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WP leader: Michael Krämer
Reporting period: 1st

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<tr>
<th>Name</th>
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<tbody>
<tr>
<td>Author(s): Urszula Jelen</td>
<td>UNIMAR</td>
</tr>
<tr>
<td>Contributor(s): Filippo Ammazzalorso (UNIMAR), Andrea Wittig (UNIMAR), Johannes Hopfgartner (MUW), Ali Reza Homayuni (MUW), Rita Engenhart-Cabillic (UNIMAR)</td>
<td>UNIMAR, MUW</td>
</tr>
<tr>
<td>Pillar coordinator: Richard Pötter</td>
<td>MUW</td>
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<td>Approved by TPB and CPO</td>
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Dissemination Level

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LIST OF ABBREVIATIONS AND DEFINITIONS

List of abbreviations

ABC - active breathing control
AC(P) - abdominal compression (plate)
AP - anterior-posterior
BB - bite block
CT - computed tomography
CBCT - cone beam computed tomography
DRR - digitally reconstructed radiograph
ERB - endorectal balloon
(E)PI - (electronic) portal image
fscp - fluoroscopy
HFJV - high frequency jet ventilation
GTC - Gill-Thomas-Cosman (frame)
IHS - individual head rest
IMRT - intensity modulated radiotherapy
LR - left-right (medio-lateral)
(micro-)MLC - multi-leaf collimator
MVCT - megavoltage computed tomography
(MV/kV)PI - (megavoltage/kilovoltage) portal image
OBI - on-board imager
RT - radiotherapy
RTT - radiotherapy technologist
Sb(F) - stereotactic body frame
SC - scotch cast
SHS - standard head rest
SI - superior-inferior (cranio-caudal)
STX - stereotaxy
(S)RS - (stereotactic) radiosurgery
STP - stereotactic thermoplastic
TP - thermoplastic
UJS - upper jaw support
UKGM - University Hospital of Giessen and Marburg
VMP - vacuum mouth piece

Definitions

setup error - The difference between the actual and planned position of the irradiated volume of the patient (with external immobilization as the focus of this study, unless stated otherwise, it refers to the bony alignment setup).

\[ \Sigma \] - Represents the population systematic error. It is calculated as the standard deviation of all the individual systematic errors obtained for each patient in the cohort (where patient systematic error is the deviation between the planned patient position and the average patient position over a course of fractionated therapy). It represents the treatment preparation errors, i.e. errors that affect all treatment fractions of a single patient in the same way and hence is a measure of the accuracy of the technique.

\[ \sigma \] - The population random error is the root-mean-square of all random errors obtained for each patient in the cohort. It represents the treatment execution variations at each single fraction, and hence represents the reproducibility of the technique.
PUBLISHABLE SUMMARY

With the increasing conformity of radiation therapy (RT), facilitated by the most modern radiation modalities and delivery technologies (IMRT, particle therapy), a precise and reproducible dose application during every single treatment fraction becomes of the utmost importance. A commonly used method to ensure this is patient immobilization by means of specialized, usually individually moulded, equipment (e.g. masks, vacuum cushions, etc.).

The aim of patient immobilization is twofold: it allows fast and reproducible setup of the patient before each treatment fraction and it helps to maintain patient position during the application of radiation. Hence, it is necessary to attempt and optimize the immobilization technique and also to assess the magnitude of the unavoidable residual uncertainties, that can be e.g. incorporated into safety margins or robust planning techniques.

Existing immobilization solutions have been reviewed, with particular consideration of issues specific for particle therapy. The published data about achievable accuracy, for specific organs/tumor localizations have been summarized. Based on these results, as well as clinical experience, recommendations have been formulated for tumor-site-specific immobilization approaches to assure the best reproducibility for particle therapy treatments.

It is apparent that the external immobilization alone is not sufficient to control the patient setup, if the patient’s anatomy changes during the course of treatment (e.g. due to tumor shrinkage, patient weight loss or gain and swelling). Therefore, suggestions have been formulated on the importance of image guidance, which allows controlling the patient’s setup and, if necessary, correcting it or, in cases of considerable changes in patient’s anatomy, may lead to plan adaptation.
CONTENTS AND SPECIFIC DOCUMENT STRUCTURE

1 Introduction

With the increasing conformity of radiation therapy (RT), facilitated by the most modern radiation modalities and delivery technologies (IMRT, helical tomotherapy, particle therapy), a precise and reproducible dose application during every single treatment fraction becomes of the utmost importance. A commonly used method to ensure this is patient immobilization by means of specialized, usually individually moulded, equipment (e.g. masks, vacuum cushions, etc.). In order to reduce the residual positioning error, present despite the use of immobilization devices, image guidance in treatment position can be applied. A third method, applicable especially in particle therapy, is the plan robustness concept [102, 103], which can be essentially understood as an effort to minimize the consequences of positioning errors already at the level of treatment planning [153, 125, 5].

The aim of patient immobilization is twofold: it allows fast and reproducible setup of the patient before each treatment fraction and it helps to maintain patient position during the application of radiation. Hence, it is necessary to attempt and optimize the immobilization technique and also to assess the magnitude of the unavoidable residual uncertainties, that can be e.g. incorporated into safety margins or robust planning techniques.

Three factors that have to be taken into account when optimizing the immobilization solution are: (1) achievable precision or reproducibility of patient setup, (2) usability from the point of view of the RTTs and compatibility with the overall treatment workflow (e.g. immobilization devices must not limit the available irradiation directions) and, last but not least, (3) patient comfort.

The reproducibility of positioning obtained with a given type of immobilization device is usually assessed, in the clinical environment, by means of repeated measurements of the patient’s setup during the treatment course and comparison to the planned position. Like any measurements, this procedure incorporates errors introduced by the measuring method (e.g. the use of planar projective verification images to match bony landmarks vs. volumetric imaging), by technical limitations (e.g. resolution of the DRRs commonly used as reference images) and by human errors (e.g. inter- and intra-observer variability when evaluating the setup through manual or semi-automatic tools) [76].

In the final measurements, such uncertainties will be combined with the intrinsic efficacy of the immobilization devices as well as with uncertainties related to the propriety of their use (e.g. experience of the RTTs in moulding thermoplastic masks encompassing significant facial features). Also the patient’s mental and physical state and her/his will or ability to collaborate with the immobilization procedure plays a direct role in the reproducibility of immobilization [76].

Hence, it is important to recognize how the achievable immobilization depends on the whole treatment chain and is therefore somehow bound to the institution performing the immobilization assessment. If on one side this property is desirable, since e.g. safety margins based on immobilization studies conducted at one facility will incorporate all possible uncertainties, on the other side it makes not straightforward the task of using data on immobilization reproducibility of a certain device published by another institution.

The authors of this deliverable put effort in presenting, in the most consistent manner possible, data about patient immobilization coming from the literature, from their own clinical experience and from the direct interaction with other particle therapy centers, in the hope that this will help creating guidelines for robust common clinical workflows. Yet, in the light of the necessary inter-facility variations
in the use of immobilization devices, the immobilization experiences summarized in this document
should be used to guide internal assessments on immobilization at single institutions, rather than as
absolute data about the reproducibility offered by each solution.

Finally, it should be noted, that external immobilization can not prevent internal organ movement and
organ deformations, which both lead especially to intra-fraction movements. Considerations and pos-
sible solutions, by means e.g. of invasive devices or medical procedures, are reported in the sections
dealing with indications for which this applies.

It is also apparent that the external immobilization alone is not sufficient to control the patient setup,
if the patient’s anatomy changes during the course of treatment (e.g. due to tumor shrinkage, patient
weight loss or gain and swelling). Such changes lead to inter-fraction movements which typically
increase over several fractions, possibly leading to time-trends in systematic setup errors. Therefore,
modern workflows include repeated imaging during the course of treatment, with plan adaptation
as the conclusive solution when too large variations are observed. It should be observed how the
increased sparing of healthy tissue achievable through particle therapy and the availability of modern
low-dose imaging devices at newer facilities (e.g. CBCTs or modulated-current CT scanners), offers
an opportunity to introduce more fine-grained a control of the patient’s setup.

2 Methods

The recommendations for immobilization in particle therapy formulated in this document are based
on (1) a literature research on immobilization solutions in RT, complemented by (2) the clinical expe-
rience in high precision conventional RT gathered in the Department of Radiotherapy and Radiation
Oncology of the University Hospital of Giessen and Marburg (UKGM) and (3) dedicated tests of im-
mobilization equipment and immobilization concepts conducted in the Department in the framework
of the preparation for the upcoming Particle Therapy Center in Marburg.

2.1 Literature studies

2.2 Aim of the literature studies

With the advent of high precision photon radiotherapy techniques (e.g. IMRT, helical tomotherapy),
which increased the requirements for reproducibility of dose application, and ever more accessible
advanced imaging devices, the achievable precision of patient positioning has been extensively tested
at numerous centers. Hence, an abundance of data exists in the literature, providing a sound base for
choice of optimal immobilization solutions.

The aim of the literature search was:

- to identify the typical sources of positioning uncertainties and magnitude of such uncertainties
  for different indications

- to survey the existing immobilization solutions and their accuracy

- to identify the better immobilization approach, if direct comparison data is available
2.3 Limitations of the literature studies

Published data on setup uncertainties during a course of radiotherapy are based usually on small patient cohorts (5-20 patients). Additionally, differences in the study methodology, e.g. patient immobilization, patient preparation (e.g. diet, enema, etc.), workflow of RTT tasks and, finally, statistical description of the acquired data, do not readily facilitate inter-comparison of reported results. E.g. for day-to-day variations typically one of the following approaches is used:

- population based systematic and random error (e.g. van Herk’s formula [159])
- pooled data: mean and standard deviation (note: it is not always clear from the publication, whether absolute or signed values were taken for averaging, yielding considerably different results)
- pooled data: median, ranges, distribution of displacements, etc.

In order to assure comparability, only studies using the first two concepts or publications where raw data was accessible enabling calculation of population based systematic and random error, were included. Data representing pooled population mean and standard deviation are reported in the following as mean ± standard deviation. Results represented using van Herk’s definitions [159] are reported as \( \Sigma(\sigma) \), where \( \Sigma \) denotes the population based systematic error and \( \sigma \) the population based random error. In some cases, where the raw data was available, the desired statistical analysis has been performed by the authors of this document. In cases where the direct comparison of the reported values was not possible, the qualitative assessments of the authors are cited. Additional exclusion criteria, regarding e.g. measurement techniques, were applied and will be discussed below in the respective sections.

It should be noted here that, due to reasons explained in the introduction to this document, the uncertainties reported in the literature, inherently contain a component stemming from errors in the whole radiotherapy chain specific to each institution, different than the immobilization device alone. In particular, the mean values and systematic errors are influenced by factors like laser alignment, couch sag, etc.

2.4 Clinical experience

The Department of Radiotherapy and Radiation Oncology of the UKGM offers stereotactic intracranial treatments, stereotactic body treatments (lung, liver) [147, 168] and IMRT treatments for the head-and-neck region [77]. The image guidance data as well as the experience acquired during application of these treatments were used retrospectively in this project.

2.5 Preparatory works at the Particle Therapy Center in Marburg

In the framework of the preparations for the upcoming Particle Therapy Center several aspects of immobilization, specific to particle therapy applications, were studied, e.g. inter-fraction stability of vacuum cushions, stability of vacuum immobilization devices in presence of treatment couch roll, stability of continuous thermoplastic mask material vs. perforated, potential prostate immobilization effect of endorectal balloons, etc. Knowledge acquired from these testing activities was used to complement and interpret literature data.
3 Recommendations for optimized fixation systems

As the first stage of this project, the groups of indications corresponding to four different body regions were identified representing different challenges for immobilization:

- **intracranial treatments** - the main source of positing uncertainties in cranial irradiations are rigid setup errors (translational and rotational)

- **head-and-neck treatments** - apart from rigid setup errors, non-rigid deformations of the neck region and other anatomical changes occur (tumor shrinkage, patient loosing weight)

- **lower abdomen / pelvic treatments** - rigid and non-rigid setup errors as well as internal anatomy changes lead to inter- and intra-fraction setup errors (organ movement is possible e.g. as a consequence of peristaltic movement, different bladder and rectum filling, etc.)

- **thorax** and **upper abdomen treatments** - rigid and non-rigid setup errors as well as internal anatomy changes occur. Furthermore, significant respiration-induced intra-fraction motion is present

- **paraspinal** and **craniospinal treatments** - rigid translational and rotational setup errors, but also relevant local deformations due to semi-independent movement of the vertebrae

In the following, for these four groups of indications, (1) the state-of-the-art immobilization approaches are presented, (2) the magnitude of the residual uncertainties despite use of these devices is reported (based on the literature data and own data collected at the Department of Radiotherapy and Radiation Oncology of the UKGM), and (3) additional considerations, specific to particle therapy are addressed.
3.1 Intracranial treatments

3.1.1 Indication-specific positioning issues and relevance to particle therapy

High precision radiotherapy is especially valuable in the treatment of cranial tumors, due to the direct vicinity of critical structures. The higher the degree of conformation, the higher is the required setup reproducibility to achieve accurate dose delivery in regions of steep dose gradients. Furthermore, the density patterns along the ray paths have a strong influence on the Bragg peak position, rendering the technique sensitive to patient/organ misalignment [4]. Particularly in head treatments the presence of severe density interfaces (e.g. bone-air) along the beam tracks can lead to clinically relevant underdosage of the target volume and/or overdosage of sensitive structures. Unlike the case of photon irradiation, addition of a safety margin around the target is often an insufficient countermeasure.

Figure 1: Effects of setup errors on a carbon ion treatment plan for a cranial tumor: (a) original treatment plan, biologically optimized with TRiP98, (b) the plan recomputed with a raster shift of 2 mm in AP direction to simulate a translational setup error.

This phenomenon is exemplified in Figure 1, from a study on the dosimetric stability of carbon ion treatments for the intracranial targets carried out at the Department of Radiotherapy and Radiation Oncology of the UKGM [4]. Figure 1 (a) presents a biologically optimized carbon ion dose distribution calculated with the TRiP98 TPS [88] for active scanning delivery [60] (brainstem set as OAR). In (b) a treatment fraction with a setup error was simulated by introducing a shift in the irradiation rasters and recomputing the dose. The negative effects on the delivered dose, both in terms of target coverage and healthy tissue involvement, are well visible in (b).

As a consequence, in head treatments, a general accuracy better than 2 mm is required in dose application. Immobilization systems for cranial radiotherapy must therefore provide an effective degree of rigidity but at the same time strike a tenuous balance offering acceptable comfort to the patient. In intracranial irradiations, direct immobilization of the skull or reproducible immobilization of surrogates like maxilla or nasal bridge significantly limits rigid translational and rotational degrees of freedom and guarantees treatment accuracy.

