4 | 0.1 |
| | Mean Dose [Gy] | 9.2 | 16.7 | 10.6 | 0.0 |
| | Median Dose [Gy] | 7.7 | 16.4 | 10.0 | 0.0 |
| **Thyroid** | Min Dose [Gy] | 14.6 | 14.0 | 5.5 | 0.0 |
| | Max Dose [Gy] | 27.7 | 30.5 | 28.1 | 0.3 |
| | Mean Dose [Gy] | 24.6 | 21.5 | 12.5 | 0.0 |
| | Median Dose [Gy] | 24.9 | 21.4 | 11.7 | 0.0 |
| | $V_{26}$ [%] | 21.9 | 15.7 | 1.0 | 0.0 |

*Table 13 Dosimetric parameters to OARs.*

*All values are the mean of nine patients. *Spleen was not available for evaluation in p-CSI plans, however estimated spleen median and minimum dose for p-CSI plan is zero.*

For the non-hematologic OARs, the results are summarized in Table 13. The aim of the optimized tomotherapy (BMTomo) was to minimize acute toxicity. This is mostly mediated by the OARs in the upper digestive tract such as oral cavity, pharynx, esophagus and salivary glands. Protons result in best sparing of these OARs as they don't deliver virtually any dose to structures lying anterior to vertebrae or skull. For oral cavity, the second-best technique is the standard 3DCRT. Using opposed lateral fields, the oral cavity is effectively

blocked and receives on average 5.7Gy as compared to 8.6Gy and 16.1Gy for BMTomo and original tomotherapy (Tomo) respectively. For pharynx on average 3DCRT and BMTomo didn't differ much (15.9Gy and 16.3Gy). On contrary, the Tomo's Dmean was 25.9Gy. 3DCRT and Tomo resulted in much higher dose to Esophagus (Dmean 28.7Gy and 23.5Gy), Larynx (19.7Gy and 18.8Gy) and parotid glands (Dmean 28.9Gy and 30.3Gy vs. 23.2Gy and 23.8Gy for left and right parotid gland respectively) as compared to BMTomo (Dmean 8.6Gy for Esophagus, 7.6Gy for Larynx and 12.4Gy and 13.7Gy for left and right parotid gland). Submandibular glands are spared well with 3DCRT receiving on average 9.2Gy (left) and 6.9Gy (right). BMTomo fares slightly worse with 10.6Gy (left) and 10.5 (right). Tomo's Dmean for the left and right submandibular gland was 16.7Gy and 16.9Gy respectively. As for other major important OARs, the Heart was spared better with BMTomo (Dmean 5.8Gy) as compared to 11.5Gy for Tomo and 15.1Gy for 3DCRT. Kidneys and Lungs are better spared with the 3DCRT (Dmean 3.0 and 3.6 for left and right kidney and 5.0Gy for the lungs) than each of the HT techniques which don't differ much from each other (Dmean 9.5Gy and 9.2Gy for the Original vs. 9.9Gy and 9.6Gy for the BMTomo for left and right kidney and 9.1Gy and 11.4Gy for the Lungs). For liver, the 3DCRT had the best results (Dmean 5.9 vs. 8.9Gy for Tomo and 8.5Gy for BMTomo). For bowel, the mean dose is lower for the 3DCRT as compared to the two HT scenarios (Dmean 7.8Gy, 10.7Gy and 9.1Gy for 3DCRT, Original and BMTomo respectively), however, the maximal dose is decreased (Dmax 41.2Gy, 33.5Gy, 29.7Gy). BMTomo resulted also to much lower dose to the thyroid gland (Dmean 12.5Gy) as compared to 24.6Gy for 3DCRT and 21.5Gy for the Tomo. Lenses were also better spared with the BMTomo as compared to the other photon techniques. For cochleae as they are inevitably part of the PTV there were no major differences between the different photon techniques and protons.

To evaluate the integral dose, the "Body" and "Body outside of the PTV" Dmean were used as surrogates. Herein the 3DCRT, Tomo, and BMTomo resulted in 108.9%, 172.3% and 153.6% dose more than the proton-CSI. However, these numbers were even higher when only the tissue outside of PTV i.e. "Body outside of the PTV" was taken into account: 309.7%, 493.8%, and 439.2%.

## 4.5 PTV Evaluation

Mean PTV volume was 3283cm$^3$ (range 2923cm$^3$ – 3600cm$^3$). The average $D_{MIN}$, $D_{MAX}$, $D_2$, $D_{98}$, $D_{MEAN}$ and $D_{MEDIAN}$ are summarized in Table 14.

| | 3DCRT | TOMO | BMTOMO | P-CSI |
|---|---|---|---|---|
| $D_{MIN}$ | 10.3 | 14.7 | 15.8 | 15.4 |
| $D_{98}$ | 30.5 | 34.5 | 33.1 | 34.2 |
| $D_{MAX}$ | 48.2 | 40.6 | 40.4 | 40.5 |
| $D_{2}$ | 43.1 | 37.2 | 37.3 | 37.0 |
| $D_{MEAN}$ | 36.5 | 36.0 | 35.9 | 35.9 |
| $D_{MEDIAN}$ | 36.4 | 36.1 | 36.0 | 36.0 |

*Table 14 Dosimetric parameters of PTV.*
*All values are the mean of nine patients (in Gy)*

The average homogeneity indices were 0.31, 0.07, 0.12 and 0.08 for 3DCRT, original tomotherapy (Tomo), optimized tomotherapy (BMTomo) and p-CSI respectively. Similarly, the average CI was 0.89, 0.98, 0.96 and 0.98. The conformation number (CN) ranged from 0.55 for 3DCRT to 0.78 for both Original and BMTomo and 0.96 for the protons. Taken into account all of these dosimetric parameters and indices the Tomo performed best in homogenous and BMTomo in conformal coverage of the PTV. However, as soon as healthy tissues are taken into account, they were outperformed by the protons as shown by the CN. 3DCRT was, as expected, the most inferior in respect to homogeneity and conformity of the PTV coverage.

