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<th>Clinical evaluation of CT-guided percutaneous procedures for malignant tumors</th>
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Clinical evaluation of CT-guided percutaneous procedures for malignant tumors
(悪性腫瘍に対するCTガイド下手技の臨床的検討)

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Contents

Summary

Publication list

Acknowledgements

Abbreviations

Chapter I

The usefulness of CT-guided percutaneous procedures in clinical practice

1. CT-guided percutaneous procedure for tumor diagnosis

2. CT-guided percutaneous procedure for tumor treatment

Chapter II

Whether PET/CT-guided percutaneous biopsy offers specific advantages over conventional CT guided biopsy for the diagnosis of mediastinal tumors
1. Introduction

1-1. Usefulness and limitation of image techniques to diagnose mediastinal tumors

1-2. CT-Guided percutaneous biopsy for mediastinal tumors

2. Purpose

3. Material and Methods

4. Results

5. Discussion

Chapter III

Evaluating the usefulness of continuous intravenous fentanyl delivery in patients with hepatocellular carcinoma (HCC) treated by percutaneous radiofrequency ablation (RFA)

1. Introduction

1-1. CT-Guided percutaneous RFA for HCC

1-2. Outcome of the RFA for HCC

1-3. Significance of pain control during percutaneous RFA in HCC patients
2. Purpose

3. Materials and Methods

4. Results

5. Discussion

General Conclusions

References
Summary

As recent years have seen remarkable advances in imaging techniques, the detection of anomalies and the diagnosis of the cancer stage has become easier. However, despite technical and methodological advances some limitations persist. It can be difficult to differentiate between early-stage cancer and benign lesions because the morphological finding on early stage cancer are not highly specific. For optimal treatment, not only information on the involved organ but also on the molecular pathology is needed. Consequently, the care and treatment of cancer patients may require biopsy. Computed tomography (CT)-guided biopsy is less invasive and more convenient than surgical biopsy and it is safer than other guided biopsies that use ultrasound (US) and X-ray imaging. Positron emission tomography (PET) with fluorine $^{18}$fluorodeoxyglucose (FDG) is a functional imaging modality that visualizes glucose metabolism in living human tissues. CT-guided biopsy of abdominal masses based on PET/CT images has been reported to improve the accuracy of biopsy.

CT-guided radiofrequency ablation (RFA) is often used to treat patients with hepatocellular carcinoma (HHC). While it is less invasive and more convenient than hepatectomy, patients may experience pain despite deep intravenous (iv) sedation or local
anesthesia. Inadequate pain control may cause them to move during RFA and this may lead to iatrogenic injury and poor treatment results. Therefore, pain control is very important during RFA.

We undertook two studies to investigate the role of percutaneous CT-guided interventional techniques in relation to two issues, whether prior PET-CT-guided mediastinal biopsy provides specific advantages over conventional CT-guided mediastinal biopsy, and whether the continuous iv delivery of fentanyl mitigates pain in HCC patients undergoing percutaneous RFA.

In study 1 we enrolled 106 patients who underwent CT-guided percutaneous biopsy for mediastinal tumors. In 56 patients (group 1) PET-CT scans were- and in the other 50 (group 2) they were not acquired before biopsy. Comparison of diagnostic accuracy showed that it was 96% for group 1 and 93% for group 2, the difference was not statistically significant.

In study 2 we enrolled 83 HCC patients who underwent RFA; 41 received one shot of fentanyl (group 1) and in the other 42 (group 2), fentanyl was delivered continuously during the procedure. For quantitative evaluation of the pain reported by these patients we used the Visual Analogue Scale (VAS) score. We compared the two groups with respect to the VAS score, the RFA outcome, the local recurrence rate, and
anesthetic complications.

We found that the VAS scores of the two groups were not significantly different. The local recurrence rate 3 months after the procedure was 4.9% in group 1 and 2.4% in group 2; the difference was not statistically significant. Major anesthetic toxicity was recorded in 11 group 1- and 2 group 2 patients; the difference between the groups was statistically significant.