The PubMed database was searched systematically with the following key words and their permutations: “patient immobilization”, “radiotherapy”, “stereotactic mask”, “thermoplastic mask”, “bite block” and publications regarding cranial immobilization were selected.
3.1.2 Immobilization devices for cranial irradiations

Rigid stereotactic immobilization systems
In the most demanding intracranial stereotactic radiosurgery (SRS) treatments, high precision is achieved by rigid fixation of the skull to a stereotactic system using invasive procedures (e.g. Brown-Robert-Wells frame). This technique provides sub-millimeter precision [45, 143, 71, 92, 127]. However, such frames generally can be applied for single fraction treatments only (the CT-scan for treatment planning and RS are performed on the same day). Although relocatable invasive systems have been proposed (e.g. TALON frame [136]) offering similar accuracy and less patient discomfort, these systems still require an invasive procedure and remain a choice exclusively for highly hypofractionated regimes.

At the Department of Radiotherapy and Radiation Oncology of the UKGM only patients treated with RS for arteriovenous malformations and trigeminal neuralgia are currently routinely immobilized in invasive frames. According to available information, also other institutions follow in general this line of action.

Stereotactic “frameless” immobilization systems
Recent improvements in image-guidance technology have enabled the introduction of “frameless” localization techniques, based on head masks, bite blocks or ear plugs, considered currently the state-of-the-art solution for high precision fractionated intracranial treatments. These systems are more
suited for fractionated treatments; however, the reproducibility and accuracy of patient setup is inferior to the rigid invasive head ring [143, 92].

*Relocatable non-invasive frame systems based on maxilla*

Several systems are based on the immobilization of the maxilla and thus are in direct mechanical contact with the cranium. Such systems usually consist of a dental impression (bite block) and an occipital head rest (e.g. Gill-Thomas-Cosman frame [49], see Figure 2 on the facing page (a)) which reliably minimize translations and rotations of the patient’s skull.

*Relocatable non-invasive stereotactic frame systems based on external auditory canals*

A system based on external auditory canals was proposed by Laitinen et al. [91] and is registered to the patient’s head by means of two ear plugs and a nasion support. It offers accuracy within better than 2 mm [67, 36, 83] and is currently used predominantly in pediatric treatments (where a bite block based system would be inappropriate).

*Stereotactic mask based systems*

The two most common stereotactic mask types reported in the literature are: (1) scotch cast (SC) mask shown in Figure 2 (b) and (2) stereotactic thermoplastic (STP) mask shown in Figure 2 (c-d).

A scotch cast mask is built in a fashion similar to an orthopedic plaster cast around the head of the patient. After solidification the cast is cut open in two approximately equal halves encompassing the back of the head and the face of the patient. During construction sockets are created for the support rods (that couple the mask with the stereotactic frame and support the head from behind) and hinge-like elements are mounted on the sides to allow opening/closing the mask. Scotch cast stereotactic masks offer elevated reproducibility of head positioning: they have been investigated e.g. at the Department of Radiotherapy and Radiation Oncology of the UKGM [56] for highly conformal photon irradiation (e.g. with use of a micro-MLC) and also, by Karger et al., for treatment with carbon ions [84]. The most notable disadvantage of SC masks is the time-consuming preparation procedure, which requires experience and can be distressing for the patient (initial tight bandaging around the head, relatively long drying time, removal with a plaster cutter, etc.)

A thermoplastic stereotactic mask is made of three components: a posterior layer (lower half mask) that fixes and supports the back of the head, a middle layer reinforcing the immobilization of the most prominent facial features (shape of the nose/cheekbones, forehead/supraorbital ridge and nasion), and a frontal layer (upper half mask) attached to the middle layer and encompassing also the remaining frontal skull features (chin, face, forehead). Variations, employing upper jaw supporting (UJS) systems (Figure 2 (c)) or dental moulds (d) are available for further reduction of the residual patient movement.

One potential drawback of such systems is the presence of some elements in the irradiation field (e.g. the horizontal bar connecting the halves of the mask (see Figure 2 (c) and (d)). In case of patient misalignment with respect to the mask, which can be corrected by image guidance based on bony structures, these elements may modify the particle range.

*Thermoplastic mask systems*

Non-stereotactic thermoplastic mask systems are widespread in head treatments. Various solutions have been commercialized employing different materials (e.g. perforated vs solid) of varying thickness and with various fixation systems. These masks, moulded to the patient’s facial features (nasion, chin) and applied in combination with different head support solutions (standardized or individually moulded head rests) provide stability against misalignment and rotations. Benefits of such immobilization include ease of fabrication and quick setup time. One disadvantage of thermoplastic masks, although limited in the recent years by material vendors, is material shrinkage. Shrinkage of the thermoplastic is mainly observed during the first 24 h after moulding.
**Figure 3:** Different types of thermoplastic material for 3-point head immobilization masks (Unger Medizintechnik, Mühlheim-Kärlich, Germany) tested at the Department of Radiotherapy and Radiation Oncology of the UKGM: (a) non-perforated low-temperature-mouldable material [77], (b) perforated low-temperature-mouldable material.

**Figure 4:** (a) A typical base plate employed in conventional radiotherapy (Cantilever Board™, FR-Aquaplast/Qfix, Avondale, PA, USA), (b) A base plate designed for proton irradiations (AccuFix BoS™Frame, FR-Aquaplast/Qfix, Avondale, PA, USA).

An additional issue in thermoplastic mask usage is the choice of the base plate. For particle therapy applications, such device should exhibit high rigidity and radiological homogeneity (the latter applies also to other accessories like head supports, etc. if they should find themselves in the irradiation field) [24, 96] and, for proton treatments, allow patient setup as close as possible to the treatment nozzle (see Figure 4 (b)).

### 3.1.3 Precision of cranial immobilization systems

The review of publications regarding the repositioning precision of the systems outlined above is summarized in Table 1. Mostly papers reporting the results in terms of mean ±standard deviation have been selected (as it was the predominant way of reporting). Exceptions were made for three papers directly comparing different systems (Tryggestad *et al.* [152], van Santvoort *et al.* [164] and Gilbeau *et al.* [48]) and for one study carried out in the framework of the ULICE project (Reza Homayuni [70]), all using the concept of systematic and random error in reporting. In general, the discrepancy between the localizer-based setup (stereotactic reference system or treatment room lasers for non-stereotactic systems) and image guided setup is reported as the measure of the system’s accuracy and precision. Typically, only one system was available at each institution, hence only a few studies provide direct comparisons of various immobilization systems. Moreover, there is a considerable variability in the methods used for such assessments. Among the most commonly found imaging methods are megavoltage or kilovoltage portfilm images (MVPI, kVPI), simulation films, 3D X-ray
Table 1: Review of the published data on inter-fraction accuracy and reproducibility of cranial immobilization systems.\(^8\)

<table>
<thead>
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<th>PUBLICATION</th>
<th>METHODS</th>
<th>no of patients / no of images immobilization</th>
<th>accuracy/reproducibility [mm] mean ± std dev or (\sigma)</th>
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<td></td>
<td></td>
<td>AP</td>
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<td><strong>stereotactic thermoplastic mask</strong></td>
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<tr>
<td>Verbakel 2010 [173]</td>
<td>4p/135 STP mask (BrainLab)</td>
<td>kVOBI</td>
<td>-0.5±0.7</td>
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<tr>
<td>Ali 2010 [2]</td>
<td>8p/50 STP mask (Brain Lab)</td>
<td>kVOBI</td>
<td>-1.1±0.9</td>
</tr>
<tr>
<td>Minniti 2010 [110]</td>
<td>16p/64 STP mask (BrainLab) + UJS</td>
<td>CT</td>
<td>0.1±0.4</td>
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<tr>
<td>16p/456 STP mask (BrainLab) + UJS(^2)</td>
<td>EPI</td>
<td>-0.2±1.0</td>
<td>0.2±1.1</td>
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<td>Pasquier 2009 [123](^7)</td>
<td>25p/11 STP mask (BrainLab) + UJS</td>
<td>CT</td>
<td>0.1±0.5</td>
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<tr>
<td>Bednarz 2009 [13]</td>
<td>32p/714 GTC frame (BB)</td>
<td>kVOBI</td>
<td>2.0±1.0*</td>
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<td>37p/782 STP mask (BrainLab)</td>
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<tr>
<td>Hong 2009 [71]</td>
<td>13p/309 STP mask (BrainLab) + UJS</td>
<td>kVOBI</td>
<td>0.0±0.9</td>
</tr>
<tr>
<td>van Santvoort 2008 [164]</td>
<td>20p/1122 STP mask (BrainLab) + UJS</td>
<td>kVOBI</td>
<td>0.5(0.8)</td>
</tr>
<tr>
<td>20p/1122 STP mask (BrainLab) + VMP</td>
<td>kVOBI</td>
<td>0.5(0.5*)</td>
<td>1.1(1.0*)</td>
</tr>
<tr>
<td>Solberg 2008 [143]</td>
<td>37p/565 stereotactic mask</td>
<td>kVOBI</td>
<td>0.2±1.3</td>
</tr>
<tr>
<td>35p/ rigid stereotactic mask</td>
<td>kVOBI</td>
<td>0.2±0.8</td>
<td>0.1±0.6</td>
</tr>
<tr>
<td>Jin 2006 [80]</td>
<td>12p/127 STP mask (BrainLab) + UJS</td>
<td>kVOBI</td>
<td>0.9±1.0</td>
</tr>
<tr>
<td>Baumert 2005 [10]</td>
<td>17p/50 STP mask (BrainLab) + BB</td>
<td>CT</td>
<td>-0.1±0.8</td>
</tr>
<tr>
<td>35p/57 STP mask (BrainLab) + UJS</td>
<td>kVOBI</td>
<td>-0.6±1.4</td>
<td>1.5±2.6</td>
</tr>
<tr>
<td>5p/7 STP mask (BrainLab)</td>
<td>kVOBI</td>
<td>-0.7±1.4</td>
<td>1±1.3</td>
</tr>
<tr>
<td>Lopatta 2003 [104]</td>
<td>11p/weekly STP mask (BrainLab)</td>
<td>kV</td>
<td>±0.9</td>
</tr>
<tr>
<td>18p/weekly STP mask (BrainLab) + UJS</td>
<td>kV</td>
<td>±0.6*</td>
<td>±0.5*</td>
</tr>
<tr>
<td>Willner 1997 [174]</td>
<td>16p/22 STP mask (BrainLab)</td>
<td>CT</td>
<td>0.1±1.2</td>
</tr>
<tr>
<td><strong>bite block / vacuum mouthpiece</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kunieda 2009 [90]</td>
<td>15p/72 HeadFix (VMP)</td>
<td>CT</td>
<td>0.7±0.5</td>
</tr>
<tr>
<td>Kumar 2005 [89]</td>
<td>15p/123 GTC frame (BB)(^7)</td>
<td>EPI</td>
<td>-0.2±1.0</td>
</tr>
<tr>
<td>Olch 2002 [120]</td>
<td>13p/156 HeadFix frame (VMP)</td>
<td>PI</td>
<td>1.8±0.6</td>
</tr>
<tr>
<td>Sweeney 2001 [148]</td>
<td>4p/95 HeadFix frame (VMP)</td>
<td>EPI</td>
<td>1.9±1.2</td>
</tr>
<tr>
<td>Rosenberg 1999 [131]</td>
<td>10p/19 CTG frame (BB)</td>
<td>kV</td>
<td>1.1±0.6</td>
</tr>
<tr>
<td>Rosenthal 1995 [132]</td>
<td>8p/18 TP mask + BB</td>
<td>PI</td>
<td>0.1±1.1</td>
</tr>
<tr>
<td><strong>scotch cast mask</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Guckenberger 2007 [58]</td>
<td>12p/1 SC mask (Leibinger)</td>
<td>CT</td>
<td>3.0±1.7</td>
</tr>
<tr>
<td>8p/3-point TP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boda 2006 [19]</td>
<td>14p/daily SC mask (Leibinger)</td>
<td>CBCT</td>
<td>0.0±1.7</td>
</tr>
<tr>
<td>7p/daily 3-point TP</td>
<td></td>
<td></td>
<td>-1.5±2.8</td>
</tr>
<tr>
<td>Gross 2003 [56](^1)</td>
<td>41p/1 SC mask (Leibinger)</td>
<td>PI</td>
<td>0.6±0.7</td>
</tr>
<tr>
<td>Karger 2001 [84](^2)</td>
<td>4p/52 SC mask (Leibinger)</td>
<td>kV</td>
<td>1.2±0.3</td>
</tr>
<tr>
<td>Kortmann 1999 [87]</td>
<td>20p/400 SC mask (Leibinger)</td>
<td>PI</td>
<td>0.7±0.6</td>
</tr>
</tbody>
</table>

Continued on next page
localization techniques, analysis of surface external registration points, CT scout images or volumetric CT/CBCT data sets.

**Stereotactic mask vs bite block**

Reported 3D repositioning reproducibility for stereotactic thermoplastic mask head immobilization systems ranges widely from as low as 0.5±0.4 mm to 3.7±2.8 mm (see Table 1 on the preceding page) and precision of bite block based systems from 0.7±0.5 mm to 2.3±1.6 mm. The published data on the less widespread scotch cast masks is within 1.5±0.8 mm and 3.1±1.5 mm.

Three studies directly comparing the use of a stereotactic thermoplastic mask with or without mouth piece [10, 164] or with GTC frame (only bite block) [13] report statistically significant improvement of immobilization by means of the mouth piece. The reported intra-fraction stability of these two systems is comparable (see Table 2 on the next page).

**Thermoplastic mask vs stereotactic systems**

In two studies by Guckenberger *et al.* [58] and by Boda *et al.* [19] the accuracy of 3-point thermoplastic masks was directly compared with stereotactic masks and scotch cast type masks demonstrating a slight advantage of the scotch cast mask (4.6±2.1 mm vs 3.0±1.7 mm and 4.7±1.7 mm vs 3.1±1.5 mm). However, the accuracy of thermoplastic masks reported in these two works is lower than reported by other authors (from 1.6±0.8 to 3.2±1.5 mm).

Two works addressed the possible improvement of thermoplastic mask precision by adding a bite
block [107] and individual head support [43] not yielding however statistically significant effect. In a paper by Tryggestad et al. [152], four immobilization systems for cranial irradiations, including long masks, have been compared and an advantage of the 5-point mask with a mouth piece in combination with an individual head rest has been shown.