# 5 Discussion

## 5.1 Dosimetry and toxicity

To my knowledge, dosimetric evaluation of the proliferating bone marrow based on its quantitative assessment as described by Campbell (Campbell 2015), in CSI, is first evaluated in this thesis. A novel parameter “weighted bone marrow exposure (WBME)” and a dose activity histogram (DAH) are introduced. WBME/DAH are proposed to be used instead of classical DVH as it accounts more for the function of the particular bone marrow compartment than the traditional volumetric based information of a DVH.

Average proliferating bone marrow $D_{MEAN}$ for patients included in our dosimetric study was 12.0, 18.8, 16.7, and 16.0Gy for p-CSI, Tomo, and BMTomo respectively. The average mean value of weighted bone marrow exposure ($WBME_{DMEAN}$) were 10.9, 19.2, 16.2 and 17.3Gy. HT, when not optimized (i.e. Tomo) delivered a higher dose to the proliferating bone marrow than the standard 2D/3D field setup. This is true when considering only the volumetric information as well as when considering the different activity of the particular bone marrow compartments i.e. $WBME_{DMEAN}$. However, the difference between the two techniques was slightly lower when considering the $WBME_{DMEAN}$. The optimized tomotherapy (BMTomo) plans used X-form like beams in order to spare the critical structures lying anterior to the vertebra and also to try to spare its most anterior parts. This resulted on average in a slightly higher mean dose to the bone marrow if traditional DVH is considered. Yet, when $WBME_{DMEAN}$ is taken into account the BMTomo resulted in lower average exposure to the proliferating bone marrow.

This is due to the higher dose that is deposed in the vertebrae by the standard 2D/3DCRT treatment technique. A large amount of proliferating bone marrow resides in thoracic and lumbar vertebrae (on average 17.7% and 14.8% respectively). On the other hand, ribs, scapulae, and clavicles compose 16.6%, but they are mostly affected only by the exit dose which is much lower when using HT. Lastly, protons proved their superiority of sparing proliferating bone marrow, where $WBME_{DMEAN}$ resulted in further dose reduction as compared to standard volumetric based model (i.e. DVH). As already stated above this being due to lower dose to anterior vertebrae.

Our dosimetric results indicate that p-CSI confers the highest benefit in respect to bone marrow sparing when compared with traditional as well as advanced photon techniques for adult CSI treatment. That this translates into clinical benefit was shown by the study of Barney et al (Barney 2014). He reviewed a collective of 50 patients treated with vertebral

body-sparing p-CSI at a single institution. Further, “the median percent WBC, hemoglobin and thrombocytes nadir were 52% (range, 13%–100%), 97% (65%–112%), and 61% (10%–270%) of the baseline counts, respectively”. Only 8% out of 80% of the patients who received chemotherapy as part of their treatment developed grade ≥3 cytopenias. Our patients’ median nadirs were below the reported results with 42% (range 4%–89%), 90% (range 75%–100%), 39% (range 20%–61%) and 30% (range 5%–118%), 87% (range 59%–113%), 27% (range 2%–73%) for the median percent WBC, hemoglobin and thrombocyte nadir for 2D and HT, respectively. Also, grade 3 or higher cytopenias were more common within our patient collective. This is in accordance with the dosimetric results presented in this work. As the mean dose to the proliferating bone marrow and $WBME_{DMEAN}$ is 12Gy and 10.9Gy in p-CSI compared to 16Gy and 17.3Gy in 3DCRT, 18.8Gy and 19.2Gy in original tomotherapy (Tomo), 16.7Gy and 16.2Gy in optimized tomotherapy (BMTomo). In the study by Barney et al., CSI dose was not associated with the hematological toxicity. This is understandable as only a small part of the proliferating bone marrow is irradiated in p-CSI. As we showed when the prescription dose is 36Gy-RBE the mean dose to the proliferating bone marrow is on average 12Gy which is already low so even a ca. 30% prescription dose decrease, meaning an average $D_{MEAN}$ of ca. 8Gy to the proliferating bone marrow doesn’t have to have a clinical impact. Moreover, when adjusted for the activity, this difference is even less.

Brown et al. compared clinical outcomes in adult medulloblastoma patients treated either with protons (n=19) or photons (n=21)(Brown 2013). In this study, standard field setup was used (opposed, slightly angled lateral beams for the cranium and attached dorsal beams to cover the spine) for both techniques. Patients receiving treatment with photons were treated in the prone position as compared to patients receiving treatment with protons who were placed supine. As for pretreatment characteristics, slightly more patients received chemotherapy before RT in the 3D-CRT group (n=7 vs. 4 in the p-CSI group). The authors of the study also contoured vertebrae to assess the dose-volume data and compare them with the clinical data. They found out that increasing mean vertebral dose was significantly associated with a nadir in WBC and thrombocytes and for the hemoglobin levels one month after completion of CSI. Thus, patients treated with photons in this study experienced a more prominent decrease in all blood cell lines: ”Median percent baseline WBC 46% versus 55%, p=0.04; hemoglobin 88% versus 97%, p=0.009; platelets 48% versus 65%, p=0.05 for photon and proton CSI respectively.” In our cohort, only the thrombocytes ratio (nadir/baseline) distribution and not the thrombocytes median according to treatment technique was statistically significant. Even though it was not statistically significant when

taken together with the dosimetric information generated by this study (higher exposure to the proliferating bone marrow with Tomo than 3DCRT) it is at least hypothesis-generating that if the bone marrow isn't taken into account, HT, but also other IMRT-techniques may cause more hematologic toxicity. However, more homogeneous and larger patient cohort with prospective data collection would be needed to answer this question.