Conventional CT-guided biopsy can yield a correct diagnosis of most mediastinal tumors. Although FDG-PET can provide tumor metabolic information, we could not identify special advantages of PET-CT-guided biopsy. The continuous infusion of fentanyl provided effective and safe analgesia in HCC patients undergoing percutaneous CT-guided RFA.


5. Ikeda O, Nakasone Y, **Yokoyama K**, Inoue S, Tamura Y, Yamashita Y. Simultaneous

Acknowledgements

These academic investigations were performed during my postgraduate study period from 2011 to 2015 at the Department of Diagnostic Radiology, Kumamoto University Graduate School of Medical and Pharmaceutical Sciences.

I wish to extend my sincere thanks to Professor Yasuyuki Yamashita, Chairman of the Department of Diagnostic Radiology, Kumamoto University Graduate School of Medical Sciences, for general guidance and constructive instructions.

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Of course, I owe much to my colleagues in the Department of Diagnostic Radiology, Drs. Kawanaka, Shiraishi, Tamura, Nakasone, Yoshida, Sakamoto, and Inoue for their cooperation and help with my work.
## Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>CT</td>
<td>Computed tomography</td>
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<td>HCC</td>
<td>Hepatocellular carcinoma</td>
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<td>TAE</td>
<td>Transcatheter arterial embolization</td>
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<td>RFA</td>
<td>Radiofrequency ablation</td>
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<td>MRI</td>
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<td>IVR</td>
<td>Interventional radiology</td>
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<td>Ultrasound</td>
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<td>RCC</td>
<td>Renal cell carcinoma</td>
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<td>PET</td>
<td>Positron emission tomography</td>
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<tr>
<td>FDG</td>
<td>Fluorine 18 fluorodeoxyglucose</td>
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<td>AFP</td>
<td>Alpha fetoprotein</td>
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<tr>
<td>GLUTs</td>
<td>Glucose transporters</td>
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<td>CT-HA</td>
<td>CT-assisted hepatic arteriography</td>
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<td>CT-AP</td>
<td>CT during arterial portography</td>
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<td>DSA</td>
<td>Digital subtraction angiography</td>
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Chapter I

The usefulness of CT-guided percutaneous procedures in clinical practice

1. **CT-guided percutaneous procedure for tumor diagnosis**

2. **CT-guided percutaneous procedure for tumor treatment**
1. **CT-guided percutaneous procedure for tumor diagnosis**

Cancer is one of the most important diseases in a person’s life. If it is diagnosed in the early stage, a complete cure can be expected. To improve its prognosis, early diagnosis and the early start of treatment are necessary. Recent years have seen remarkable progress in imaging techniques, advances in ultrasound (US), computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET) have made it easier to detect abnormal findings and to diagnose the cancer stage. PET and CT using fluorine $^{18}$fluorodeoxyglucose (FDG) are functional imaging modalities employed to visualize glucose metabolism in living human tissues [1]. FDG, an analog of glucose, is transported into cells by glucose transporters (GLUTs) and phosphorylated by hexokinase. It is then metabolically trapped and accumulates within the cells at a rate proportional to their glucose utilization (Figure 1) [1]. FDG preferentially accumulates in cancer cells because of their increased glucose metabolism. This makes it possible to detect and diagnose early stage cancers by using imaging techniques.
Structure and metabolism of FDG. In FDG, $^{18}$F is substituted for the normal hydroxyl group (-OH) at the C-2 position in the glucose molecule. FDG is transported into cells by GLUTs in parallel with glucose. Hexokinase-phosphorylated FDG is metabolically trapped and accumulates in cells at a rate proportional to their glucose metabolism.