An improved immobilization by means of enhancing conventional thermoplastic masks, has also been reported in the framework of the ULICE project and as preparatory work for the upcoming combined proton/carbon ion therapy center (MedAustron), by the Medical University of Vienna (WP5 member). At the Department of Radiotherapy of the MUW a novel variation of a commercially available mask system (HeadSTEP™, Elekta, Crawley, UK) was implemented. Double-layered thermoplastic material was applied for individualization of the masks as well as an integrated upper jaw fixation (BiteSTEP™, Elekta, Crawley, UK) decreasing rotational degrees of freedom around the cranio-caudal axis. The new approach consisted of additional patient’s head immobilization by fixing specific anatomic regions prone to motion, i.e. forehead, nasal area and lower jaw. Further stabilization was facilitated by the addition of thermoplastic material (Adapt-IT™thermoplastic pellets, WFR-Aquaplast/Qfix, Avondale, PA, USA) to the latter regions. Investigations utilizing CBCT on a group of 21 patients (10 of which using the reinforced masks) revealed that statistically significant reduction of uncertainties could be achieved when applying such additional fixation [70].

Table 2: Review of the published data on intra-fraction accuracy/reproducibility of cranial immobilization systems.\(^{†}\)

<table>
<thead>
<tr>
<th>PUBLICATION</th>
<th>no of patients / no of images immobilization</th>
<th>accuracy/reproducibility [mm]</th>
<th>AP</th>
<th>SI</th>
<th>LR</th>
<th>3D</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>stereotactic thermoplastic mask</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verbakel 2010 [173]</td>
<td>43p/79 STP mask (BrainLab)</td>
<td>kVOBI</td>
<td>-0.1±0.2</td>
<td>0.0±0.3</td>
<td>0.0±0.2</td>
<td>0.4±0.2</td>
</tr>
<tr>
<td>Ramakrishna 2010 [127]</td>
<td>7p/110 STP mask (BrainLab)</td>
<td>kVOBI</td>
<td>0.7±0.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lamba 2009 [92]</td>
<td>79p/214 STP mask (BrainLab)</td>
<td>kVOBI</td>
<td>0.1±0.3</td>
<td>0.1±0.5</td>
<td>0.1±0.3</td>
<td>0.5±0.3</td>
</tr>
<tr>
<td>Hong 2009 [71]</td>
<td>6p/28 STP (BrainLab) mask + UJS</td>
<td>kVOBI</td>
<td>0.1±0.8</td>
<td>0.0±1.3</td>
<td>0.4±1.0</td>
<td></td>
</tr>
<tr>
<td>van Santvoort 2008 [164]</td>
<td>20p/400 STP mask (BrainLab) + UJS</td>
<td>kVOBI</td>
<td>0.1(0.7)</td>
<td>0.3(1.0)</td>
<td>0.2(0.3)</td>
<td>0.6(0.6)</td>
</tr>
<tr>
<td></td>
<td>20p/400 STP mask (BrainLab) + VMP</td>
<td>kVOBI</td>
<td>0.1*(0.4*)</td>
<td>0.1*(0.3*)</td>
<td>0.2(0.3)</td>
<td>0.4*(0.4)</td>
</tr>
<tr>
<td><strong>bite block / vacuum mouthpiece</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ruschin 2010 [135]</td>
<td>12p/333 eXtend (BB)</td>
<td>CBCT</td>
<td>0.1(0.2)</td>
<td>0.2(0.4)</td>
<td>0.2(0.2)</td>
<td>0.4±0.3</td>
</tr>
<tr>
<td>Bolsi 2008 [22] (^1)</td>
<td>56p/daily BB</td>
<td>scout</td>
<td>0.2±1.3</td>
<td>-0.5±1.8</td>
<td>-0.1±1.0</td>
<td></td>
</tr>
<tr>
<td>Rosenthal 1995 [132]</td>
<td>5p/20 TP mask + BB</td>
<td>PI</td>
<td>0.3±0.4</td>
<td>0.0±0.5</td>
<td>-0.4±0.5</td>
<td>0.9±0.4</td>
</tr>
<tr>
<td>Masi 2008 [107]</td>
<td>33p (TP mask + BB or TP)</td>
<td>CT</td>
<td>0.0±0.6</td>
<td>0.1±0.6</td>
<td>0.2±0.6</td>
<td></td>
</tr>
</tbody>
</table>

\(^{†}\) - all abbreviations used in the table explained in section List of abbreviations and definitions

\(^1\) - Paul Scherrer Institute, Villigen, Switzerland

\(*\) - statistically significant difference
3.1.4 Summary and recommendations

All modern non-invasive head immobilization systems offer reproducibility within 1-2 mm, although review of the literature suggests a slight advantage of the bite block systems over the stereotactic mask systems and little improved fixation of the latter when compared to plain thermoplastic masks. Where possible, the use of a bite block or a stereotactic mask system is therefore recommended. However, due to additional factors, e.g. the frame limiting the irradiation directions, sharp edges within the irradiation field introducing particle range uncertainties, CT artefacts or patient’s non-compliance, the use of a thermoplastic mask is sometimes indispensable. More frequent imaging to verify the setup is recommended in treatments conducted with simple thermoplastic masks. The reproducibility of the head tilt obtained with thermoplastic masks can be improved by application of custom mouth pieces attached directly to the mask (as opposed to frame based bite blocks).

Care must be taken in choosing a particular system to:

- ensure reproducible placement of the patient on the couch (through an indexing system), in particular if an absolute positioning procedure is planned
- allow patient setup as close as possible to the treatment nozzle in proton treatments
- avoid the presence of any objects in the way of the irradiation beam or if it is necessary, assure its radiological homogeneity (base plate, head supports, etc.) [24, 96]
- achieve reduction of the systematic error, e.g. the planning CT scan should therefore be acquired at least 24 h after the moulding to limit the influence of mask material shrinkage
- obtain reproducibility of immobilization of the patient through the choice of optimal material (rigidity, limited shrinkage) as well as development of guidelines on the mask moulding procedure (adjusting the mask to the patients facial features, assuring reproducible head “nod” and neck curvature).
3.2  Head-and-neck treatments

3.2.1  Indication-specific positioning issues and relevance to particle therapy

Radiotherapy of tumors in the head and neck region often requires concave dose distributions with sharp dose gradient towards the critical organs. To assure a precise delivery of these sharp dose gradients, an accurate patient positioning and immobilization is required. Patients with extracranial tumors are more commonly immobilized using less-invasive techniques ensuring an acceptable level of comfort and patient compliance. However, the design of immobilization devices must ensure adequate rigidity for maximal immobilization.

The main difficulty in head-and-neck immobilization stems from the neck’s flexibility. Unlike the case of cranial treatments, a reliable surrogate of patient position does not always exist. If the immobilization device is not rigid enough and does not fix the patient’s neck adequately, considerable misalignment may occur including: head rotation, “nodding movement”, deformation of the neck flexion [46]. Furthermore, the shoulder positioning is very variable which, for some patients with the target volume extending far caudally, may be dosimetrically important.

For instance, the immobilization device in use may provide stable fixation of the head, but still leave relative freedom of movement to the cervical spine region. As a consequence, the applied setup correction, typically based on rigid matching to the cervical vertebrae, may introduce a positioning error in the cranial region. On account of this, in compiling the review of immobilization solutions for head-and-neck treatment, particular attention was given to studies investigating immobilization reproducibility through modern piecewise-deformable approaches.

In Figure 5 the (simulated) case is presented of a head-and-neck patient displaying a 2 mm LR shift only at the cranial end of the target volume (in the nasopharyngeal region). The carbon ion treatment plan (a) created with TRiP98 [88] was recomputed on the deformed CT (b). Target coverage is visibly affected.

![Figure 5: Dosimetric effects of imperfect immobilization on head-and-neck treatment with carbon ions: (a) original dose distribution (planning CT), (b) treatment plan recomputed on an artificially deformed CT (2 mm LR shift introduced at the level of the nasopharynx).](image-url)
Figure 6: Dosimetric effects of treatment-induced anatomical changes, e.g. weight loss and tumor regression, in carbon ion treatments for head and neck: (a) a planned dose distribution at the neck level on the original treatment plan (planning CT), (b) the treatment plan on the left recomputed on a verification CT, in presence of noticeable weight loss, showing considerable target underdosage, (c) another planned dose distribution at the nasopharynx level on the original treatment plan (planning CT), (d) the treatment plan on the left recomputed on a verification CT, in presence of noticeable tumor regression, showing considerable negative effects in terms of target coverage and healthy tissue involvement.

Moreover, even in presence of optimal immobilization to ensure a highly reproducible patient bony setup, head and neck irradiations are often characterized by changes in the soft tissue, like swelling caused by chemotherapeutic drugs, congestion/decongestion of involved mucosae and, last but not least, the (desired) reduction of the tumor mass. The dosimetric relevance of these effects for radiotherapy with protons and carbon ions is under investigation at the Department of Radiotherapy and Radiation Oncology of the UKGM and has been addressed through some planning tests based on repeated CTs of IMRT patients [6]. Two examples are visible in Figure 6: in the upper row the possible effects on dose delivery of weight loss are shown, while in the lower row the effects of the regression of a tumor, extending in the cranial direction to the nasopharynx are presented. In both cases the original plans created with TRiP98 (left column), once recomputed on verification CTs acquired towards the end of the treatment course (right column), present visible negative effects in terms of target coverage and, for the lowermost, also of healthy tissue involvement.

In appreciation of these issues, recommendations about the frequent use of imaging, possibly leading
to the adaptation of immobilization devices and treatment plans, were added in the remainder of the chapter.

The PubMed database was searched systematically with following key words and their permutations: “patient immobilization”, “radiotherapy”, “stereotactic mask”, “thermoplastic mask”, “bite block” and publications regarding head-and-neck immobilization were selected.

### 3.2.2 Immobilization devices for head-and-neck irradiations

#### Stereotactic masks

Similarly to cranial irradiations, stereotactic mask systems have been applied for head and neck immobilization. In order to assure reproducible neck flex, such systems are combined with individualized evacuated pillows or vacuum moulds [51].

#### Thermoplastic masks

Owing to their non-invasive nature, ease of fabrication and fast setup, thermoplastic masks are the most common system for immobilization of head-and-neck patients. However, care must be taken to minimize the effects of shrinkage, which is one of the disadvantages of thermoplastic materials.

![Examples of different materials and fixation systems for head-and-neck immobilization masks](image)

*Figure 7:* Examples of different materials and fixation systems for head-and-neck immobilization masks: (a) high-temperature mouldable continuous material and (b) low-temperature mouldable perforated material with 5-independent push-pin fixation bars (Unger Medizintechnik, Mühlheim-Kärlich, Germany) tested at the Department of Radiotherapy and Radiation Oncology of the UKGM [77], (c) perforated material with rigid fixation frame (Civco Medical Solutions, Kalona, Iowa, USA).

![Two solutions for the immobilization of the head-and-neck region](image)

*Figure 8:* Two solutions for the immobilization of the head-and-neck region: (a) a “full-length” head-and-neck thermoplastic mask (b) combination of a head-only thermoplastic mask with a “bear claw” shoulder depressor (WFR-Aquaplast/Qfix, Avondale, PA, USA)[134].
Various solutions have been commercialized employing different materials (perforated/solid) of varying thickness and various fixation systems (Figure 7 on the preceding page). Precuts of thermoplastic material of various shapes are offered: short ones, depending on their fixation to the base plate referred to as 3-point or U-frame masks and long, 4-point/5-point masks or S-frame masks. The former one immobilize only the head while the latter two extend to include the shoulders. These masks, moulded to the patient’s facial features (nasion, chin), around the neck and covering the patient’s shoulders are applied in combination with different head support solutions (standardized or individually moulded) to provide the stability against misalignment and rotations of the head, but also reduce the variation in neck flexion and shoulder position. Bite block frames are not commonly used in head-and-neck treatments, where the target volume extends below the level of the mandible. However, thermoplastic masks with mouth moulds are available.

Thermoplastic mask solutions in general are designed as a trade-off between patient comfort and stability of the immobilization, understood mostly as malleability during the moulding procedure in order to precisely encompass significant anatomic landmarks and rigidity of the moulded and hardened mask. For conventional therapy, the general trend is to use relatively thin (in the order of 2 mm) and perforated thermoplastic sheets to mould masks, in order to minimize the shrinking effect all thermoplastic materials are subject to when cooling down. Regular perforated masks can contain as little as 60% of the original material, significantly reducing the shrinking effect but possibly hindering the immobilizing ability of the mask. Therefore at the Department of Radiotherapy and Radiation Oncology of the UKGM, along with perforated mask, non-perforated masks are being tested in preparation for the upcoming Particle Therapy Center [77], although conclusive results are not yet available. A recently introduced Kevlar® (WFR-Aquaplast, Wyckoff, NJ, USA) among the material’s components supposedly reduces the shrinking effect and improves rigidity at the same time.

Similarly to the case of cranial irradiations, the base plate employed together with the mask system, should exhibit high rigidity and radiological homogeneity (the latter applies also to other accessories like head supports, etc. if they should find themselves in the irradiation field) [24, 96] and, for proton treatments, allow patient setup as close as possible to the treatment nozzle (Figure 4 on page 12 (b)).

**Head supports / vacuum pillows / shoulder depression systems / hand grip arrays**

A variety of additional equipment like head rests (standardized and individually moulded), vacuum pillows and full body vacuum moulds can be used together with the thermoplastic masks to limit the variability of the neck position (Figure 9). Modern immobilization boards enable additionally appli-
cation of indexed shoulder depression systems like “bear-claw” or hand grips to achieve reproducible placement of the patient’s shoulders (Figure 8).

### 3.2.3 Precision of immobilization solutions for head-and-neck treatments

The available data on inter- and intra-fraction setup errors in head-and-neck treatments are summarized in Table 3 and Table 4 on the next page.