In fact, the study by Petersson et al. points also to this direction. He compared patients treated with 3DCRT and HT CSI. Altogether 20 patients were evaluated, eight receiving CSI with HT and twelve with 3DCRT. They found a "significant correlation between the volume of red bone marrow exposed to low dose and severity of thrombopenia during treatment. For patients treated with HT they also found a significant correlation between the relative volume of the body exposed to low dose and the severity of anemia and leukopenia (Petersson 2014)." This was different to our study results were the treatment technique had no impact on hemoglobin and WBC. In our study, only chemotherapy within three months of the onset of CSI proved to have a significant impact on severe leukopenia or thrombopenia. Marks et al. evaluated 37 patients of whom 17 did and 20 did not receive chemotherapy prior to CSI. They found that the chemotherapy group had a statistically significant decline in their WBC, thrombocytes, and hematocrit when compared to a patient who did not get any chemotherapy. Also, patients who received chemotherapy were more likely to have treatment breaks (Marks 1995). Jefferies et al. also studied hematological toxicities in 66 patients receiving CSI. In their patients' collective, "age and prior chemotherapy were independent predictive factors for hematological toxicity" (Jefferies 1998). Chang evaluated acute toxicity in children and also found that chemotherapy before CSI leads to increased acute hematologic toxicity (Chang 2002) .

In the study by Brown, the patients had a longer follow-up, and the differences in WBC and thrombocytes weren't statistically significant anymore one month after the end of the therapy. In a subgroup analysis, which excluded patients who received chemotherapy before RT the results were similar. There was one discontinuation in the treatment due to severe thrombocytopenia and two treatment breaks due to nausea/vomiting and fatigue in patients treated with photon CSI.

In our study, five (12%) patients had treatment breaks and 11 (26%) patients discontinued the treatment. However, our study included 19 patients treated in palliative setting and also some of the patients in the curative were extensively pretreated explaining the increased drop-out rate.

Even though in our dosimetric study, we examined adult patients and there are no data regarding the proliferating bone marrow distribution based on FLT-PET in pediatric cancer patients, the sparing of vertebrae in children might not only lead to lesser bone marrow toxicity but also to not impair the growth of the patient. The feasibility of vertebral column sparing p-CSI in pediatric patients was addressed by Giantsoudi et al. They demonstrated that for a prescription dose of 23.4Gy (RBE) the V10 decreased from 100% for whole vertebrae irradiation to 59.5% - 76.8%, 29.9% - 34.6% and 20.6% - 25.1% for cervical, thoracic and lumbar anterior vertebrae respectively. Similarly, the V20 decreased from 99% for whole vertebrae irradiation to 17.8% -20%, 7.2% - 7.6% and 4% - 4.6%. This result is even better than our dosimetric study (Giantsoudi 2017). The explanation could be different contouring of the anterior vertebra compartment and no CTV to PTV margin as well as a more advanced technique using intensity modulated p-CSI with two dorsal oblique fields. More importantly, a clinical study with vertebrae sparing CSI in the thoracic and lumbosacral spine in growing children from the same group is foreseen. There are also cases of clinical evidence regarding vertebrae sparing CSI in children already available (Yuh 2004) (MacEwan 2017).

The studies by Brown et al. and Barney et al. give a rationale for decreasing dose to bone marrow, but also to other OARs. In the study by Barney et al., median doses to the thyroid gland and cochleae were 0.003Gy(RBE) and 33.9Gy(RBE) that are similar to doses reported in our dosimetric study. Brown et al. showed that p-CSI significantly reduced the need for treatment for nausea/vomiting (71% vs. 26%) and esophagitis (57% vs. 5%) as compared to 2D/3D-CRT. The weight loss was also greater in patients treated with 2D/3D-CRT (Brown 2013).

Esophagitis and/or mucositis are a well-known side effect of CSI/WSI as the esophagus lies anterior to the spinal canal, and hence was historically included in the treatment field. With IMRT-techniques such as HT, the dose to the esophagus can be significantly reduced. The mean dose to the esophagus in the dosimetric part of this thesis was 28.7Gy, 23.5Gy and 8.6Gy for the standard 3DCRT, original tomotherapy (Tomo) and optimized tomotherapy (BMTomo) respectively. The trade-off for the lower dose to the esophagus is the increased lung dose. 3DCRT delivered on average 5Gy whereas Tomo increased the mean dose to 9.1Gy and BMTomo to 11.4Gy. Also, V5 is much higher for the lungs when IMRT-techniques are used. In our study both HT techniques delivered 5Gy to >4-times larger lung volumes when compared with the 3DCRT. As for V20, another important dosimetric parameter for lungs, the differences weren't that significant (9.4%, 8.8% and 12% for