ADP = adenosine diphosphate
ATP = adenosine triphosphate
$6P$ = 6-phosphate

Adapted from Kobayashi 2012 [1]
Morphological findings on early-stage cancer are not highly specific [2, 3]. Because early cancers are small, their discovery and the evaluation of their malignancy can be difficult. Furthermore, increased glucose metabolism is not specific to cancer. FDG uptake can be seen in many noncancerous disorders including inflammation and infection. Like malignant cells, inflammatory cells such as activated lymphocytes, neutrophils, and macrophages exhibit increased expression of GLUTs and high intracellular levels of hexokinase [1, 4, 5]. An increased affinity of GLUTs for deoxyglucose is also observed in these cells, probably due to the presence of various cytokines and growth factors [1, 6].

It is difficult to distinguish between early cancer and benign lesions by using imaging techniques only. Advanced cancer tends to have spread widely and its complete cure is difficult. In such cases, the main treatment strategy is chemotherapy. In recent years, many kinds of drugs, including molecularly-targeted drugs have been developed [7, 8]. For the selection of optimal chemotherapy regimens not only the involved organ(s) but also the molecular pathology must be known.

Although imaging techniques are useful for detecting the location of tumors and metastases, it is difficult to identify the cancer-involved organ(s) and to obtain molecular pathological information by imaging techniques only. Consequently, biopsy is necessary to diagnose malignant tumors.
Interventional radiology (IR) is applied not only to diagnose but also to treat tumors; IR techniques can be vascular and non-vascular. Vascular IR techniques include transcatheter arterial chemoembolization (TACE) for HCC, for arterial aneurysms and arterial bleeding, and for stent graft repair of the thoracic and abdominal aorta [9, 10]. Image-guided biopsy, image-guided drainage, image-guided radiofrequency ablation (RFA) for tumors, and image-guided cryoablation are non-vascular interventional techniques [10, 11].

For pathologic studies tissue specimens are needed. These can be obtained by surgical biopsy under direct vision and while large tissue specimens can be acquired, surgical biopsy is highly invasive, and requires general anesthesia.

On the other hand, image-guided percutaneous biopsy, a common IR procedure, can be performed under local anesthesia and leaves a small wound [12]. Because the biopsy is carried out under real-time image guidance using CT, fluoroscopy or US, it avoids iatrogenic injury of large vascular structures and organs. The targeted lesion locations are large in the thorax, mediastinum, peritoneum, retro-peritoneum, pelvis, and muscle. Image-guided biopsy yields smaller specimens than surgical biopsy, however, large needles (16 - 18 gauge) can be used to harvest specimens large enough to diagnose involved organs and to identify the molecular pathology [13].
Fluoroscopy is a real-time, widely available technique that is typically reserved for large masses that impinge on fluoroscopically visible structures. As it yields only two-dimensional information, it requires two-plane verification of the needle position and carries the risk of traversing intervening organs [14, 15]. The use of US, also a real-time technique, is limited to masses located in the retroperitoneum and deep pelvis and to masses surrounded by lung, bone, and bowel [14, 16]. As CT provides real-time three-dimensional (3D) information and facilitates the observation of organs surrounded by bone and of the lung, CT-guided percutaneous biopsy is a feasible and safe procedure for obtaining a tumor diagnosis.

Similarly to malignant cells, inflammatory cells such as activated lymphocytes, neutrophils, and macrophages exhibit increased expression of GLUT and high intracellular levels of hexokinase [1, 4, 5]. Increased affinity of GLUT to deoxyglucose is also observed in these cells, presumably because of the presence of various cytokines and growth factors [1, 6].

Then it is difficult to distinguish between early cancer and benign lesion by using imaging technique only. And, an advanced cancer is usually spread widely and it is difficult to cure completely. That case, the main treatment strategy is chemotherapy. In recent years, many kinds of drugs included the molecularly-targeted drugs have been developed [7, 8]. Thus to select an optimum regimen of chemotherapy it is needed to
clarify not only arising organ but also molecular pathology.

Although the imaging technique is useful to detect the location of tumors and metastasis, it is difficult to clarify the arising organ and molecular pathological information by imaging technique only. Then, biopsy is necessary to diagnose malignant tumors.