**Table 3:** Review of the published data on inter-fraction accuracy and reproducibility of immobilization for head-and-neck treatments.Ⅵ

<table>
<thead>
<tr>
<th>PUBLICATION</th>
<th>METHODS</th>
<th>no of patients / no of images immobilization</th>
<th>accuracy/reproducibility [mm]</th>
<th>mean ± std dev or $\Sigma(\sigma)$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>AP</td>
<td>SI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>systematic and random error $\Sigma(\sigma)$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Giske 2010</td>
<td>45p/488</td>
<td>SC mask + vacuum cushion CT</td>
<td>1.1(1.2)</td>
<td>1.3(1.1)</td>
</tr>
<tr>
<td>Houweling 2010</td>
<td>10p/weekly</td>
<td>5-point TP mask + SHR CBCT</td>
<td>3.1(1.8)</td>
<td>1.3(1.4)</td>
</tr>
<tr>
<td></td>
<td>12p/weekly</td>
<td>5-point TP mask + IHR CBCT</td>
<td>1.9(0.9)</td>
<td>1.7(0.9)</td>
</tr>
<tr>
<td>Velec 2010</td>
<td>11p/daily</td>
<td>5-point TP mask (Aquaplast) CBCT</td>
<td>1.0(1.6)</td>
<td>1.0(1.5)</td>
</tr>
<tr>
<td>Schubert 2009</td>
<td>30p/839</td>
<td>TP mask MVCT</td>
<td>1.6(1.9)</td>
<td>1.9(1.9)</td>
</tr>
<tr>
<td>Vaandering 2009</td>
<td>75p/daily</td>
<td>5-point TP mask (Sinmed) MVCT</td>
<td>1.5(1.5)</td>
<td>1.6(1.5)</td>
</tr>
<tr>
<td>Bolsi 2008</td>
<td>28p/daily</td>
<td>TP mask + vacuum cushion scout CT</td>
<td>1.9(3.1)</td>
<td>2.3(3.4)</td>
</tr>
<tr>
<td>Li 2008</td>
<td>10p/50</td>
<td>5-point TP mask + SHS CBCT</td>
<td>1.8(1.4)</td>
<td>1.9(1.4)</td>
</tr>
<tr>
<td></td>
<td>11p/50</td>
<td>5-point TP mask + IHS CBCT</td>
<td>0.8(1.8)*</td>
<td>0.6(1.9)</td>
</tr>
<tr>
<td>Gupta 2007</td>
<td>25p/93</td>
<td>TP mask EPI</td>
<td>1.0(1.9)</td>
<td>1.2(2.5)</td>
</tr>
<tr>
<td>Polat 2007</td>
<td>11p/100</td>
<td>in 3-point TP mask CBCT</td>
<td>1.6(1.6)</td>
<td>1.3(1.4)</td>
</tr>
<tr>
<td>Oita 2006</td>
<td>8p/175</td>
<td>TP mask + IHS kVOBI</td>
<td>1.1(1.6)</td>
<td>1.6(1.4)</td>
</tr>
<tr>
<td>Donato 2006</td>
<td>10p/136</td>
<td>plastic mask (Uvex) EPI</td>
<td>2.6(1.9)</td>
<td>1.6(3.8)</td>
</tr>
<tr>
<td>Humphreys 2005</td>
<td>21p/354</td>
<td>PVC shell EPI</td>
<td>1.1(0.7)</td>
<td>0.9(0.6)</td>
</tr>
<tr>
<td>van Lin 2003</td>
<td>17p/137</td>
<td>4-point TP mask (Ortfit) + SHS EPI</td>
<td>2.3(1.6)</td>
<td>2.3(1.6)</td>
</tr>
<tr>
<td></td>
<td>19p/147</td>
<td>4-point TP mask (Ortfit) + IHS EPI</td>
<td>1.4*(1.0)</td>
<td>1.2*(1.1)</td>
</tr>
<tr>
<td>de Boer 2001</td>
<td>31p/180</td>
<td>PVC cast EPI</td>
<td>1.6(1.6)</td>
<td>2.1(1.4)</td>
</tr>
<tr>
<td>Gilbeau 2001</td>
<td>10p/weekly</td>
<td>3-point TP mask (head) EPI</td>
<td>1.0(0.7)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10p/weekly</td>
<td>4-point TP mask (head) EPI</td>
<td>0.8(0.9)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10p/weekly</td>
<td>5-point TP mask (head) EPI</td>
<td>0.9(1.0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10p/weekly</td>
<td>3-point TP mask (neck) EPI</td>
<td>0.8(0.9)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10p/weekly</td>
<td>4-point TP mask (neck) EPI</td>
<td>1.0(1.0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10p/weekly</td>
<td>5-point TP mask (neck) EPI</td>
<td>2.2(1.0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10p/weekly</td>
<td>3-point TP mask (shoulders) EPI</td>
<td>1.2(2.3)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10p/weekly</td>
<td>4-point TP mask (shoulders) EPI</td>
<td>1.1(0.8)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10p/weekly</td>
<td>5-point TP mask (shoulders) EPI</td>
<td>1.1(1.2)</td>
<td></td>
</tr>
<tr>
<td>Willner 1997</td>
<td>29p/136</td>
<td>BB PI</td>
<td>1.9(2.0)</td>
<td>1.8(1.9)</td>
</tr>
<tr>
<td>Hunt 1993</td>
<td>6p/10</td>
<td>TP mask PI</td>
<td>1.7(2.2)§</td>
<td>0.8(1.6)§</td>
</tr>
</tbody>
</table>

Continued on next page
### Table 3 – continued from previous page

<table>
<thead>
<tr>
<th>METHODS</th>
<th>accuracy/reproducibility [mm]</th>
<th>PUBLICATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>immobilization</td>
<td>mean ± std dev or ( \Sigma(\sigma) )</td>
<td>no of patients / no of images</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Velc 2010 [166]
- 1p/daily 5-point TP mask (Aquaplast)
  - CBCT: ±1.7 ±1.6 ±1.7

#### Murthy 2008 [113]
- 20p/143 (TP Ortfit)
  - EPI: 1.2±1.1 1.3±1.5

#### Rotondo 2008 [134]
- 10p/30 S-TP mask (upper)
  - CT: ±1.8 ±2.5 ±1.7
- 11p/34 U-TP maks + bear-claw (upper)
  - ±2.0 ±5.8 ±1.2
- 10p/30 S-TP mask (lowers)
  - ±6.4 ±1.7 ±4.9
- 11p/34 U-TP mask + bear-claw (lower)
  - ±6.0 ±4.6 ±6.4

#### Li 2007 [95]
- 37p/daily TP mask
  - MVCT: 0.2±1.3 0.1±2.2 0.3±1.2

#### Gupta 2007 [59]
- 25p/93 TP mask
  - EPI: -0.3±3.1 0.5±3.4 -0.5±2.6 3.8 (avr)

#### Boda 2006 [19]
- 14p/3-point TP mask
  - CBCT: 1.8±4.8 2.3±2.4 -1.6±2.1 5.9±2.9
- 7p/3-point TP mask
  - 1.4±3.9 4.1±5.2 2.1±3.0 7.3±4.5

#### Oita 2006 [119]
- 8p/175 TP mask + IHS
  - kVOBI: 0.9±1.6 -0.3±2.0 0.1±2.2 3.3±1.6

#### Linthout 2006 [97]
- 13p/385 5-point TP mask (all)
  - kVOBI: -0.2±2.0 0.5±2.4 0.5±1.5
  - - 2.0 mm thickness: 0.0±2.1 0.6±1.7 0.3±1.6
  - - 1.6 mm thickness, micro perforation: -1.3±1.5 2.2±1.7 0.5±0.9 *b
  - - 2.4 mm thickness, micro perforation: 0.5±1.4 -3.8±3.4 1.8±1.5 *b

#### Willner 1997 [174]
- - 29p /136 BB
  - PI: -0.6±2.7 0.0±2.5 0.6±3.1 4.2 (avr)

#### Weltens 1995 [172]
- 10p/100 TP mask (Ortfit)
  - PI/EPI: ±2.2 ±2.3

#### Hunt 1993 [75]$^5$
- 6p/10 TP mask
  - PI: 0.3±1.7 0.6±0.8 -2.1±1.8

---

$^\S$ - all abbreviations used in the table explained in section List of abbreviations and definitions

*a* - statistically significant difference

*$^b$ - based on ranges

### Table 4: Review of the published data on intra-fraction accuracy and reproducibility of immobilization for head-and-neck treatments

<table>
<thead>
<tr>
<th>METHODS</th>
<th>accuracy/reproducibility [mm]</th>
<th>PUBLICATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>immobilization</td>
<td>mean ± std dev or ( \Sigma(\sigma) )</td>
<td>no of patients / no of images</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Houweling 2010 [73]
- 10p/weekly 5-point TP mask + SHR
  - CBCT: (1.1) (0.8) (0.9)

#### Velc 2010 [166]
- 12p/weekly 5-point TP mask + IHR
  - CBCT: 0.9(0.4) (0.5) (0.3)*
- 11p/weekly 5-point TP mask (Aquaplast)
  - ±1.0 ±0.9 ±0.8
  - 0.7 (0.8) 0.5 (0.7) 0.3 (0.8)

#### Bolsi 2008 [22]
- 28p/daily TP mask + vacuum cushion
  - scout: 1.4±2.4 -0.1±2.1 -0.4±2.4

#### Oita 2006 [119]
- 8p/175 TP mask + IHS
  - kVOBI: 0.6(1.9) 0.5(2.0) 0.2(1.0) 0.7(2.5)

#### Linthout 2006 [97]
- 13p/385 5-point TP mask (all)
  - kVOBI: -0.5±1.2 0.3±0.7 0.0±0.7
  - - 2.0 mm thickness: -0.3±1.0 0.3±0.6 0.0±0.5
  - - 1.6 mm thickness, micro perforation: -0.1±1.5 0.0±0.8 0.5±0.9
  - - 2.4 mm thickness, micro perforation: -1.3±1.2 1.0±0.9 -0.3±0.8

---

$^\S$ - all abbreviations used in the table explained in section List of abbreviations and definitions

* - statistically significant difference
The majority of the original studies investigating setup errors for head-and-neck treatments relied on a rigid alignment of the control images to the reference ones. The setup uncertainties reported in selected publications are usually expressed as three separate components (AP, SI and LR directions). Expressed as the standard deviation of pooled measurements the reproducibility of thermoplastic head-and-neck masks is in the order of 1-2 mm ranging from 1.1 to 3.6 mm in AP, from 0.8 to 5.2 mm in SI and from 0.9 to 3.0 mm in LR direction. The random errors (as defined by van Herk [159]) are ranging: 0.7-3.1 mm, 0.6-3.4 mm and 0.4-3.1 mm in AP, SI and LR direction respectively. Three studies [73, 93, 162] showed that the application of individually moulded, rather than standard, head rests reduces the setup uncertainties, in particular in anterior-posterior direction, likely through stabilization of the neck curvature. However, several works signaled differences in measured setup errors depending on the chosen landmarks [134, 126, 48].

Detailed studies employing piecewise deformable analysis have shown substantial changes in the head-and-neck anatomy resulting in significantly larger local misalignment errors. The figure 10 illustrates that the local systematic error increases in caudal direction highlighting the need to immobilize the vertebral column observed in different patient cohorts [51, 73, 160]. Systematic and random errors of the position relative to C1-C3 vertebrae of up to 2.54(2.1) mm in the region of the mandible [73] and up to 3.5(4.2) mm in the caudal cervical and cranial thoracic spine have been reported [51]. Note that in the study by Giske at al. [51] patients were immobilized with stereotactic scotch cast mask combined with a full body vacuum cradle, while in the remaining three studies, 5-point thermoplastic masks and head rests were used. No significant difference can be observed between immobilization
with the long thermoplastic masks and with the scotch cast mask (head only), provided that care was taken to ensure a good imprint of the shoulders and reproducible positioning of the patient within the vacuum device (here: tattoos placed on both shoulders). The effect of the individualized head support as compared to the standard one can be observed as the reduction of the systematic uncertainty in the skull base position in AP direction as observed by Houweling *et al.* [73]. The figure 10 suggests also that a mouthpiece would be helpful to control inclination of the head (which can be important for patients with an invasion of the base of the skull).

A similar study was conducted at the Department of Radiotherapy and Radiation Oncology of the UKGM based on piecewise deformable registration of daily portal images acquired in 12 IMRT patients performed with use of an in-house developed matching software [18, 3], to assess the accuracy of the mask system intended for the upcoming Particle Therapy Center (see figure 10). Additionally the usability and acceptance of the system by the patients were assessed in the clinical routine [77].

### 3.2.4 Summary and recommendations

The most common immobilization solutions for head-and-neck are based on thermoplastic masks immobilizing the patient’s head and applied in combination with various solutions to ensure reproducible placement of neck and shoulders. Although the overall reported precision of such systems is in the order of 1-2 mm in each direction (2-3 mm 3D), detailed studies have revealed significantly larger, semi-independent local deviations, e.g. in the region of mandible and caudal cervical spine.

It is recommended, therefore, to use a rigid thermoplastic material in combination with carefully chosen head rests, possibly individually formed and shoulder depression systems or vacuum moulds suppressing shoulder position variability. Similarly to cranial irradiations the reproducibility of the head tilt can be significantly improved by application of a moulded mouth piece attached directly to the mask (as opposed to a frame based bite block) [181].

Care must be taken in choosing a particular system to:

- ensure reproducible placement of the patient on the couch (through an indexing system), in particular if an absolute positioning procedure is planned;
- achieve reduction of the systematic error, e.g. the planning CT scan should therefore be acquired at least 24 h after the moulding to limit the influence of mask material shrinkage
- allow patient setup as close as possible to the treatment nozzle in proton treatments
- avoid the presence of any objects in the way of the irradiation beam or if it is necessary, assure its radiological homogeneity (base plate, head supports, etc.) [24, 96]
- obtain reproducibility of immobilization of the patient through the choice of optimal material (rigidity, limited shrinkage) as well as development of guidelines on the mask moulding procedure (adjusting the mask to the patients facial features, assuring reproducible head “nod” and neck curvature);

Additionally, head-and-neck patients show substantial anatomical changes caused by edema, tumor regression and weight loss in the course of treatment. These systematic changes should be controlled over the time of the fractionated treatment by repeated imaging and in case of considerable anatomy change hindering the position reproducibility, the immobilization devices should be readjusted or remade. In critical cases, when moulding of new immobilization devices is required (e.g. new thermoplastic mask), clearly, also a new treatment plan will be prepared. This effectively counteracts
also dosimetric issues related e.g. to tumor mass reduction, like those exemplified in the introductory section (see Figure 6 on page 18). Prospective CT imaging is therefore desirable during a course of precision radiotherapy for head-and-neck cases to appraise such changes as they can considerably influence the spatial dose distribution even if positioning of the isocenter is correct during each fraction.


3.3 Lower abdomen / pelvis

3.3.1 Indication-specific positioning issues and relevance to particle therapy

Two types of positioning errors can be distinguished in pelvic irradiations: (1) setup uncertainties and (2) internal target movement. Furthermore, the target localization within the patient body can vary both, between the (daily) fractions as well as during each irradiation session. These two types of position variability are referred to as inter- and intra-fraction motion and have been traditionally addressed separately.