3DCRT, Tomo, and BMTomo respectively). In our patients' cohort, ten patients had mucositis/dysphagia and four patients had a candida infection. With the use of BMTomo, this side effect could be probably further reduced with no extra-added clinical toxicity as no patient experienced clinically apparent pneumonitis as a result of the higher lung dose when Tomo was used. Similar to this study, Yoon et al. also compared 3DCRT, HT, and proton-CSI. "The delivered doses to esophagus, stomach, liver, lung, pancreas and kidney were 19.4Gy, 0.6Gy, 0.3Gy, 2.5Gy, 0.2Gy, and 2.2Gy for p-CSI, which was significantly lower than HT (22.9Gy, 4.5Gy, 6.1Gy, 4.0Gy, 13.3Gy, and 4.9Gy) or 3DCRT (34.6Gy, 3.6Gy, 8.0Gy, 4.6Gy, 22.9Gy, and 4.3Gy)". The prescription dose was 36Gy. Interestingly the delivered dose to the lung was higher in 3DCRT than HT. Also, no clinically significant difference can be seen in the kidney dose between the two techniques. This is contrary to our findings were BMTomo delivered higher doses to these two OARs. The reason for the difference lies in the sparing of anterior vertebrae part in BMTomo (Yoon 2011). Sugie et al. showed that for most OARs the volumes receiving >10Gy were lower in HT as compared to 3DCRT. The trade-off for this was increased mean dose to lung, kidneys, liver, and V5 of the most OARs (Sugie 2011). Several other authors demonstrated a benefit with better PTV coverage and in sparing OARs from the high dose with advanced photon techniques and even more benefit with p-CSI (St Clair 2004, Hong 2011, Kusters 2011, Sugie 2011, Yoon 2011, Studenski 2013, Myers 2014, Bandurska-Luque 2015). These findings are in accordance with this work.

Xerostomia is deemed an unrecognized side effect as parotid glands are often not considered an OAR when treating with CSI. However, depending on one's anatomy large part of parotid glands can be included when treating with the standard 2D/3D-CRT field setup. Hence, doses reaching above the QUANTEC suggested a threshold of 25Gy are often applied in this way (Deasy 2010). King et al. reviewed 50 patients previously treated with CSI where the prescription dose was above 26Gy. "The Radiation Oncology Group dose constraint (Dmean<26Gy) was exceeded in 22 patients, but in none of the patients treated with volumetric arc therapy (King 2016)." Cho et al. performed a planning study comparing lower field margin in 53 patients undergoing whole brain radiotherapy with 30Gy. The parotid dose was significantly lower when the caudal field border was fitted to the brain tissue as compared to lower atlas border. Fifteen out of the 53 patients had a mean parotid dose of both glands >20Gy (Cho 2013). Similar studies were performed also by others (Noh 2011, Loos 2012). A study by Cairncross et al. describes parotitis and hyperamylasemia as a side effect due to WBRT (Cairncross 1980). Our dosimetric results are in accordance with the published studies showing clinically significant higher doses to the parotid glands for

3D-CRT when compared to HT. When the parotid glands are really recognized as an OAR and taken into consideration by treatment planning further reduction can be achieved (i.e. Tomo vs. BMTomo). Our clinical data have shown that xerostomia wasn't really a common side effect (n=3/41). Interestingly dysgeusia was reported as a side effect in five patients, two of which also had xerostomia. As hyposalivation can lead to dysgeusia, perhaps this side effect can also be attributed to the parotid glands. Due to retrospective nature of this study and xerostomia and dysgeusia not being recognized as a side effect of the CSI it may well be that they were underreported.

We demonstrated that dose to OARs that are responsible for acute toxicities such as pharynx, esophagus, parotid glands and bowel can be significantly reduced not only with protons but to a clinically significant extent with the use of modern IMRT techniques such as HT (i.e. BMTomo). This is of great importance as CSI is often withheld in palliative treatment setting due to its believed toxicity, which can be argued to be historic to certain extent, when modern radiotherapy techniques are used. As demonstrated in this study, 11 out of 19 patients treated in palliative treatment setting benefited from the treatment either for survival prolongation or for the improvement of pain or neurological deficits.

## 5.2 Survival

### 5.2.1 Germinoma

All of our germinoma patients were alive at the point of this analysis. The prescribed regimen was 24Gy in 1.6Gy and a focal boost to 40Gy with the same daily fractionation. This is in accordance with the published literature (Linstadt 1988, Dattoli 1990, Haddock 1997, Matsutani 1997, Aoyama 1998, Haas-Kogan 2003, Shikama 2005). However, as suggested by Murray (Murray 2015) it seems that CSI although providing excellent results could mean an overtreatment in localized intracranial germinoma without leptomeningeal spread and that the treatment of choice in this setting is whole ventricle irradiation rather than CSI. However, CSI remains the standard treatment for intracranial germinoma with leptomeningeal seedings or positive CSF cytology. The results with radiation as a sole modality are perfect and due to the low dose needed to treat germinomas, it remains unclear whether the addition of chemotherapy and de-escalation of radiotherapy will be of added benefit to the patients. If so, most probably only for small children.

### 5.2.2 Medulloblastoma and PNET

In our medulloblastoma patients, median overall survival was 53 months with two of the five patients still alive at last follow-up. For the two patients with pinealoblastoma the OS was 39,5 months and 66,2 months. All of our medullo-/pinealoblastoma patients were adults (>18 years).

Silvanie et al. conducted a prospective phase II trial assessing chemotherapy before the initiation of CSI in adult medulloblastoma patients. The chemotherapy regimen consisted of three cycles of cisplatin and etoposide. Though no definitive answer could be given regarding the benefits of the added chemotherapy, the median OS for the whole group (n=28) was 11.3 years (Silvani 2012). Moots et al. also investigated pre-CSI chemotherapy in 11 adult medulloblastoma patients. The response rate to chemotherapy with cisplatin, etoposide, cyclophosphamide, and vincristine was lower than anticipated and though it didn't compromise the delivery of CSI, it also didn't provide a rationale for the use of this chemotherapy regimen. The 5-year PFS and OS were 27% and 55%, respectively (Moots 2016). A register study by Kann et al. evaluated medulloblastoma patients aged 18 years and older who were diagnosed with medulloblastoma between 2004 and 2012. This large study included 751 patients out of which 520 (69.7%) received chemotherapy and CSI, and 231 (30.8%) received CSI only. In contrast to the aforementioned prospective phase II studies, this study has shown that the addition of chemotherapy yields better results: 5-year OS 86.1% vs. 71.6% for patients undergoing treatment with combined radiochemotherapy vs. RT only. These results were significant even for M0 patients who received CSI with 36Gy (Kann 2017).