The technique of interventional radiology covers very wide in clinical practice. Not only tumor diagnosis but also tumor treatment techniques are included. Liberally interpreted, techniques of interventional radiology are divided into vascular and non-vascular technique. The transcatherter arterial chemoembolization for hepatocellular carcinoma, transcatherter arterial embolization for arterial aneurism and arterial bleeding, stent graft repair of thoracic and abdominal aorta, and so on are divided as a vascular interventional radiology techniques [9, 10]. On the other hand, image guiding biopsy, image guiding drainage, image guiding radiofrequency ablation for tumor, image guiding cryoablation, and so on are divided as a non-vascular interventional techniques [10, 11].

For accurate diagnose and pathological information tissue specimen are needed. The surgical biopsy is one of the methods of obtaining tissue specimen. Although surgical biopsy can be performed under direct vision and obtain large tissue specimen, surgical biopsy is highly invasive, and general anesthesia is needed.

On the other hand, image guided percutaneous biopsy, commonly performed as
interventional radiological procedure, is under local anesthesia and has small wound[12].

Because the biopsy is performed under the real time image guide by using CT, fluoroscopy or US, it is able to avoid the large vascular structure and important organ injury. Moreover, the targets of lesion locations are very wide within thorax, mediastinum, peritoneum, retro-peritoneum, pelvis, and muscle. The size of tissue specimen obtained by image guided biopsy is smaller than surgical biopsy. However on image guided biopsy it is able to use the large size needle that size are 16Gauge to 18Gauge. Then we can obtain enough size tissue specimen to diagnose not only arising organ but also molecular pathology [13].

Fluoroscopy is real-time and widely available, but it is typically reserved for large masses that impinge upon fluoroscopically visible structures. The fluoroscopy provides only two-dimensional information. Then, fluoroscopy requires two-plane verification of the needle position and carries a risk of traversing intervening organs [14, 15]. US is also real-time but is limited in masses located in the retroperitoneum and deep pelvis and masses surrounded by lung, bone, and bowel [14, 16]. CT provides real-time and three-dimensional information. In addition, it is easy to observe organs surrounded by bone or lung. Therefore, CT-guided percutaneous biopsy is feasible and safe procedure for obtaining tumor diagnosis.
2. **CT-guided percutaneous procedure for tumor treatment**

Tumor treatment strategies are divided into local treatment and systemic chemotherapy. Early-stage cancer is usually treated by surgical resection, but advanced cancers cannot be resected surgically. Percutaneous RFA is widely used to treat focal malignant tumors such as HCC and metastatic liver tumors [17-20]. On the other hand, liver cancer as a result of virus infection, alcohol, and non-alcohol fat deposition induces chronic hepatic damage [21, 22]. As some patients with liver cancer manifest decreased liver function and lower functional reserve, the feasibility of surgical resection is limited to avoid postoperative liver failure. Image-guided microwave ablation and percutaneous alcohol injection therapy were reported to be useful liver cancer treatments [23-25].

RFA has been performed to treat early-stage liver cancer. In Japan, the procedure is covered by insurance only in patients with liver cancer. It has been reported that RFA was effective for the treatment of lung cancer, renal cell carcinoma (RCC), bone tumors, and breast cancer [26-30]. In Japan, RFA for these diseases is considered to be a highly advanced medical treatment. It uses a radiofrequency (RF) electrode to heat and coagulate targeted tissue. The RF energy is delivered via a 17-gauge electrode. Three types of RF electrodes are commercially available; there are two brands of retractable needle electrodes (model 70 and model 90 Starburst XL needles, RITA Medical Systems, Mountain View, CA and the LeVeen
needle electrode from Boston Scientific, Boston, MA) and an internally cooled electrode (Cool-Tip RF electrode; Radionics, Burlington, MA) [31].