The setup errors can be limited with appropriate external immobilization, and the residual uncertainties can be incorporated into CTV-to-PTV margin, but internal target movement (e.g. caused by peristaltic movement, different bladder and rectum filling, etc.) can be mitigated only indirectly. Unlike in photon treatments, where the internal target displacement can be compensated by patient realignment, in particle therapy a risk exists that such re-alignment may lead to a significant change in the Bragg peak depth and therefore to an undesirable dose distribution deterioration.

For instance, in Figure 11, taken from one of the studies on dosimetric stability of carbon ion treatments performed at the Department of Radiotherapy and Radiation Oncology of the UKGM [79], possible consequences of patient re-positioning (after target localization) are shown for two prostate plans prepared with TRiP98 [88]. For the original plan in (a), a setup correction, aimed at compensating a target movement in AP direction, generated cold spots because of the inadequate PTV-to-CTV margin (see (b)). In a similar scenario, the plan in (c), prepared with an adequate safety margin, preserved CTV coverage with the prescribed dose, even after patient repositioning (see (d)).

**Figure 11:** Simulated treatment of a prostate case (CTV in green) with carbon ions, with different PTV-to-CTV margins, using patient re-positioning based on target localization: (a) close-up of the original plan computed with a 2 mm safety margin (blue contour), (b) consequences on the plan on the left of patient re-positioning aiming at compensating a target movement of 5 mm in AP direction: cold spots have appeared, (c) close-up of the original plan computed with a 5 mm safety margin (orange contour), (b) consequences on the plan on the left of patient re-positioning aiming at compensating a target movement of 10 mm in AP direction: full CTV coverage is still ensured.
Hence, in the treatment of pelvic indications with particle therapy, on-line re-alignment protocols should be applied with caution and reproducibility of irradiation geometry should be assured. For instance, the aforementioned study on the robustness of proton and carbon ion plans for prostate treatment, suggests that, with daily target localization, internal organ movements of up to 7 mm in AP direction and up to 5 mm in LR direction can be compensated by simple patient re-alignment to assure target coverage (SI direction remains insensitive to such corrections) [76]. This requires, though, that the chosen safety margins correctly incorporate the expected uncertainties deriving from target movement. Therefore, in the following, also some considerations on the use of patient preparation protocols and internal immobilization devices (endorectal balloons) are included.

The PubMed search engine was used with the following keywords: “(prostate OR cervix) AND (movement OR positioning) AND (markers OR fiducial) AND radiotherapy”, to identify the relevant publications regarding pelvic immobilization. An additional search was conducted with focus on endorectal balloon as prostate immobilization device. The PubMed query for “rectal balloon prostate radiotherapy” resulted in 45 hits, of which 10 were judged relevant. Additionally, 6 studies known to the authors were included in the comparison.

3.3.2 Immobilization devices for pelvic irradiations

Rigid external immobilization
The most widespread approaches to reduce the setup error in lower abdomen/pelvic treatments are (see Figure 12 on the following page):
- supine on a flat table top with use of knee-support and foot holders
- supine with use of rigid full body shell (vacuum cushion or alpha-cradle) with or without thermoplastic pelvic mask
- supine with use of thermoplastic pelvic mask with foot holders
- prone in rigid full body shell (vacuum cushion or alpha-cradle) with or without thermoplastic pelvic mask
- prone in belly-board (especially rectal cancer irradiations)

One potential problem associated with the use of vacuum cushions for particle therapy comes from the CT reconstruction diameter. Some part of the cushion may lie outside the field of view, possibly leading to erroneous particle range calculation (see Figure 13 on the next page).

Reduction of internal organ motion

Patient preparation
A correlation between the daily variation of the bladder and rectum volumes and the prostate position [129, 32, 151, 140] as well as the uterus and cervix position [23, 149] has been demonstrated by several authors. One method to reduce the internal organ movement is through appropriate patient preparation (drinking protocol, diet, enema) aiming at making organs involved reproducible in volume/shape and to minimize some of the physiological causes of their movement e.g. intestinal gas. Although this can not be viewed strictly as an immobilization technique, it’s efficiency has been reviewed in this study.
Figure 12: Some external immobilization devices for the pelvic region, exemplifying the three major components that can be combined to achieve a reproducible pelvic setup (feet-knees fixation on the left, anatomically shaped pelvic lodging in the middle and fixation to the treatment couch on the right) for both supine (upper row) and prone (lower row) position: (a) indexed knee-feet support (Civco Medical Solutions, Kalona, Iowa, USA), (b) vacuum cushion moulded for the supine position (here complemented with a restraining vacuum sheet) (Elekta, Crawley, UK) [139], (c) pelvic thermoplastic mask for the supine position, (d) feet support used in the prone position [86], (e) belly board for prone patient positioning (Civco Medical Solutions, Kalona, Iowa, USA), (f) pelvic thermoplastic mask for the prone position [106].

Figure 13: A potential issue in the use of vacuum cushions for particle therapy coming from the CT reconstruction diameter: (a) CT slice of a vacuum cushion, reconstructed using a larger diameter, with the typical 50 cm diameter marked by the dashed circle. A significant part of the cushion, possibly important for particle range calculation, lies outside the field of view. (b) Detail of the CT slice (white rectangle) showing how the larger reconstruction diameter geometrically contains the whole cushion, but may produce inaccurate density values (the barely visible outline of the cushion has been marked with a thick white line).
Different types of endorectal balloons (ERB) were reported in the literature. Five of them, commercially available, are shown in Figure 14 [141]. In a direct comparison of three balloon types reported by van Lin at al. [161] patients preferred ERB shown in figure 14 (b) whereas the inflation of ERB shown in figure 14 (c) was painful in 25% of the patients. Technologists instead preferred the ERB in figure 14 (a), as being the easiest to handle and to insert. A review of the literature regarding the accuracy and reproducibility of placement of the balloons will be presented in section 3.3.3.

3.3.3 Precision of pelvic immobilization systems

The majority of published studies regarding patient immobilization in the pelvic area are based on data acquired in prostate treatments. Various methods have been applied to measure the patient setup and internal target position variability, most commonly:

- measurement of bony anatomy / implanted fiducials positions on planar, orthogonal portal images (EPIs or port films)
- measurement of bony anatomy / implanted fiducials positions in repeated CTs
- direct measurement of bony anatomy / prostate position in repeated CTs
- measurement of the prostate position with help of dedicated ultrasonographic (US) apparatus

In the light of reports on the discrepancies between the CT and US prostate localizations, the studies employing ultrasound systems were excluded from the analysis. Furthermore, only the publications giving all the details about the patient immobilization and preparation protocol were selected.

External immobilization

With the internal target motion considered to be the predominant difficulty in pelvic treatments targeting, many studies focus on the total positioning error (relevant for therapy delivery) and address only
marginally the study of the separate error components (e.g. setup errors needed to evaluate the immobilization approach). Therefore published data on patient setup errors is rather sparse. Several studies reporting the reproducibility of the bony anatomy re-positioning and works comparing different treatment positions and immobilization devices are summarized in Table 5 on the next page.

Liu at al. [100] and Bayley at al. [12] have demonstrated a larger setup uncertainty in prone position as compared to supine. Kneebone at al. [86] found that use of a rigid plastic pelvic mask can significantly reduce setup variability in prone position. In contrary, Malone at al. [106] found a reduced setup uncertainty in prone position. The advantage of the supine position is however clear in reducing the internal prostate movement [12] and the ventilatory movement [31], as well as when the patient’s comfort is regarded [12].

Concerning rigid immobilization, a few studies demonstrated the advantage of the use of individually moulded alpha-cradle or vacuum cushion as compared to no immobilization, pointing out that immobilization of the patient’s lower extremities is of importance [41]. Published data do not clearly support the advantage of such rigid external fixation as compared to standardized foam knee-and-feet supports (Figure 12 on page 28 (a)). According to several personal communications between the authors of the studies and the authors of this document [175], at some institutions an increase in the setup uncertainties was observed after introducing such rigid devices. Presumably, this is due to difficulties in getting the patient in and out of the mould, hindering the stabilizing effects of the devices. With the use of reclining devices during the daily patient immobilization, as included in the workflow of most of new particle therapy centers, this problem will be likely alleviated.

An alternative to rigid moulds is the use of a thermoplastic pelvic mask alone in supine position. According to own experience, this solution provides similar accuracy but enables much simpler immobilization workflow.

Similar immobilization solutions have been used for cervix and uterine cancer treatments, however the available literature is much sparser. Most recently Haripotepornkul at al. [66] reported a total targeting error of 4.2±3.5 mm, 4.1±3.2 mm and 1.9±1.9 mm in AP, SI and LR directions respectively, assessed by means of x-ray imaging of the implanted seeds for cervix patients immobilized in an alpha cradle. The setup error alone however was not addressed.

A further issue that, to the best knowledge of the authors, is not addressed in the literature, is the stability of immobilization devices, with particular attention to vacuum cushions, in case of treatment couch movements that include roll and pitch. Such problem does not exist in conventional radiotherapy, where the availability of linacs with rotating gantries provides the necessary freedom in choosing beam setups. Concerning particle therapy, instead, especially for centers with high-LET particles like carbon ions, the availability of a fixed irradiation nozzle only is a likely situation. Most newly built and upcoming facilities intend to compensate for this geometric limitation with the use of robotic treatment couches offering 6 degrees of freedom. Currently the only clinically implemented solution ensuring stable and safe roll of patients for the needs of particle therapy employs pods, tub-shaped treatment couches inside which the patient is stabilized with a wrapping vacuum mould [57]. At the Department of Radiotherapy and Radiation Oncology of the UKGM the stability, against roll and pitch, of vacuum cushions of different size and type is currently under test. No conclusive data are available, the existence of this potential problem is included in this report for information.
Table 5: Literature review of studies regarding external immobilization in pelvic treatments (note: only studies assessing the reproducibility of the bony anatomy alignment were included).§

<table>
<thead>
<tr>
<th>PUBLICATION</th>
<th>METHODS</th>
<th>ACCURACY/REPRODUCIBILITY [MM]</th>
<th>AP</th>
<th>SI</th>
<th>LR</th>
<th>3D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liu 2008 [100]</td>
<td>10p/10 supine</td>
<td>CT</td>
<td>0.9±2.3</td>
<td>0.2±2.3</td>
<td>-2.8±3.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10p/10 prone on belly board</td>
<td></td>
<td>1.3±5.1</td>
<td>1.2±5.1</td>
<td>0±3.5</td>
<td></td>
</tr>
<tr>
<td>Boda 2008 [20]</td>
<td>8p/54 knee and feet support</td>
<td>CBCT</td>
<td>3.2±4.6</td>
<td>-1.2±5.4</td>
<td>2.0±4.6</td>
<td></td>
</tr>
<tr>
<td>McNair 2008 [109]</td>
<td>30p/408 knee and feet support</td>
<td>MVPI</td>
<td>-0.4±3.5</td>
<td>-0.2±2.7</td>
<td>0.0±2.6</td>
<td></td>
</tr>
<tr>
<td>Han 2006 [63]</td>
<td>34p/250 vacuum cushion</td>
<td>MVCT</td>
<td>-0.6±2.0</td>
<td>-2.3±5.9</td>
<td>-0.5±5.7</td>
<td></td>
</tr>
<tr>
<td>Kaiser 2006 [82]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bayley 2004 [12]</td>
<td>20p/267 supine in vacuum</td>
<td>PI</td>
<td>-0.1±3.3</td>
<td>-0.1±3.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>cushion for half of the</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>treatment and prone with</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>thermoplastic pelvic mask</td>
<td></td>
<td>0.0±3.7</td>
<td>0.1±4.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kneebone 2003 [86]</td>
<td>48p/weekly prone no</td>
<td>PI</td>
<td>5.2 (avr)</td>
<td>4.1 (avr)</td>
<td>3.1 (avr)</td>
<td>8.5</td>
</tr>
<tr>
<td></td>
<td>immobilization</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>48p/weekly prone + pelvic mask</td>
<td></td>
<td>2.9* (avr)</td>
<td>3.9 (avr)</td>
<td>2.1* (avr)</td>
<td>6.2*</td>
</tr>
<tr>
<td>Baunert 2002 [11]</td>
<td>10p/daily non immobilized</td>
<td>EPI</td>
<td>0.4(med)</td>
<td>0.3 (med)</td>
<td>0.2 (med)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.3 (med)</td>
<td>0.3 (med)</td>
<td>0.15 (med)</td>
<td></td>
</tr>
<tr>
<td>Alasti 2001 [1]</td>
<td>33p in alpha-cradle</td>
<td>PI</td>
<td>0.2±2.0</td>
<td>-0.2±1.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malone 2000 [106]</td>
<td>20p/ foam leg support</td>
<td>PI</td>
<td>3.2±2.5</td>
<td>3.4±2.9</td>
<td>3.2±2.9</td>
<td></td>
</tr>
<tr>
<td></td>
<td>24p/ full body alpha-cradle</td>
<td></td>
<td>3.2±2.7</td>
<td>3.2±2.2</td>
<td>2.7±2.4*</td>
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</tr>
<tr>
<td></td>
<td>33p/ prone-thermoplastic pelvic mask</td>
<td></td>
<td>2.3±1.8*</td>
<td>2.6±1.8*</td>
<td>1.9±1.4*</td>
<td></td>
</tr>
<tr>
<td>Mitine 1999 [112]</td>
<td>10p/180/ no immobilization</td>
<td>MVPI</td>
<td>±5.2</td>
<td>±4.9</td>
<td>±5.1</td>
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<tr>
<td></td>
<td>10p/172 alpha-cradle</td>
<td></td>
<td>±2.6</td>
<td>±4.2</td>
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<td></td>
<td>10p/172 thermoplastic cast</td>
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<td>±2.7</td>
<td>±3.5</td>
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<tr>
<td>Fiorino 1998 [41]</td>
<td>25p/weekly alpha-cradle (pelvis)</td>
<td>PI</td>
<td>2.4±4.4</td>
<td>-1.5±3.3</td>
<td>0.3±3.6</td>
<td>5.0±2.8</td>
</tr>
<tr>
<td>Italia 1997 [78]</td>
<td>27p/weekly alpha-cradle (legs)</td>
<td></td>
<td>0.9±2.6*</td>
<td>-1.3±2.7</td>
<td>0.4±2.4*</td>
<td>3.0±1.4*</td>
</tr>
<tr>
<td></td>
<td>21p/178 non immobilized</td>
<td></td>
<td>1.0±3.7</td>
<td>-1.3±3.1</td>
<td>-0.4±3.4</td>
<td>4.4±2.4</td>
</tr>
<tr>
<td>Greer 1998 [55]</td>
<td>11p/160 no immobilization</td>
<td>PI</td>
<td>-3.3±4.6</td>
<td>-0.5±1.6</td>
<td>0.5±2.8</td>
<td></td>
</tr>
<tr>
<td>Rattray 1998 [128]</td>
<td>non immobilized pelvic</td>
<td>PI</td>
<td>3.9±3.6</td>
<td>3.8±3.3</td>
<td>2.5±3.5*</td>
<td>2.0±2.0*</td>
</tr>
<tr>
<td>Catton 1997 [26]</td>
<td>alpha-cradle</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3.2(2.5)</td>
</tr>
<tr>
<td></td>
<td>significantly better positioning in AP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.8*(2.0*)</td>
</tr>
<tr>
<td>Bentel 1995 [17]</td>
<td>30p/130 non immobilized</td>
<td>PI</td>
<td>4.0 (avr)</td>
<td>4.0 (avr)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>44p/213 in alpha-cradle</td>
<td></td>
<td>2.0 (avr)</td>
<td>2.0 (avr)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rosenthal 1993 [133]</td>
<td>12p no immobilization</td>
<td>PI</td>
<td>4.0 (avr)</td>
<td>4.0 (avr)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>10p in alpha-cradle</td>
<td></td>
<td>2.0 (avr)</td>
<td>2.0 (avr)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

