General introduction
**Accuracy:**
The closeness of agreement between a test result and the accepted reference value.

**Precision:**
The closeness of agreement between independent test results obtained under stipulated conditions.

BS ISO 5725-1: “Accuracy (trueness and precision) of measurement methods and results - Part 1: General principles and definitions.”, pp.1 (1994)

Figure 1: (first image, left to right) high accuracy, high precision, (second image) low accuracy, high precision, (third image) high accuracy, low precision, (fourth image) low accuracy, low precision
Introduction

Orthopaedic oncology is the medical field that specialises in the surgical treatment of bone tumours: primary bone sarcoma, intermediate and benign bone tumours, and metastases. Sarcomas are malignant tumours deriving from cells of non-hematopoietic mesenchymal origin (e.g. cartilage, muscle, bone, vessels). While bone makes up around 13-15% of the human adult body weight, cancers of the bone are relatively rare (1). The registry of the IKKNL (Netherlands Integral Cancer Centre) shows an incidence rate of 0.97/100,000 (world standardised rate) for primary bone tumours in the Netherlands in 2013, or less than 0.2% of all neoplasms (2). This includes not only sarcomas but also intermediate-grade and benign lesions. The Dutch incidence is comparable to reported rates from other Western countries like the UK and United States (3, 4). Incidence of malignant tumours has two peaks. The first is in children and adolescents, primarily osteosarcoma and Ewing sarcoma, and the second around 40-60 years of age, primarily chondrosarcoma. Treatment of these tumours often involves major and challenging procedures.

Thanks to advances in surgical techniques, adjuvant/neoadjuvant chemotherapy and knowledge of tumour biology, there has been a trend in orthopaedic oncology not only towards better survival rates but also towards more minimal and less invalidating procedures. Examples are the increase in limb salvage surgery for osteosarcoma using tumour prostheses, joint salvaging procedures using allografts, and the development of periacetabular resections (5-7). At the heart of this transformation lies a difficult balance, as each procedure requires a careful weighing of two competing interests: margin and function. Adequate margins are required to lower the chances of recurrence or, in case of malignant tumours, improve survival rates. As the margin is presumably healthy tissue, resection impacts function in terms of decreasing mobility or increasing the chances of complications. This is the fine line that an orthopaedic oncology surgeon is expected to juggle during a procedure – enough margin to prevent recurrence, but not too much so function can be protected. And when the margin of error is small, accuracy is vital.

Surgical orientation systems

Multiple tools are used in the operating theatre to assist the surgeon in surgical orientation, which is the process of finding the points of interest, resection planes, screw entry points, etc. during the procedure. Imaging data is displayed on large screens on the wall. Preoperative plans are drawn, often referencing anatomical landmarks. This is frequently measured using rulers. Currently there are two options for intraoperative orientation support, one widely applied and one new.
Fluoroscopy

Fluoroscopy machines are intraoperative X-ray devices that are widely used in orthopaedic and trauma surgery. Just like a standard X-ray machine, a fluoroscopic imaging modality works by displaying variances of absorption of X-ray photons, also known as Röntgen radiation, by different human tissues. The name is derived from a form of luminescence called fluorescence. Light or other electromagnetic radiation, in this case X-ray radiation, strikes a substance that absorbs and then re-emits the energy when electrons fall back to their ground state. Due to energy losses in this process, the electromagnetic radiation produced is of a lower wavelength. When the right material is chosen, it becomes visible light.

The effect was discovered in 1895 by Wilhelm Röntgen, who noticed that a barium platinocyanide screen glowed when exposed to X-radiation (8). Early medical use required darkened rooms, red darkness adaptation goggles and head-mounted screens with funnels due to low image brightness. With the development of image intensifiers in the 1950’s, fluoroscopy could be used in illuminated rooms. Recording of fluoro-cine or fluoro-movies (with the accompanying decreased image frame rate, thus decreased exposure) and image storage became possible with camera integration. Current fluoroscopy machines use a digital flat panel detector, further decreasing the required radiation dose while producing a similar or better image. Even so, intraoperative radiation is not harmless (the linear no-threshold model holds that every exposure has a risk) and thus requires strict protocols (9, 10). Inherent to the technique is that single imaging only provides two-dimensional (2D) images. There is also a need to balance patient dose and image quality. Using an isocentric arm and reconstruction software a fluoroscope can be used to produce intraoperative, CT-like, three-dimensional (3D) datasets. This technique is called 3D fluoroscopy or isocentric (iso-c) 3D scanning.

Computer-Assisted Surgery

Computer-Assisted Surgery (CAS) is the term used to describe a relatively new concept of applying computers to enable preoperative planning and provide intraoperative orientation, instrument feedback and/or guidance. This concept enables surgeons to objectify the spatial position of anatomical locations, instruments or implants. This is done by using imaging datasets or computational models. The first rudimental CAS systems were developed in the early 1970s, only about 40 years after the theoretical description of a modern computer by Alan Turing (11). These systems did computations for and gave feedback on instrument positioning in stereotactical neurosurgery (12). The development of computer tomography (CT) provided detailed three-dimensional datasets; this was quickly applied in the first stereo-optical CAS systems (13). The first application of CAS in orthopaedic surgery was a total knee arthroplasty in 1997 (14). The first orthopaedic oncology
procedures reported were three high-grade pelvic sarcoma resections in 2004 (15).