The LeVeen needle electrode (Figure 2) consists of 10 retractable curved prongs that are expandable to a maximum diameter of 3.5 cm. An RF of 460 kHz and a maximum power output of 200 W are applied using a monopolar RF generator. In the first phase of the two-phase application process, the initial generator output is 20 W for one minute; it is subsequently increased by 5 W per minute to a maximum of 60 W. The output is maintained at this level until an increase in the circuit impedance of more than 200 Ω roll-off is observed. The electrical power output is turned off at the moment roll-off is observed; the impedance then returns to the baseline. In the second phase, the process is repeated 30 seconds later at 30 W. The output is again increased by 5 W per minute to a maximum of 60 W until impedance roll-off. The temperature in the ablation area is around 90°C or 100°C at the moment of roll-off [17].
Figure 2

The LeVeen needle (Boston Scientific, Boston, MA) consists of 10 retractable curved prongs that are expandable to a maximum diameter of 3.5 cm.
There are two RFA methods to treat liver cancer, i.e. percutaneous RFA under image guidance by CT or US and RFA under laparoscopy or opening using US guidance. Image-guided percutaneous RFA is an IR technique. In patients with early liver cancer, the local control elicited by RFA was equal to resection. In a randomized trial of RFA versus surgical resection in patients with a solitary HCC less than 5 cm in diameter, there was no difference in the overall survival- and the cumulative recurrence-free survival rates [10, 32].

RFA offers advantages, it can be performed under local anesthesia, and can be repeated upon tumor recurrence(s). On the other hand, a disadvantage of RFA is its potential cooling effect on the blood flow; this has a considerable negative impact on its effectiveness. In addition, patients suffer strong pain during RFA. While RFA is a non-invasive technique to address tumors, its drawbacks require careful patient management.
Chapter II

Whether PET/CT-guided percutaneous biopsy offers specific advantages over conventional CT guided biopsy for the diagnosis of mediastinal tumors

1. Introduction

1-1. Usefulness and limitation of image techniques to diagnose mediastinal tumors

1-2. CT-guided percutaneous biopsy for mediastinal tumors

2. Purpose

3. Materials and Methods

4. Results

5. Discussion
1. Introduction

1-1. Usefulness and limitations of image techniques to diagnose mediastinal tumors

The mediastinum is located in the center portion of the thorax between the two pleural cavities, the diaphragm, and the thoracic inlet[33]. Mediastinal tumors are frequently asymptomatic and difficult to detect on chest radiograms because the lesions overlap with the shadow of other organs. Mediastinal tumors are often discovered accidentally by chest CT, or as a huge tumor with chest pressure symptoms. The evaluation of these tumors often proceeds to CT or MRI studies of the chest with contrast material. The specific location and appearance of mediastinal tumors on CT or MRI scans is important for the planning of additional diagnostic procedures and for the development of treatment strategies. As the contrast-enhanced area provides useful information about the tumors, imaging techniques are used for the diagnosis of mediastinal tumors.

The treatment of mediastinal tumors depends on their diagnosis. Many are addressed by surgical resection, chemotherapy, and radiation therapy. If the tumor is small and non-invasive on the image, surgical resection may be performed for diagnosis and treatment. However a definite diagnosis is necessary to treat most tumors. Mediastinal masses span a wide spectrum of diseases such as thymoma, sarcoidosis, granuloma, teratoma, thymic cyst, Castleman’s disease, thymic carcinoma, metastatic tumor,
lymphoma, lung cancer, and neuroendocrine tumor. Because many are of similar imaging appearance, it can be difficult to diagnose mediastinal tumors by using imaging techniques alone [34, 35] and a pathological diagnosis is needed for the selection of appropriate surgical and medical treatments. For example, advanced-stage thymic neoplasms have been shown to benefit from neoadjuvant treatment before surgical resection [36, 37], lymphomas are primarily treated with chemotherapy or radiotherapy or both, and germ cell tumors are subjected to a combination of surgery, chemotherapy, and radiotherapy, depending on the subtypes [36]. A histologic diagnosis is often needed for the proper assessment of mediastinal tumors.
1-2. **CT-guided percutaneous biopsy for mediastinal tumors**

Biopsy for mediastinal tumors includes imaging-guided-, surgical-, and mediastinoscopic biopsy. Imaging-guided trans-thoracic biopsy is less invasive than mediastinoscopic or surgical biopsy and it requires only local anesthesia. Imaging-guided percutaneous trans-thoracic needle biopsy is adequate for characterizing mediastinal lesions and can be used before invasive surgical diagnostic procedures [38-44]. Core needle biopsy with large needles usually yields samples of good quality that facilitate evaluation of the tumor architecture, immunohistochemical staining, and in some cases molecular biology studies [45, 46].