§ - all abbreviations used in the table explained in section List of abbreviations and definitions
† - only abstract available
* - statistically significant difference
a - for prostate, rectum and cervix patients
b - patient immobilization described
Internal organ movement (prostate)

Patient preparation
Selected publications were grouped, according to the patient preparation procedures undertaken to limit the targeting errors. An additional distinction has been made between those studies in which the preparation protocol was given to the patients as suggestions and those in which it was either enforced through a controlled regime [142] or verified with daily MVCT control scan followed, if required, by instructions to reproduce the desired bladder/rectum filling from the day of the planning CT [40]. The results of the literature study are presented in Figures 15, 16, 17 and 18. In Figures 15 and 16 the systematic and random components [159] of the total prostate displacement (i.e. position of the prostate during the irradiation as compared to the planned position) are shown. The total uncertainty of prostate localization is in the order of 4.0(4.0) mm in anterior-posterior direction, 2.5(2.5) mm in superior-inferior direction and 2.5(2.5) mm in medio-lateral direction. In Figures 17 and 18 the systematic and random components of the prostate displacement with respect to the bony anatomy are shown. The uncertainty in the localization of the prostate due to organ movement is in the order of 2.5(2.5) mm in AP direction, 2.5(2.5) mm in SI direction and 1.0(1.0) mm in LR direction. It should be noted that the very small organ displacement in medio-lateral direction is consistent with observations by many authors [121, 109, 14, 114] that the prostate movement in medio-lateral direction is strongly correlated with the bony setup error.

Comparison of published data suggests that advising the patient on the bladder/bowel preparation protocol can help to reduce slightly both, the systematic and random positioning error in AP directions (both, internal movement and total error). The effect of such procedure is however only minor [157, 98]. A strict dietary/voiding regime instead, results in significant reduction of the inter-fraction prostate movement [142].

Endorectal balloon
Based on this search and a recent review by Smeenk et al. [141], the conclusions on the immobilizing effects of ERBs are summarized in Table 6 on page 37.

Endorectal balloon for prostate immobilization. A concluding comparison between the results from different studies is difficult, due to:

- different balloon types and inflated volumes used
- different imaging techniques employed (e.g. port films, repeated CTs)
- different values measured (e.g. distance from the fixed bony landmark, balloon/prostate position with respect to the planning CT, etc.)
- different statistical quantities reported (mean, standard deviation, range, maximum, etc.)

Of particular interest are studies which compared patient cohorts treated with and without ERB. Two publications, by Vargas et al. [165] based on cine-MRI of 7 patients over 4 minutes and D’Amico et al. [30] based on 3 CT scans repeated within 3 minutes in 10 patients, report reduced intra-fraction motion of the prostate with use of ERB. Two studies, by Gerstner et al. [47] and by Canning et al. [25], report reduction of the inter-fraction motion of the prostate with respect to the bony landmarks, however other authors did not observe significant differences between cohorts of patients imaged with and without the ERB [163, 81]. Some studies report good reproducibility of the ERB placement in the order of ±1.8 mm [170, 27] - ±3.3 mm [38], but other authors report unacceptable standard deviations of daily balloon placement of ±7.0 mm [47, 169] to ±9.9 mm [28]. Furthermore, Court et al. [29] observed a mean intra-fraction shift of the ERB wall of 1.8 mm (maximum 7.2 mm), mainly in the posterior direction and attributed it to patient relaxation after insertion.
Figure 15: Results of the literature review: systematic component [159] of the total positioning error (Van den Heuvel et al.[156], Greer et al.[54], van Lin et al.[163], Frank et al.[140] and Alasti et al.[1] the statistical evaluation based on raw data made by the authors of this document).
Figure 16: Results of the literature review: random component [159] of the total positioning error (Van den Heuvel et al.[156], Greer et al.[54], van Lin et al.[163], Frank et al.[140] and Alasti et al.[1] the statistical evaluation based on raw data made by the authors of this document).
Figure 17: Results of the literature review: systematic component [159] of the inter-fraction organ movement (Van den Heuvel at al.[156], Greer at al.[54], van Lin at al.[163], Frank at al.[140] and Alasti at al.[1] the statistical evaluation based on raw data made by the authors of this document).
Figure 18: Results of the literature review: random component [159] of the inter-fraction organ movement (Van den Heuvel et al.[156], Greer et al.[54], van Lin et al.[163], Frank et al.[140] and Alasti et al.[1] the statistical evaluation based on raw data made by the authors of this document).
Table 6: Results of literature research on prostate immobilization by means of endorectal balloon.

<table>
<thead>
<tr>
<th>PUBLICATION</th>
<th>METHOD</th>
<th>RESULTS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>inter-fraction motion</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>van Lin 2005 [163] †</td>
<td>22p (s) w ERB (80cc air) and 30 w/o ERB, daily EPI with fiducial markers</td>
<td>internal prostate motion (relative to the bony structures) comparable for both patient groups</td>
</tr>
<tr>
<td>Canning 2005 [25] †</td>
<td>14p w ERB and 15 w/o, daily EPI with fiducial markers</td>
<td>average range reduced: 13.4 to 9.6 mm (AP), 10.4 to 9.1 mm (SI), 9.3 to 8.2 mm (LR). Even with the ERB the daily re-alignment shifts were necessary</td>
</tr>
<tr>
<td>Kagawa 2002 [81] †</td>
<td>16p (s), 6 MRI w and w/o water-filled ERB</td>
<td>prostate motion not significantly reduced: 3.1±2.0 (0.5-8.2) mm w/o ERB to 2.9±1.9 (0-7.4) w ERB</td>
</tr>
<tr>
<td>McGary 2002 [108] c</td>
<td>10p (p) w ERB (100cc air) with brachytherapy seed positions measured in 10 CTs</td>
<td>internal prostate movement: 0.42±0.35 mm (AP), 0.92±1.78 mm (SI), 0.83±0.38 mm (LR)</td>
</tr>
<tr>
<td>Teh 2002 [150] c</td>
<td>10p (s) 3 CTs w and w/o ERB (40cc air)</td>
<td>prostate movement relative to bony landmarks: 0.9±5.8 (AP), 4.2±6.6 (SI), 1.2±2.3 mm (LR)</td>
</tr>
<tr>
<td>Ciernik 2002 [28] b</td>
<td>9p (s) w ERB (40cc air), position of the prostate and the ERB measured in 4 CTs</td>
<td>reduction of the SD of prostate position (3 measurements)</td>
</tr>
<tr>
<td>Gerstner 1999 [47], Wachter 2002 [169] b</td>
<td>10p (s) 3 CTs w and w/o ERB (40cc air)</td>
<td>reproducibility of the ERB placement</td>
</tr>
<tr>
<td>Cho 2009 [27] dev</td>
<td>5p (s) w ERB (60cc air), position of the balloon with respect to bony landmarks measured in 3 CTs</td>
<td>ERB boundaries position: lower: ±2.6, ±2.8, ±2.2, ±2.4 mm, middle: ±1.8, ±2.4, ±1.7 and ±1.6 mm and upper part: ±1.3, ±2.5, ±1.3 and ±1.3 mm in A, P, L, R respectively.</td>
</tr>
<tr>
<td>Wang 2007 [170]</td>
<td>20p (p) w ERB (60cc air) weekly EPI, position of the balloon with respect to bony landmarks measured</td>
<td>mean displacement of ERB: 1.3, 1.8 and 0.1 mm, systematic and random error: 4.9(3.9), 3.3(4.5) and 4.0(3.0) mm in AP, SI and LR directions respectively.</td>
</tr>
<tr>
<td>El-Bassiouni 2006 [38] b</td>
<td>15p w ERB (60cc air) weekly EPI, position of the balloon with respect to bony landmarks measured</td>
<td>mean displacement of ERB: 3.8±3.3 (AP), 4.1±2.0 (SI) and 2.0±1.4 (LR) mm, systematic and random error: 3.9(2.7), 2.4(3.1) and 1.6(1.6) mm in AP, SI and LR directions respectively</td>
</tr>
<tr>
<td>Miralbell 2004 [111]</td>
<td>32p (s) w ERB (60 cc air) simulation and re-simulation CT compared</td>
<td>in 10 patients unacceptable ERB repositioning errors (&gt;20 ml volume variations and &gt;8 mm shifts in the LR or AP)</td>
</tr>
<tr>
<td>Ciernik 2002 [28] b</td>
<td>9p (s) w ERB (40 cc air), position of the prostate and the ERB measured in 4 CTs</td>
<td>balloon placement relative to prostate: 3.1±6.0 (AP), 4.8±9.9 (SI), -0.1±4.3 mm (LR)</td>
</tr>
<tr>
<td>Gerstner 1999 [47], Wachter 2002 [169] b</td>
<td>10p (s) 3 CTs w and w/o ERB (40cc air)</td>
<td>ERB placement reproducibility: ±4.3 mm (AP), ±7 mm (SI), ±3 mm (LR)</td>
</tr>
</tbody>
</table>

**intra-fraction stability of the ERB position**

| Court 2006 [29]          | 9p, ERB (60 cc air) outline compared in pre- and post treatment RL/LR port films | mean shift: 1.8±0.9 mm posterior (86% of all shifts posterior), max. shift: 7.2 mm |

* a,b,c - balloon types see Figure 14 on page 29  
* dev - a specially designed balloon was used, similar to Figure 14 on page 29 (b)  
* 1 Hyogo Ion Beam Medical Center, Ibo-gun, Japan  
* 2 University of Florida Proton Therapy Institute, Jacksonville, FL, USA  
* (s) - supine  
* (p) - prone  
* § - all other abbreviations explained in section List of abbreviations and definitions  
* $ - calculated by authors of this document based on the raw data presented in the publication  
* † - only abstract available
Table 6 – continued from previous page

<table>
<thead>
<tr>
<th>PUBLICATION</th>
<th>METHOD</th>
<th>RESULTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vargas 2010 [165]</td>
<td>7p cine-MRI in prone and supine position w and w/o ERB (100 ml water)</td>
<td>ERB reduces intra-fraction motion in both the supine and prone setup</td>
</tr>
<tr>
<td>D’Amico 2001 [30]</td>
<td>10p (s) 3 CTs every 1 minute taken w and w/o ERB (60cc air), positions of brachytherapy seeds measured</td>
<td>mean displacement between CT1 and CT3 reduced (1.3 to 1 mm), max. displacement between CT1 and CT3 reduced (4.3 to 2 mm)</td>
</tr>
</tbody>
</table>

abc - balloon types see Figure 14 on page 29
\(\text{dev} - \) a specially designed balloon was used, similar to Figure 14 on page 29 (b)
1 Hyogo Ion Beam Medical Center, Ibo-gun, Japan
2 University of Florida Proton Therapy Institute, Jacksonville, FL, USA
(s) - supine
(p) - supine
§ - all other abbreviations explained in section List of abbreviations and definitions
$ - calculated by authors of this document based on the raw data presented in the publication
† - only abstract available

With contradicting data reported in the literature, an MRI study assessing the possible prostate motility reduction with ERB has been commenced at the Department of Radiotherapy of the UKGM, employing a double balloon (Figure 14 on page 29 (e)). Preliminary, unpublished results confirm its immobilizing effects [146].

**Endorectal balloon in particle therapy.** In proton therapy water-filled ERBs are commonly used in order to minimize the risk of introduction of additional range uncertainties caused by presence of gas [81, 165, 57, 7].

**Other aspects of the endorectal balloon.** Five of the analyzed studies [27, 170, 108, 169, 30] report good tolerance of the patients to the daily balloon placement procedure. Additionally, dedicated studies report in detail on the patient tolerance of the ERB in large cohorts:

- Ronson at al. [130] - treatment with ERB completed in 97.6% of 3561 patients
- Goldner at al. [52] - 96% of 442 patients (including patients cohort described by Gerstner at al. [47] and Wachter at al. [169]) completed the treatment with ERB
- Bastasch at al. [9] all of 396 patients (including patients cohort described by McGary at al. [108] and Teh at al. [150]) completed the course of treatment with ERB

Four of the twelve analyzed studies [27, 28, 150, 169] show also dosimetric advantage of ERB. Numerous other studies discuss the reduced late rectum toxicity with use of ERB, detailed analysis of this issue is however beyond the scope of this document.

### 3.3.4 Summary and recommendations

Two types of positional uncertainty, setup error and internal target movement have, to be addressed in pelvic irradiations in order to assure correct dose application. While the former one can be effectively reduced by means of the external immobilization, the latter can be limited only to some extent. In order to reduce the setup error, irradiation in supine position and the use of external immobilization devices is recommended, assuring reproducible feet rotation and knees flex [21]. The literature
data does not clearly prove the advantage of the most common rigid external immobilization devices (alpha-cradle, vacuum cushion) over standardized feet and knees supports. Presumably, such devices can be implemented with their full advantages at the institutions equipped with reclinable tables, making stepping in and out of the device easier for the patients and helping to avoid deformations of the mould over the course of treatment. Additionally, a thermoplastic pelvic mask can be added.

As an alternative to this, we propose the use of individually moulded thermoplastic pelvic masks formed around the patient’s hips and upper part of the legs combined with feet holders to ensure reproducible rotation of the lower extremities.