Most orthopaedic CAS systems are based around a stereoscopic optical device. There are two digital cameras, on a mount, that register and follow instrument and patient trackers. These trackers can be active, emitting infrared light, or passive, reflecting infrared light from light sources in the camera mount. Using the difference between the two cameras, timing data between pulses, distance between the reflectors/light-emitting diodes (LEDs) and orientation of the reflectors/LEDs, the computer can calculate the position of the tracker relative to the camera. This measurement data can then be used for intraoperative measurements, imageless navigation or – with matching of spatial and virtual coordinates in CT and/or MRI datasets – image-based navigation. There are CAS systems that use electromagnetic radiation for instrument localisation. This technique has the advantage that it does not require a direct line of sight between the cameras and the trackers; the signal is vulnerable to interference though.

Software and offered functionalities differ between manufacturers, but the two basic modi operandi are comparable for all systems. There is an imageless mode, based on computational kinematic and/or statistical models, that is used in prosthetic placement. Image-based mode uses three-dimensional imaging datasets. This requires matching of the imaging dataset and the real-world coordinates. Usually this is done by landmark (point-to-point) and surface matching (bone surface detection), but can also be performed using image acquisition (fluoro-matching) or positional referencing (tracking of the intraoperative CT using an isocentric fluoroscope).

**Application of orientation systems**

Without the use of a CAS system, surgical orientation is mostly subjective. The
localisation of the tumour and resection planes depends on knowledge of anatomy and the skill to translate two-dimensional imaging (radiographs, fluoroscopy or 2d views of 3d datasets) into three-dimensional actions. Both skills depend heavily on an accurate frame of reference [Fig. 2]. The occurrence of inadequate surgical margins is highest in the bones with the most complex three-dimensional anatomy. Recent large studies report the occurrence of intralesional pelvic tumour resection in at least one of the margins of 26 and 30% (16, 17). Experimental studies have demonstrated that this is due not only to the localisation within a complex anatomical region or to the characteristics of pelvic tumours. Simulation of pelvic resections by Cartiaux et al. has shown that even experienced surgeons struggle with this. Four surgeons could achieve a good 10-mm resection margin, with 5-mm tolerance, on sawbones (without soft tissue) in only half of resections (18). The authors called for larger margins to compensate for the inaccuracy. A subsequent follow-up study to check these surprising results, using 10 senior and 13 junior surgeons, found 5 out of 23 intralesional resections in the freehand group (19). Studies like these can explain the high number of intralesional resections and (partially) local recurrences in the surgical treatment of pelvic sarcoma (20-22). Our frame of reference and thus our accuracy may not be as good as we think it is.

While complicated pelvic resections that rely heavily on accurate resection plane placement are currently the most common application of CAS in orthopaedic oncology, other orthopaedic oncology procedures depend on high accuracy too. An example is the creation and reconstruction of intercalary or hemicortical bone defects or multi-planar resections. These types of procedures, while offering large benefits to patients over tumour prostheses, require two separate surgical plans and highly accurate resections to get a safe oncological result and functional reconstruction (23, 24). As CAS can be used as a three-dimensional spatial measurement system, its use can hypothetically improve resection and reconstruction accuracy.

As a modality that offers three-dimensional imaging, CAS can also be used as a replacement of fluoroscopy for the curettage of bone tumours. Hypothetically improved, real-time orientation in 3D can reduce the observed occurrence rate of post-procedure (potential) residue (13%) or recurrence (3.5% and 13.3%) (25-27), while reducing ionising radiation exposure to the team and the patient.

Imageless CAS is a technique that has been applied mainly to total knee (TKA) and hip (THA) arthroplasty. While the discussion on its use and usefulness, primarily in terms of actual clinical results, still rages, meta-analyses show that CAS leads to a decrease in outliers in cup placement and knee joint line reconstruction (28-30). This observation shows that objective navigation can still show improvements on an already highly evolved surgical procedure and instruments. As reconstruction length of tumour prostheses is far larger, small errors in deviation angle have a larger overall effect. Hence correct positioning will rely even more on accurate
placement. This is something that imageless CAS can potentially improve, if it can reliably be applied to tumour prosthesis placement.

Overall, CAS use can potentially decrease the impact of a diagnosis of bone cancer on the lives of patients, in terms of effect on clinical outcome and functioning after the procedure.

**Present thesis**

The main goal of this thesis is to investigate the indications, surgical parameters and clinical outcome of the application of CAS in orthopaedic oncology. This thesis will also test and discuss the possibilities and high-end applications, as well as cited disadvantages of CAS – primarily that the set-up takes up valuable OR time and that the system has a steep learning curve (31). It will also describe and test the adaptation of existing surgical techniques and the creation of new techniques and tools using CAS. Finally, the thesis provides research questions for forthcoming years, exposing unsolved issues and describing a future work vision.

**Chapter Two** explores the possibilities of the application of CAS in orthopaedic oncology. A retrospective study of 130 patients describes clinical results across four types of procedures supported with CAS.

**Chapter Three** describes the literature and the possibilities of CAS in joint salvage procedures, in this case a grade-2 periacetabular chondrosarcoma.

**Chapter Four** is a retrospective comparative study between fluoroscopy and CAS use in the treatment of atypical cartilaginous tumours/chondrosarcoma grade 1 by means of curettage.

**Chapter Five** describes a novel method of creating hemicortical grafts by copying resection planes in three-dimensional space using computer-assisted surgery.

**Chapter Six** is an experimental study on the accuracy of resection and reconstruction of a multiplanar distal bone tumour model using freehand technique, CAS and a novel CAS guide.

**Chapter Seven** presents a general discussion on the studies from this thesis in context with the literature, and explores future possibilities.
References


(10) Mehlman CT, DiPasquale TG. Radiation exposure to the orthopaedic surgical team during fluoroscopy: “how far away is far enough?”. J Orthop Trauma 1997;11(6):392-398.


(27) Verdegaal SH, Brouwers HF, van Zwet EW, Hogendoorn PC, Taminiau AH. Low-