Data for PNETs in adults are scarce and are mostly limited to case reports. The reported 3y- and 5-year OS for patients with PNET was 38.2% and 26% (Ohba 2008). For adult patients with pinealoblastoma, Chang reported a series of eleven patients treated between 1975 and 1992. All patients got staging of their neuroaxis and stage was predictive for OS. The OS for five patients with metastases was 30 months from the date of surgery whereas the patients with no metastases were all alive without disease progression at a median follow-up of 26 months (Chang 1995). Another series of 12 adult patients with pinealoblastoma stated „that only 5 died of the disease with an average survival length of 118 months and with 5 patients still being alive at an average follow-up of 92 months. As for the other two patients, one died of unrelated causes and one was lost to follow-up."(Gener 2015). Larger series reported 31 patients with pinealoblastoma from M.D. Anderson Cancer Center between 1982 and 2012. The median age of this patients' group

was 18.2 years, meaning half of the patients were adults. Median OS for the entire group 8.7 years (Farnia 2014). In most of this studies stage (M+ vs M-) was an important prognostic factor, whereas the residual tumor after surgery didn't significantly influence the outcome (i.e. subtotal vs. gross tumor resection). Similarly, the study by rare cancer network concluded that dissemination at diagnosis influences survival. In this study, however, age was also a prognostic factor, with patients younger than 36 years faring poorer than their older counterparts. However, the limitation of this study is that it included also other histological subtypes such as PPTID and pineocytoma. Still, the majority, 21 of 36 patients included were patients with pineoblastoma. The median OS was not reached and median DFS was 82 months (Villa 2012). A bigger cohort of pooled SIOP-E and US Head Start data included 135 patients with pinealoblastoma (Mynarek 2017). However, it included patients aged 0-20.7 (median 4.9 years). „In the 78 patients >4 years, the PFS/OS were 72±7%/73±7% for patients without metastases and 50±10%/55±10% with metastases." The median follow-up was 7.3 years.

Although at the first sight the results of our medulloblastoma patients may seem slightly inferior to the published literature, this may be due to short follow-up and small patient number. As to whether chemotherapy yielded any benefit within our patient cohort, no definitive statement can be made. Three patients in our group received chemotherapy, two of which were irradiated with 23.4Gy, and one with 36Gy CSI. One of the two patients remaining alive was treated with the 23.4Gy CSI with a boost to posterior fossa to 54Gy with simultaneous vincristine and adjuvant cisplatin, vincristine and CCNU and the other one received 36Gy CSI and a posterior fossa boost to 54Gy without chemotherapy. For PNET our group consisted of two pinealoblastoma patients. One (aged 28 years) was treated with hyperfractionated twice daily CSI schema with 1Gy per fraction to 40Gy and with preceding boost to whole brain with 3x2Gy, once daily and further sequential hyperfractionated boost to posterior fossa (total dose 56Gy), spinal seedings (total dose 50Gy) and pineal region (total 62Gy). The patient also underwent high dose chemotherapy with autologous stem cell rescue and was disease-free for 30 months when a diffuse leptomeningeal seeding was diagnosed. He succumbed to his disease 39.5 months after the initiation of CSI. The second patient was diagnosed with pineocytoma and received interstitial brachytherapy to pineal gland with iodine seeds (total dose 60Gy). Seven years later an intraspinal extramedullary tumor at $Th_{12}$ was resected. The pathological examination revealed „pineal parenchymal tumor of intermediate differentiation with a tendency to pinealoblastoma". The patient then underwent CSI with 36Gy with a boost to tumor site to 54Gy. He was disease-free after CSI for four years, thereafter a spinal

recurrence occurred. The patient underwent further surgery, chemotherapy, and RT, but finally died 66.2 months after the initiation of CSI. Our survival data match that of the study by Chang, yet are inferior to other published series. Interesting is the long PFS of 30 and 48 months and then developing a new recurrence along the craniospinal axis in both of our patients.

### 5.2.3 Ependymoma

All of our ependymoma patients (n=5) were alive with a median follow-up of 85 months. This excellent results can be explained due to the fact that there were no anaplastic ependymomas in the entire group. In a recent study by Schiopu et al., 10 ependymoma patients were treated with CSI on HT and for those with M1 (n=5), a median OS between 9 and 32 months was calculated. The other 5 patients (M0) had 5-years OS of 100% (Schiopu 2017). However, it remains questionable if they were good candidates for treatment with CSI as CSI isn't nowadays a standard of care when M0. Survival data from major Ependymoma studies are presented in the table 15.

| Series | Time Period | Patients | 5-year EFS | 10-year EFS | 5-year OS | 10-year OS |
|---|---|---|---|---|---|---|
| Akyuz | 1972-1991 | 62 | - | 36% | - | 50% |
| Perilongo | 1977-1993 | 92 | - | 35% | - | 56% |
| Shu | 1980-2000 | 49 | 41% | 31% | 66% | 56% |
| Oya | 1961-1999 | 48 | 42% | 42% | 62% | 47% |
| Pollack | 1975-1993 | 40 | 46% | 36% | 57% | 45% |
| Jaing | 1985-2002 | 43 | 46% | - | 54% | - |
| V. Veelan | 1980-1999 | 83 | 48% | 46% | 73% | 51% |
| Robertson | 1986-1992 | 32 | 50% | - | 64% | - |
| Mansur | 1964-2000 | 60 | 58% | 46% | 71% | 55% |
| Merchant | 1997-2007 | 153 | 74% | 69% | 85% | 75% |

*Table 15 Results of selected radiotherapy series for Ependymoma (Merchant 2009)*

More specific studies are needed in order to better assess the outcome of patients with metastatic ependymoma treated with modern CSI techniques such as HT, IMRT, and p-CSI.