In order to minimize the internal target position uncertainty in prostate or cervix/uterus treatments, the application of a strict patient preparation protocol is recommended (bowel evacuation / comfortable and reproducible bladder filling). The patient compliance to this preparation should be monitored. Based on positive experience of several proton [57, 7] and heavy ion centers [81] as well as preliminary results of tests conducted at the Department of Radiotherapy and Radiation Oncology of the UKGM, the application of ERBs for inter-fraction prostate gland stabilization is recommended (provided compatibility with the external immobilization). However, in the light of publications reporting poor reproducibility of ERB placement, we recommend that, when using ERBs, position verification and correction protocols continue to be used to prevent large day-to-day variations. To avoid positioning errors caused by patient relaxation, a waiting time of several minutes after ERB placement should be allocated before imaging/treatment.

Care must be taken in choosing a particular system to:

- ensure reproducible placement of the patient on the couch (through an indexing system), in particular if an absolute positioning procedure is planned
- achieve reduction of the systematic error, e.g. if the patient preparation protocol is used to obtain reproducibility of the internal anatomy during the course of treatment, this protocol has to be applied before the planning CT scan. The scan should be controlled to assess the patient’s compliance to the protocol and repeated if a risk exists that a systematic error was introduced
- obtain reproducibility of immobilization of the patient through the development of guidelines on the cradle / thermoplastic mask moulding procedure

Inter- and intra-fraction internal target motion can be expected for prostate but also for cervix/uterus, bladder and rectum irradiations. Hence, in high precision radiotherapy image guided targeting is necessary with use of techniques allowing to visualize the target, like CT or CBCT, or surrogates of the target, like portal imaging with fiducial markers. In particle therapy, additionally, other anatomical changes have to be monitored, as e.g. patient weight gain/loss, as the change in the thickness of the subcutaneous tissue can influence the particle ranges and hence lead to the deterioration of the spatial dose distribution even if positioning of the isocenter is correct during each fraction.
3.4 Upper abdomen and thorax

3.4.1 Indication-specific positioning issues and relevance to particle therapy

In addition to the inter-fraction setup uncertainty, tumors localized in the upper abdomen and thorax (e.g. lung, liver, pancreas tumors) are subject to substantial intra-fraction respiratory movement. Additionally, for lung tumors inter-fraction displacements from the original position occur (base line shift). This internal target movement is the predominant source of uncertainties in treatment of tumors localized in the upper abdomen and thorax and can not be suppressed with use of external immobilization devices. However, stable and reproducible patient positioning is essential, especially in particle therapy due to the known sensitivity of the particle range to the density of traversed material. As a consequence of this sensitivity, in the presence of considerable density heterogeneities modifying the Bragg peak position, it is difficult to specify the required accuracy limits for patient setup in thoracic irradiations. Furthermore, for actively scanned particle treatments, an additional deterioration of the delivered dose may come from the interplay between the patient’s breathing frequency and the beam scanning frequency. Such effect has not been addressed in clinical literature yet, being the current particle therapy experience with respiration-induced target motion entirely connected to passively scattered beams.

Consequently, the recommendations formulated in the following aim at achieving as good as possible immobilization.

The PubMed search for “lung immobilization radiotherapy” resulted in 142 hits, of which 25 were judged relevant for the lung immobilization issue. A search for “liver immobilization radiotherapy” resulted in three additional relevant hits.

3.4.2 Immobilization for thoracic irradiations

External immobilization devices for thoracic irradiations

The most common immobilization device in high precision treatments in the region of the upper abdomen and thorax treatments is an alpha-cradle or vacuum cushion (often used in conjunction with a stereotactic body frame). Patients are immobilized with their arms above the head, often resting on a specially designed support, e.g. T-bar (see Figure 19 on the next page (b)). Vacuum cushion immobilization can be combined with secondary devices encompassing the immobilized patient’s thorax/body and providing further stabilization, like a thermoplastic thorax mask or a vacuum body sheet (e.g. BodyFix®, Elekta, Crawley, UK, see Figure 20 on the facing page (a)).

Internal organ movement

To overcome the problem of respiratory motion, active techniques like beam gating or tumor tracking have been proposed and applied in conventional radiotherapy. Both techniques utilize a respiration signal, detected through internal fiducial markers or external surrogates, such as the movement of the chest or abdominal wall or spirometric control. As mentioned in the previous paragraph, the precise yet sensitive dose deposition mechanisms of charged particles, introduce a completely new level of complexity to the issue of respiratory motion. Therefore the topic will be addressed, through technical solutions related to the planning/delivery system, as a separate task of WP4 in the ULICE Project. We will outline here, however, a few techniques that allow to reduce respiratory movement in compliant patients, by means of external devices, patient coaching or medical procedures, and that can be currently applied independently of the technical specifications of single treatment facilities.
Abdominal compression (AC)
Mechanical abdominal compression by means of specially designed devices can be applied (see Figure 20) to obtain a reduction in tumor motion. Abdominal compression, also referred to as forced shallow breathing, works by limiting diaphragmatic excursion, and thereby the breathing-induced motion of the tumor. Two common immobilization devices that employ abdominal compression are the Bodyfix® system, and the abdominal compression plate (Figure 20 (b)). Since abdominal compression is a form of external immobilization, it’s effectiveness is reviewed in the following section.

Breathing control techniques
To limit the respiration motion of lung tumors, various breathing control techniques have been applied, e.g. Active Breathing Control or High Frequency Jet-Ventilation.

Active Breathing Control (ABC). In this technique breathing is controlled with a computer-driven valve and can be suspended for a preset duration (breath-hold technique).

High Frequency Jet-Ventilation (HFJV). The patient is narcotized and ventilated at high frequency which causes a standstill in respiratory motion; i.e., although sufficient oxygenation takes place, there is no respiratory motion of the lungs.
3.4.3 Precision of immobilization devices for thoracic irradiations

External immobilization

The amount of data concerning setup errors for thoracic irradiation is very limited as most of the studies focus on the total positioning error (relevant for therapy delivery). Additionally, a problem when assessing the setup errors for lung cancer irradiations is how to choose relevant matching anatomic structures. A review of available literature is presented in the Table 7. With the use of rigid immobilization devices, setup uncertainties have been reported with standard deviations in the range of 3 to 5 mm, which is mainly caused by the lack of rigid structures like the skull or hipbones, that can be used to immobilize the patient, and by the presence of breathing motion.

Two additional studies are be cited, which directly compare modern immobilization methods, although reporting the results in terms of total error. Four immobilization methods were evaluated in a study by Wang et al. [171]: (1) thermoplastic mask, (2) thermoplastic mask with ABC, (3) stereotactic body frame, (4) stereotactic body frame with ABC in 67 patients with lung tumors. The target position from the daily CBCT data set was automatically registered to the tumor contoured in the planning CT. The measured setup errors were: 0.1±3.1 mm in AP, -0.7±6.2 mm in SI and -0.4±3.1 mm in LR directions for thermoplastic mask alone and -0.3±2.9 mm in AP, -0.6±6.9 mm in SI and -1.5±3.7 mm in LR directions for thermoplastic mask applied with ABC, 0.9±3.6 mm in AP, -0.8±5.3 mm in SI and -0.2±3.1 mm in LR directions for SB frame and -2.0±3.5 mm in AP, -0.4±4.4 mm in SI and -1.1±3.5 mm in LR directions for SB frame with ABC. The positioning accuracies of the stereotactic body frame and thermoplastic body mask were similar. The application of active breathing control increased the absolute positioning error, but reduced the respiratory movement.

Table 7: Literature review on the external immobilization in treatments in the thorax and upper abdomen.§

<table>
<thead>
<tr>
<th>PUBLICATION</th>
<th>METHODS</th>
<th>accuracy/reproducibility [mm]</th>
<th>3D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heinzerling 2008 [68]**</td>
<td>5p/23fx SBRT</td>
<td>CT</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.9 (avr)</td>
<td>1.9 (avr)</td>
</tr>
<tr>
<td>Nelson 2007 [115]**</td>
<td>5p/weekly vacuum cushion + T-bar</td>
<td>4DCT</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>3.2(3.9)</td>
<td>5.8(7.0)</td>
</tr>
<tr>
<td>Giraud 2007 [50]**</td>
<td>21p/weekly vacuum cushion + T-bar</td>
<td>PI</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.7±3.0</td>
<td>0.9±3.1</td>
</tr>
<tr>
<td>Hansen 2006 [65]**</td>
<td>30p/69 vacuum cushion + SB frame</td>
<td>CT</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>±0.8</td>
<td>±1.9</td>
</tr>
<tr>
<td>Fuss 2004 [44]**</td>
<td>36p/109 double-vacuum device</td>
<td>CT</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.3±3.6</td>
<td>-0.1±1.6</td>
</tr>
<tr>
<td>Nevinny-Stickel 2004</td>
<td>10p/187 double-vacuum device</td>
<td>PI</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.5±1.1</td>
<td></td>
</tr>
<tr>
<td>Samson 1999 [137]**</td>
<td>16p/45 only hand grip</td>
<td>EPI</td>
<td>+3.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2.0(2.8)</td>
</tr>
<tr>
<td>Halperin 1998 [61]**</td>
<td>5p only T-bar 5p only custom cradle</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>±5.1</td>
<td>±5.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>±5.4</td>
<td>±5.3</td>
</tr>
<tr>
<td>Van de Steene 1998</td>
<td>16p/97 only hand grip</td>
<td>EPI</td>
<td>0.1±4.5</td>
</tr>
<tr>
<td>Bentel 1997 [16]**</td>
<td>30p/209 no immobilization 30p/229 alpha-cradle</td>
<td>PI</td>
<td>frequency of setup corrections</td>
</tr>
</tbody>
</table>

§ - all abbreviations used in the table explained in section List of abbreviations and definitions
† - only abstract available
a - different treatment areas: paraspinal, intraabdominal, liver, prostate
h - based on liver patients
p - based on lung patients

ULICE-GA n°228436
Table 8: Literature review on the external respiratory motion reduction techniques in thoracic treatments. *

<table>
<thead>
<tr>
<th>PUBLICATION</th>
<th>METHODS</th>
<th>accuracy/reproducibility [mm]</th>
<th>no of patients / no of images immobilization</th>
<th>AP</th>
<th>SI</th>
<th>LR</th>
<th>3D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Han 2010 [64]</td>
<td>24p/1fx no immobilization</td>
<td>4DCT</td>
<td>1.7 (avr)</td>
<td>5.3 (avr)</td>
<td>1.0 (avr)</td>
<td>6.1 (avr)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>24p/1fx BodyFix</td>
<td></td>
<td>1.6 (avr)</td>
<td>4.6* (avr)</td>
<td>0.6 (avr)</td>
<td>5.3 (avr)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>24p/1fx ACP</td>
<td></td>
<td>1.6 (avr)</td>
<td>4.0* (avr)</td>
<td>0.8 (avr)</td>
<td>4.7 (avr)</td>
<td></td>
</tr>
<tr>
<td>Bengua 2010 [15]</td>
<td>5p/1fx SBF (middle/lower lobe)</td>
<td>fscp</td>
<td>4.4±3.6</td>
<td>9.9±5.7</td>
<td>2.9±2.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>5p/1fx SBF + ACP (middle/lower lobe)</td>
<td></td>
<td>3.6±2.6</td>
<td>9.4±6.7*</td>
<td>2.5±2.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>5p/1fx SBF (upper lobe)</td>
<td></td>
<td>3.0±1.5</td>
<td>4.2±2.8</td>
<td>2.0±2.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>5p/1fx SBF + ACP (upper lobe)</td>
<td></td>
<td>3.1±1.3</td>
<td>3.8±2.6*</td>
<td>3.2±2.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baba 2009 [8]</td>
<td>5p/1fx non immobilized</td>
<td>fscp</td>
<td>9.2±7.1</td>
<td>2.7±1.9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>5p/1fx double vacuum device</td>
<td></td>
<td>7.5±6.4</td>
<td>2.1±1.2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wunderink 2008 [178]</td>
<td>12p/3fx ST frame free breathing</td>
<td>fscp</td>
<td>2.4 (med) (+38%)</td>
<td>4.1 (med) (+62%)</td>
<td>1.8 (med) (-15%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heinzlerling 2008 [68]</td>
<td>10p/1fx no AC</td>
<td>4DCT</td>
<td>13.6 (avr)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>10p/11x medium AC</td>
<td></td>
<td>8.3 (avr)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>10p/11x high AC</td>
<td></td>
<td>7.2 (avr)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negoro 2001 [179]</td>
<td>10p/1fx vacuum pillow ±ACP</td>
<td>fscp</td>
<td>the mean diaphragm movement reduced from 12.3 to 7.0 mm</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Herfarth 2000 [69]</td>
<td>24p/1fx vacuum pillow + ACP</td>
<td>fscp</td>
<td>the diaphragm movement reduced to: 7.3±2.7 mm</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* - all abbreviations used in the table explained in section List of abbreviations and definitions
* - statistically significant difference
h - based on liver patients
p - based on lung patients

In a study by Li et al. [94] three groups of patients with stage I non-small-cell lung cancer tumors were immobilized (1) in evacuated cushion, (2) in evacuated cushion with abdominal compression and (3) with chest board. The systematic and random setup error for patients immobilized in the evacuated cushion was: 4.6 (2.5) mm in AP, 4.1 (2.8) mm in SI and 5.2 (2.2) mm in LR directions and respectively 3.1 (1.5) mm, 5.9 (2.3) mm and 3.8 (1.7) mm using AC and 4.7 (1.4) mm, 4.2 (1.6) mm and 2.7 (1.2) mm using the chest-board. Only small differences in effectiveness between the tested devices were observed and the authors concluded in favour of the most generic device, the chest board, for the sake of device re-usability and uniformity of the immobilization procedures.

In both studies however, partitioning of the patients into different immobilization cohorts was based on preliminary fluoroscopic/4DCT examination to assess the respiratory tumor excursion. This has presumably biased the presented results, to disadvantage of the methods offering better motion mitigation. Nevertheless the publications deliver information on the achievable accuracy and represents a reference for the clinical application of the investigated devices.

The jet-ventilation technique is applied in clinical routine at the Department of Radiotherapy of the St. Marien-Krankenhaus (Siegen, Germany). The patient undergoes the jet-ventilation procedure twice: on the day of acquisition of the treatment planning CT and on the actual RS delivery day. The tumor position is reproduced with precision better than 2 mm in 70% of the patients [42]. A treatment planning study has been conducted in cooperation with the St. Marien-Krankenhaus confirming that the reproducibility of jet-ventilation is sufficient for (hypo)fractionated particle therapy irradiation, i.e. ion beam treatment plans were optimized using planning CTs acquired under HFJV and re-computed.
on verification CT data acquired several days later (also under HFJV).

**Reduction of the respiratory movement**

A review of literature on the effectiveness of systems with an abdominal compression plate and double vacuum systems (BodyFix®) is presented in Table 8 on the preceding page. All identified studies regarding the effectiveness of abdominal compression report reduced mean diaphragm movement \[64, 69, 179\] or respiratory target movement as compared with free-breathing condition. However, the effectiveness of controlling respiratory-induced organ motion by applying compression of the diaphragm, appears to be highly dependent on the individual, leading in some patients to effects, which are opposite than expected. In the study by Han *et al.* [64] the two solutions were directly compared. Both the Bodyfix and the ACP significantly reduced the superior-inferior (SI) and overall respiratory tumor motion compared to free breathing and the ACP further reduced the SI and overall respiratory tumor motion compared to the BodyFix. Additionally, ACP was judged faster to set up and rated more comfortable by patients.

The day-to-day reproducibility of the motion reduction with AC was studied by Wunderink *et al.* [178] for liver lesions. The motion of fiducial markers, implanted in the healthy liver tissue surrounding the tumor, was measured through fluoroscopic video imaging during free breathing and with varying levels of abdominal compression. The measurements were done on the planning day and repeated before each treatment fraction. Abdominal compression effectively reduced liver tumor motion, yielding small and reproducible excursions in three dimensions. With the jet-ventilation technique in turn, the respiratory motion is reduced to less than 2 mm [42].

### 3.4.4 Summary and recommendations

Based on recent recommendations of the European Organization for Research and Treatment of Cancer (EORTC) [34] and on several years of experience with stereotactic body irradiations (lung/liver radiosurgery) at the Department of Radiotherapy and Radiation Oncology of the UKGM, the whole body vacuum cushion (with/without abdominal compression, depending on the individually expected benefit) is recommended for external patient immobilization [168]. The limited amount of data currently available indicates that the systematic and random setup errors in lung or upper abdomen irradiations are about 3.5 mm with such “state of the art” immobilization systems. If possible, patients should be positioned with both arms above the head, as this position grants greater freedom in choosing beam setups. Reproducible patient positioning can be achieved by using a stable arm support, possibly in combination with a knee support, improving also patient comfort.

Care must be taken in choosing a particular system to:

- ensure reproducible placement of the patient on the couch (through an indexing system), in particular if an absolute positioning procedure is planned
- obtain reproducibility of immobilization of the patient through the development of guidelines on the cradle / thermoplastic mask moulding procedure

In appreciation of the amount of possible internal anatomy changes that can dramatically influence the particle ranges in the patient like e.g. tumor shrinkage, patient’s weight gain/loss, tumor base line shift, organ movement (liver, pancreas), the daily patient positioning procedure for thoracic treatments must include verification by means of volumetric imaging modalities. If available, active techniques like beam gating should be applied to ensure correct target coverage, as the immobilization alone cannot guarantee stable tumor position during the treatment. The latter is particularly important for
scanned beam applications where the interplay between patient movement and beam movement may lead to very significant deterioration of the dose distribution. Appropriate methods for on-line motion surveillance are still under development. Usually, these methods use external surrogates rather than direct tumor tracking. The correspondence between the surrogate and the real breathing signal should be established individually for each patient.
3.5 Paraspinal irradiation and craniospinal irradiation

3.5.1 Indication-specific positioning issues and relevance to particle therapy

Although anatomically located in the body regions already presented, the paraspinal and craniospinal treatments do not exhibit internal motion and hence pose a different challenge for immobilization. Therefore, they are discussed separately in brief in this section.

Due to the direct proximity of the spinal cord, effective radiotherapy of radioresistant paraspinal tumors to high doses requires very conformal dose distributions. Hence, particularly accurate patient setup is necessary in such treatments, as an overdosage to the spinal cord may lead to motoric deficiencies in the patient. Similarly, high accuracy is required in craniospinal irradiation, very often applied in children, as a geographical miss may lead to disease relapse.

The PubMed search for “paraspinal immobilization” resulted in 18 hits. The query for “craniospinal immobilization” resulted in 9 hits, of which none provided data on the effectiveness of the immobilization in craniospinal irradiations. One work known to the authors of this document is presented in the following.

3.5.2 Precision of immobilization for paraspinal and craniospinal irradiation

Paraspinal irradiations

Results of the literature review on immobilization strategies in paraspinal tumors are reported in Table 9. Essentially, two types of immobilization for paraspinal treatments have been reported in the literature: full body vacuum cushion in a stereotactic body frame [145, 53] and torso/abdomen scotch cast mask combined with head mask [145, 101]. Although offering better precision, the latter device requires 3-4 hours preparation which maybe prohibitive in clinical practice of a high throughput facility.

Table 9: Literature review on the immobilization techniques to reduce the setup error in paraspinal treatments.

<table>
<thead>
<tr>
<th>PUBLICATION</th>
<th>METHODS</th>
<th>accuracy/reproducibility [mm]</th>
<th>mean ± std dev or (\Sigma(\sigma))</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>AP</td>
<td>SI</td>
</tr>
<tr>
<td>Stoiber 2009 [145]</td>
<td>11p/90 cervical, SC torso + head mask</td>
<td>CT</td>
<td>0.3±0.8</td>
</tr>
<tr>
<td></td>
<td>21p/153 thoracic, SC torso + head mask</td>
<td>CT</td>
<td>0.3±0.8</td>
</tr>
<tr>
<td></td>
<td>13p/78 lumbar, SC pelvis + head mask</td>
<td>CT</td>
<td>0.0±0.9</td>
</tr>
<tr>
<td>Bolsi 2008 [22]</td>
<td>10p/daily vacuum mould + TP cast</td>
<td>scout</td>
<td>2.7(3.5)</td>
</tr>
<tr>
<td>Gong 2008 [53]</td>
<td>9p/daily vacuum mattress (SBF)</td>
<td>CBCT</td>
<td>-0.2±3.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2.3(3.2)</td>
</tr>
<tr>
<td>Lovelock 2005 [105]†</td>
<td>na/300 EPIs vacuum mattress</td>
<td>EPI</td>
<td>±1.3</td>
</tr>
<tr>
<td>Yenice 2003 [180]</td>
<td>7p/33 vacuum mattress (SBF)</td>
<td>CT</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lohr 1999 [101]</td>
<td>na/24 thoracic, SC torso + head mask</td>
<td>CT</td>
<td>1.4±1.0</td>
</tr>
<tr>
<td></td>
<td>na/7 lumbar, SC torso + head mask</td>
<td>CT</td>
<td>1.2±0.7</td>
</tr>
</tbody>
</table>

§ - all abbreviations used in the table explained in section List of abbreviations and definitions
† - only abstract available
As demonstrated by Lovelock 2005 et al. [105] vacuum cushion immobilization ensures also intra-fraction stability - the standard deviations of the differences between the pre- and post-treatment portal images was found to be less than 1 mm in all directions.

Craniospinal irradiations
Craniospinal irradiation is often applied in children, therefore has to be not only precise and reproducible, but also comfortable and safe for the patient. Conventionally, the craniospinal irradiations are applied in prone position, which to facilitates field patching. Typical immobilization for such treatment consists of a full body vacuum cushion and a thermoplastic head mask Figure 21. With daily image guidance, supine positioning with use of face-masks and body molds, preferable also when sedation or anesthesia is required, is becoming more widespread.

To our knowledge, no studies were published comparing the setup uncertainties occurring in these two immobilization approaches. A recent study by Stoiber et al. [144] reports on the setup uncertainties in 6 patients treated with helical tomotherapy, who received daily MVCT of the skull and weekly CT of the abdominal region. Patients were positioned supine with a long thermoplastic mask immobilizing the head and shoulders. Patients were tattooed in the abdominal region, to facilitate correct setup and minimize rotations. The local systematic and random setup error of the lumbar vertebrae with respect to the skull was: 4.6(2.9) mm in AP, 3.9(3.3) mm in SI and 5.0(3.9) mm in LR direction and increased after rotational corrections based on the registration of the skull area to the planning CT was performed. These results demonstrate that substantial deformation occur during the course of treatment and highlight the importance of correct immobilization to avoid geographical misses.

3.5.3 Summary and recommendations
Similarly to thoracic irradiations, the full body vacuum rigid device is recommended for external patient immobilization in paraspinal treatments. The choice of immobilization for craniospinal irradiations depends on the availability of the irradiation directions at a given institution, e.g. fixed beam facilities with vertical or oblique nozzle necessitate immobilization in prone position, whereas at centers equipped with a rotational gantry, supine immobilization may be preferred due to above mentioned issues.

Care must be taken in choosing a particular system to:

- ensure reproducible placement of the patient on the couch (through an indexing system), in particular if an absolute positioning procedure is planned
- obtain reproducibility of immobilization of the patient through the development of guidelines on the cradle / thermoplastic mask moulding procedure

In appreciation of the highly variable spine positioning and of the high precision required in such treatments, regular position verification is recommended to complement the achieved immobilization.
CONCLUSIONS

A summary of the immobilization reproducibility achievable with various devices for selected treatment sites has been presented, based on multiple sources (literature, clinical experience of the authors, personal communication with other radiotherapy and particle therapy facilities).

Differences in the anatomy at the various treatment locations originate different potential causes of positioning errors, with different magnitudes. For instance, on account of the rigid structure of the human head cranial treatments are affected solely by translational and rotational positioning errors, while thoracic treatments additionally present inter- and intra-fraction organ motion. Therefore immobilization devices are specifically designed for each treatment site and a review of immobilization solutions as the one presented in this document is bound to present results in the context of the indication being treated.

Focus was put on external immobilization devices and therefore among the available sources studies were selected that investigated the reproducibility of the patient’s setup, intended as position of the body, traditionally through positioning of known bony structures, solely or separately from the overall targeting reproducibility, which includes, for some indications, such as abdominal and thoracic tumors, internal organ displacement or respiratory movement.

In fact, in the present deliverable, four groups of indications were selected and for these (1) the “state-of-the-art” immobilization approaches were presented, (2) the magnitude of the residual uncertainties despite use of such devices was reported and (3) additional considerations, specific to particle therapy, were addressed.

Intracranial treatments. The precision of all contemporary immobilization solutions for cranial treatments is in the order of 1 mm (1D displacement), although the literature review suggests a slight disadvantage of solutions based on thermoplastic masks. Where possible, the use of a bite block or a stereotactic mask system is therefore recommended.

Head-and-neck treatments. A similar overall precision (<2 mm) has also been reported for long (including shoulders) thermoplastic masks in head-and-neck treatments. However, a few recent publications underlined how this magnitude, often represents an underestimation of the problem, due to rigid translation/rotation correction approaches, and showed significantly larger local errors as consequence of semi-independent anatomy deformations. These deformation effects, connected mostly to the flexion of the neck, can be reduced by combining the masks with individualized head supports or vacuum pillows and shoulder depressors.

Pelvic treatments. For indications in the pelvic region (e.g. prostate, cervix) the generally observed population-based systematic and random errors can both be constrained in the range 2.5 to 3 mm, independently of the use of vacuum cushions (nowadays state-of-the-art pelvic immobilization solutions). These values can presumably be improved with the application of tight pelvic thermoplastic masks granting higher fixation stability or with the use of recliners facilitating the patient immobilization and de-immobilization in a vacuum cushion, enabling finer corrections and relieving the moulded shape of much mechanical stress.

In this region, however, the limitation to the total target position reproducibility stems principally from changes in the internal anatomy and target motion, which can be limited only partially. The data on patient setup were complemented with a review of publications investigating the effectiveness of patient preparation protocols (e.g. drinking protocols to achieve a desired bladder volume or dietary regimes to stabilize rectal movements). Only in works where the protocol was formulated as a strict regime, rather than a guideline to the patient, significant reduction of the organ movement was
observed.

**Thoracic treatments.** Thoracic irradiation (e.g. lung, liver) poses one of the greatest challenges to conformal radiation therapy techniques. Despite the typical use of body moulds like vacuum cushions and indexed arm rests to induce a reproducible shape of the chest and shoulders, the average setup errors are larger than for the other indications reviewed, due mostly to the absence of a stable bony reference structure. For both population systematic and random errors, values equal to or smaller than 3.5 mm are to be considered state of the art.

Total targeting precision is affected mostly by respiration. Also in this case, some tools and approaches were reviewed that attempt to mitigate the consequences of such intra-fraction motion. Among these the use of diaphragm-compression plates appeared to be the most suitable for upper thorax treatment (e.g. lungs), while the application of a diet protocol (fasted stomach at treatment time) proved most efficient for the lower thorax/upper abdomen (e.g. liver, pancreas). The use of additional solutions like Active Breathing Control or Jet-Ventilation is suggested, after individual patient assessment.

**Paraspinal and craniospinal treatments.** The irradiation of paraspinal and craniospinal tumors is of special interest for particle therapy, due to the elevated conformity required for such indications in order to spare the spinal cord. Moreover for these indications no targeting error related to organ motion is expected, differently from other indications requesting immobilization at level of the torso. Therefore a separate section was dedicated to these tumors, despite the limited size of the knowledge base available in the literature. For the sake of spine immobilization the use of a vacuum cushions appears sufficient to ensure acceptable inter- and intra-fraction setup reproducibility, although in non-time-constrained environments a full body cast can provide better fixation. A thermoplastic mask can be used to further stabilize the setup and represent a requirement if the cervical spine and skull are part of the treated target. For these indications regular imaging (followed by immobilization adjustment, if required) is indispensable.

Concerning patient setup, knowledge of the achievable immobilization is crucial for the choice of the optimal equipment and data about residual positioning uncertainties coming from other institutions represents an ideal starting point to judge the suitability of an immobilization device. Therefore the present document delivers recommendations based on the surveyed data. Nevertheless, as reminded in the introduction and throughout the text, it should be noted how measurements regarding residual setup uncertainties of immobilization systems, usually performed through the evaluation of daily image guidance data, include errors generated at various stages of the treatment chain.

Ideally, institution-specific tests should be performed, with methodologies similar to those of the published works reviewed in this document, to assess the residual uncertainty of the chosen system in connection with the limitations related to the specific technical equipment (e.g. calibration of in-room lasers, type of imager, mechanical precision of the treatment couch, etc.) and to the clinical workflow (e.g. experience of the RTTs, time available for immobilizing the patients, level of interaction with the patient during moulding, etc.) [77].
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D.JRA 5.1 Recommendations for optimized fixation systems

Dissemination level PU


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[175] Wong, J. Personal communication


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