### 5.2.4 Leptomeningeal carcinomatosis

In our palliative treatment group, the OS of patients receiving CSI due to leptomeningeal carcinomatosis was 3.4 months. This is in accordance with the literature where median OS ranges between 7 and 30.3 weeks were reported. There is very limited data on the use of

CSI as a treatment for patients with LM. In the one aforementioned study by Hermann et al. the median OS for patients with CSI was 8 weeks and 16 weeks for those treated with intrathecal chemotherapy and CSI. Of note is that all patients had also synchronous extra-CNS metastases (Hermann 2001). Another recent study evaluating CSI also in palliative treatment setting was conducted by Schiopu (Schiopu 2016). Herein, 15 patients with LM from solid tumors were treated with HT. A median OS for patients treated for leptomeningeal metastasis was 3 months, with 6 and 12 months survival reaching 30% and 20% respectively, which is very similar to our data. For patients receiving CSI due to LM of breast cancer, the median OS was 6 months, for lung cancer below one month. In our group, median OS for breast cancer primary was 4.7 months, comparable to the data of Schioupu et al. However, our patients receiving CSI due to an NSCLC primary showed an increased median OS of 3.3 months and one patient surviving for more than 5 years with no evidence of disease. Similar, to our data symptom improvement, was seen in >50% of the patients. The reported spectrum of a side effect was also not different to that of our patient group, with interestingly dysphagia and xerostomia being reported by 20% of the patients, which is more than in our patient collective. Also in the study by Hermann, the major toxicities were myelosuppression (11/16), dysphagia (9/16), mucositis (7/16) and nausea (3/16). This finding shows the necessity to cautiously plan the delivery of CSI in a palliative setting in order to minimize the acute side effects. As shown in the dosimetric part of this study, optimized HT (BMTomo) can result in low doses to OARs responsible for xerostomia, dysphagia, and mucositis (parotid and submandibular glands as well as pharynx and esophagus). In the analysis of our palliative patient cohort, patients having KPS≥70 fared significantly better. Also, patients having no systemic disease showed significantly improved survival. For patients with KPS≥70 median OS was 4.7 months (20.6 weeks) compared with 1.5 months (6.6 weeks) for the rest of the group. Similar the median OS for patients with the leptomeningeal disease was only 7.3 months (31.9 weeks) and 2.8 months (12.3 weeks) for those having also systemic disease. When these factors were combined a median OS of 7.3 months (31.9 weeks) could be achieved for those who had a good KPS and no systemic disease. In those who had one or two adverse factors, the median OS was 3.3 months (14.3 weeks) and 1.5 months (6.4 weeks) respectively. These results suggest that cautious patient selection is needed in a palliative setting when considering CSI. In our collective, there was also a big drop-out rate as 47.4% of the palliatively treated patients didn’t complete their prescribed treatment, due to progressive disease or major cytopenia.

Pan et al. tested a regimen of intrathecal chemotherapy with MTX and involved field radiotherapy (whole brain or focal to spinal lesions) with 40Gy in 2Gy/fraction. 59 patients

were treated with a median OS of 6.5 months (Pan 2016). Interestingly patients with NSCLC had better OS than patients with breast cancer primary (6.7 vs 5.4 months). Perhaps this could be explained with 3 patients receiving also tyrosin-kinase inhibitors (TKIs) which are mostly used in the treatment of NSCLC and are considered to have activity in CNS. However, treatment side effects were different when compared to our patients or those by Schioupu where patients were treated without i.t. chemotherapy. The side effect herein included also acute meningitis, chronic delayed encephalopathy and radiculitis apart from myelosuppression and mucositis.

CSI is rarely viewed as a treatment of choice for patients with the leptomeningeal metastatic disease. However, this study together with the series by Schioupu and Hermann give a good rationale for offering CSI to patients who have a good performance status and none or limited and controlled systemic disease. In all of these studies, even longer-term survival for a limited number of patients was possible. Although the study by Hermann et al. suggested that patients receiving IT chemotherapy before the CSI fare better, it is somehow illogical to first use IT chemotherapy and thereafter radiation. If radiation can achieve limited control of macroscopic disease it is probably moreover so capable of controlling microscopic disease (e.g. the free tumor cells in liquor which could have been affected by the intrathecal chemotherapy). So perhaps intrathecal chemotherapy could be used after prior CSI as an “adjuvant” therapy. There are no studies to support this and there is much fear to apply methotrexate after CSI due to its side effect but perhaps CSI followed by Depocyte would be an interesting approach which requires further evaluation.

Historically, two major reasons for the underuse of CSI in patients with LM existed. The concern for acute side effects and difficult treatment application. However, with modern radiotherapy techniques which are within the scope of this thesis, CSI can be done with limited acute toxicities. Also, when using HT, there is no need for field junctions and their daily or weekly shifts as it was the case in the 2D/3D era. Although the field junctioning remains an issue for other advanced techniques (IMRT, VMAT, p-CSI), with proper treatment planning no shifting of the junction is needed. Hence none of these historical reasons apply in the modern-day radiation oncology. As compared to intrathecal chemotherapy CSI effectively targets all of the leptomeningeal metastatic disease, macroscopic and microscopic, without the need for invasive interventions (i.e. lumbar puncture or surgery to place the Ommaya reservoir). Hence, CSI could not only offer a survival benefit that is at least comparable to intrathecal chemotherapy but also enhances the quality of life of the patients as compared to intrathecal chemotherapy.

## 5.3 Limitations

Several limitations of the present work need to be stated. First, the small and heterogeneous cohort with a high dropout rate for palliatively treated patients. Therefore, some caution is needed when interpreting results onto the general population. However, studies investigating the use of CSI in the palliative setting are scarce, underlining the importance of the present study. Moreover, for some questions studied, this didn't pose a major limitation (i.e. myelosuppression and the technique and chemotherapy used). Second, due to the retrospective nature of this study, some of the side effects may be underreported. Third, different resolution and dose grids were used in the dosimetric part of the study, as a different radiation treatment planning software system was used and different resolutions were supported. Also, a one-dorsal field setup technique for p-CSI is not realistic due to the need of field junctions when treating a larger field. Only vertebral bodies were contoured as a part of the proliferating bone marrow. This was done on purpose, as the activity of the vertebral bodies is much higher as compared to the remaining parts of the vertebrae on the FLT-PET-scans. In spite of these limitations, the dosimetric results of this study are relevant to outline the differences among different treatment techniques.

# 6 Conclusion

CSI is a standard of care in multiple CNS-tumors treated in curative setting but it is rarely considered for patients with LM. Based on the results of the dosimetric study, common side effects such as dysphagia, mucositis, and xerostomia can be minimized with modern treatment techniques. HT, when not optimized for, leads to greater dose to the proliferating bone marrow. For the first time, dose activity histogram and weighted bone marrow exposure (DAH, WBME) are presented in this work. These parameters assess the delivered dose to bone marrow better than the traditional DVH, as they are not based simply on volume but rather on the percentage of residing proliferating bone marrow in its specific segment. With HT proliferating bone marrow could be spared only from higher doses (>V15). While less volume of proliferating bone marrow is irradiated with a low dose in 3DCRT when compared to HT, it seems that the traditional DVH underestimates the extent of proliferating bone marrow irradiated. Ultimately, p-CSI proved its superiority in OARs as well as in bone marrow sparing, with traditional DVH overestimating the extent of irradiated proliferating bone marrow as compared to DAH.

In the comparison of the acute hematological toxicities between 2D and HT CSI, only the distribution of thrombocytes differed but there were no differences in severe leukopenia or thrombopenia occurrence. Chemotherapy with close temporal relation to the onset of CSI was found to be a risk factor for thrombocytes nadir and for the occurrence of severe leukopenia and thrombopenia.

Our OS results for patients treated in the curative setting were in accordance with the published literature. The importance of reducing side effects is not only important for patients treated in curative setting but is of utmost importance for selected patients to whom CSI may offer a meaningful palliative treatment option. For the patients receiving CSI in the palliative setting, most of the patients in this study benefited clinically from the treatment and some achieved a longer-term survival. A simple scoring system based on KPS and the presence of extra CNS disease is suggested to help guide the clinical decision-making in patients' selection as to whom such form of treatment should be offered. With the use of the modern treatment techniques symptomatic palliation and even prolonged survival can be achieved in some patients while minimizing side effects of the treatment. In fact, when compared to intrathecal chemotherapy, patients receiving CSI don't have a risk of developing radiculitis, meningitis, and several other side effects and they are not subjects of repeated lumbar punctures which themselves are painful and thus decrease the quality of life. Hence, CSI should be considered an option for selected patients with LM.

# 7 Summary

CSI has been a well-established treatment for multiple primary brain tumors with a tendency to leptomeningeal spread. On the other hand, data for its role as a palliative treatment are scarce. Forty-two patients were treated at our institution with CSI/WSI between 2001 and 2015. Median age at treatment was 36.7 years (range 6-80 years). Patients were treated in various schedules with median daily doses of 1.6Gy (range 1.5 – 2.0Gy) to a median total dose without the boost of 30.3Gy (range 3.0 – 36.0Gy). Half of the patients (n = 21) received a further boost. Twenty-three patients were treated in curative and nineteen in palliative intention. Twenty-nine patients received treatment with HT and thirteen were treated with the standard 2D-field setup. The nadir in blood cell count did not significantly differ between 2D and HT treatment (p=0.803; p=0.178; p=0.334 for WBC, Hb, and thrombocytes -nadir respectively). The differences in change ratio (nadir/baseline) were not significantly different for WBC and Hb. However, the thrombocytes change ratio (nadir/baseline) distribution was significantly different (p=0.028). Chemotherapy within 3 months prior to initiation of the RT was associated with significantly lower thrombocytes nadir (p=0.02), while WBC and Hb nadirs were not significantly affected. CTCAE grade 4 leukopenia (WBC $<10^9$/l) and grade 3 or 4 thrombopenia (Tro $<50x10^9$/l) were separately evaluated and classified as severe leukopenia or thrombopenia as blood cell counts below these levels may lead to treatment prolongation and potentially adversely affect treatment outcome. Treatment technique did not significantly affect the grade of severe leukopenia or thrombopenia whereas chemotherapy applied within three months prior to RT did (p=0,023 for leukopenia and p=0,047 for thrombopenia). Growth factors or transfusions were given only in five patients.

Median OS in the curative group was not reached. For the major diagnosis groups, the survival was as follows: Medulloblastoma (median OS=53 months), Pinealoblastoma (median OS=39 months), Ependymoma (median OS=not reached; all patients are alive), Germinoma (median OS=not reached; all patients are alive). These results were in accordance to the published results. In the palliative treatment group, median OS was 3.4 months. As for patients' subgroups, the median OS for patients with LM by breast cancer primary was 4.7 months and for NSCLC 3.3 months. KPS and systemic disease were identified as important prognostic factors influencing OS in patients with LM. A simple score taking into account KPS and presence of systemic disease was suggested to stratify patients with LM. In our patients' cohort, the median OS was 7.3 months, 3.3 months and 1.5 months for patients with 0, 1 and 2 risk factors (KPS<70 and the presence of systemic

disease) respectively. Longer-term survivals were also seen in four patients treated in palliative intend surviving for more than 11 months.

In twenty-six patients, treatment was performed without any interruption. Five patients had treatment breaks and finally, in eleven patients the treatment was discontinued. The reasons for treatment discontinuation were mostly major cytopenia not recovering after treatment break or general status deterioration with progressive disease in spite of the treatment.

In the dosimetric part of this study, treatment plans of nine selected patients were compared. The HT plan used for the treatment origininally (Tomo) was compared to the second HT treatment plan (BMTomo) which was optimized to spare the tissues which are responsible for the acute toxicities such as pharynx, esophagus and major salivary glands. Moreover, this plan was also optimized to reduce the dose to the proliferating bone marrow as hematologic toxicities are among the major acute side effects of a treatment with CSI. Also, a standard field setup CSI (3DCRT) and proton CSI (p-CSI) plans were compared.

Mean PTV volume was 3283cm$^3$ (range 2923cm$^3$ – 3600cm$^3$). The average $D_{MEDIAN}$, $D_{98}$, $D_2$,was 36.4Gy, 30.5Gy, 43.1Gy for 3DCRT, 36.1Gy 34.5Gy, 37.2Gy for Tomo, 36.0Gy, 33.1Gy, 37.3Gy for BMTomo and 36.0Gy, 33.1Gy, 37Gy for p-CSI. The average homogeneity indices were 0.31, 0.07, 0.12 and 0.08 for 3DCRT, Tomo, BMTomo and p-CSI respectively. Similarly, the average conformity indices were 0.89, 0.98, 0.96 and 0.98. The conformation number (CN) ranged from 0.55 for 3DCRT to 0.78 for both Tomo and BMTomo and 0.96 for the p-CSI. Taken into account all of these dosimetric parameters and indices the Tomo performed best in homogenous and BMTomo in conformal coverage of the PTV. However, as soon as healthy tissues are taken into account, they were outperformed by the protons as shown by the CN. 3DCRT was, as expected, the most inferior in respect to homogeneity and conformity of the PTV coverage.

Among the photon treatment techniques, oral cavity ($D_{MEAN}$ 5.7Gy, 8.6Gy, 16.1Gy), pharynx ($D_{MEAN}$ 15.9Gy, 16.3Gy, 25.9Gy), submandibular glands ($D_{MEAN}$ 9.2Gy and 6.9Gy, 10.6Gy and 10.5Gy, 16.7Gy and 16.9Gy for left and right submandibular gland respectively), bowel ($D_{MEAN}$ 7.8Gy, 9.1Gy, 10.7Gy) and liver ($D_{MEAN}$ 5.9Gy, 8.5Gy, 8.9Gy) are best spared with 3DCRT followed by BMTomo and Tomo. Also, kidneys ($D_{MEAN}$ 3.0Gy and 3.6Gy, 9.5Gy and 9.2Gy, 9.9Gy and 9.6Gy for left and right kidney respectively) and lungs ($D_{MEAN}$ 5.0Gy, 9.1Gy, 11.4Gy) are best spared with 3DCRT succeeded by Tomo and BMTomo. On the other hand, 3DCRT ranks as the last for esophagus ($D_{MEAN}$ 8.6Gy, 23.5Gy, 28.7Gy), larynx ($D_{MEAN}$ 7.6Gy, 18.8Gy, 19.7Gy), parotid glands ($D_{MEAN}$ 12.4Gy and 13.7Gy, 23.2Gy and

23.8Gy, 28.9Gy and 30.3Gy for left and right parotid gland respectively), thyroid gland ($D_{MEAN}$ 12.5Gy, 21.5Gy, 24.6Gy), heart ($D_{MEAN}$ 5.8Gy, 11.5Gy, 15.1Gy) and lenses ($D_{MEAN}$ 5.0Gy and 4.6Gy, 5.8Gy and 5.3Gy, 15.6Gy and 14.4Gy for left and right lens respectively). For these OARs, BMTomo achieved the best results from the photon techniques. However, due to their physical characteristics, protons deliver virtually no dose to OARs lying anteriorly of the spine.

To evaluate the integral dose, the “Body” and “Body outside of the PTV” Dmean were used as surrogates. Herein the 3DCRT, Tomo, and BMTomo resulted in 108.9%, 172.3% and 153.6% dose more than the proton-CSI. However, these numbers were even higher when only the tissue outside of PTV i.e. “Body outside of the PTV” was taken into account: 309.7%, 493.8%, and 439.2%.

To better evaluate the exposure of proliferating bone marrow, novel parameters such as weighted bone marrow exposure (WBME) and dose-activity histogram (DAH) were introduced, based on quantitative studies of proliferating bone marrow with the use of 3'-deoxy-3'[18F]-fluorothymidine-PET. As compared to standard volumetric information, these newly introduced parameters consider the functional information. P-CSI outperforms photon techniques in OARs sparing including the proliferating bone marrow. As bone marrow sparing is possible only to some extend with the use of modern „well-optimized“ IMRT techniques, future studies will have to elucidate whether this will translate also to a significant clinical benefit. However, if protons are not available, modern IMRT techniques can also significantly reduce the dose to crucial OARs to minimize the most common acute side effects (i.e. dysphagia, mucositis and xerostomia). This is not only important for patients treated in curative setting but is of utmost importance for selected patients to whom CSI may offer a meaningful palliative treatment option. It seems that patients’ selection remains crucial in decision making as to whom such form of treatment should be offered. With the use of modern treatment techniques symptomatic palliation and even prolonged survival can be achieved in some patients while minimizing side effects of the treatment. Hence, CSI should be considered an option for selected patients with LM.

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