Percutaneous mediastinal biopsies are usually performed with CT or US guidance because these modalities facilitate the precise localization and documentation of the biopsy needle and target lesion. However, major vessels, bones, the lung, and the trachea often preclude a direct approach to mediastinal lesions. Different techniques performed with CT and US guidance have been advocated for percutaneous needle biopsy of mediastinal lesions [44, 47-56].

US returns real-time information but its usefulness is limited in masses located in the retroperitoneum and deep pelvis and masses surrounded by lung, bone, and bowel [14, 16]. Mediastinal masses in particular tend to be surrounded by bone, lung and important
organs. Also, it is difficult to see mediastinal tumors on US images. CT, on the other hand, yields real-time 3D information and it is easy to observe organs surrounded by bone or lung on CT scans. This renders CT-guided percutaneous biopsy a feasible and safe procedure for obtaining a mediastinal tumor diagnosis.

The accuracy of trans-thoracic biopsy for the diagnosis of mediastinal lesions ranges from 75% to 90%[43, 44, 57, 58]. A major limitation of this technique is the risk of pneumothorax; it is reported to occur in 10-60% of patients [44].
2. Purpose

PET with $^{18}$F-fluorodeoxyglucose (FDG PET/CT) is now used to evaluate and manage oncology patients and for initial staging, early response evaluation, post-treatment assessment, and follow-up. Non-enhanced CT is often performed to guide percutaneous biopsies [59]. Because the enhancement time is very short in contrast-enhanced CT, it cannot be used for biopsies. Mediastinal tumors often include necrotic material and solid components that should be biopsied for an accurate diagnosis. On unenhanced CT scans it is difficult to distinguish a solid component from necrotic material. As some lesions detected by PET may return few or no correlative CT findings [60, 61], it may not be possible to perform biopsy based on PET findings alone and non-enhanced CT-guided biopsy of such lesions may return false-negative results due to sampling error. It is reported that CT-guided biopsy of abdominal masses using previously acquired r PET/CT images improved the accuracy of biopsies [62]. Therefore, if PET information could be integrated into CT-guided biopsy procedures, more lesions would be available for biopsy and the accuracy of biopsy findings may be improved [1, 14, 59, 62-64].

In the current study we compared the diagnostic value of CT-guided percutaneous biopsy with and without the registration of prior PET/CT images in patients with mediastinal tumors.
3. Materials and Methods

Patients

Between January 2006 and June 2012 we performed clinically indicated percutaneous biopsy of mediastinal tumors in 106 patients (53 men, 53 women; mean age 57 years, range 15 - 67 years). The final diagnosis was based on surgical outcomes and imaging findings; clinical follow-up lasted at least 6 months. The mean tumor size was 5.3 cm (range 1.4 - 14 cm).

On enhanced CT or MRI scans that had been obtained no more than 14 days (mean 5.8 days) before the procedure, the lesions were solid homogenous masses with a regular (n = 53, 50%) or an irregular or invasive tumor border (n = 35, 33%); 18 tumors (17%) were cystic or necrotic. The lesions were located in the anterior- (n = 61, 57.5%), posterior- (n = 21, 19.8%), middle- (n = 16, 15.1%), or superior mediastinum (n = 8, 7.5%).

Initial Diagnostic PET/CT Scan

The patients were divided into two groups; group 1 (n = 56) underwent CT-guided percutaneous biopsy with the registration of PET images that had been obtained no more than 22 days (mean 7.3 days) earlier. Group 2 (n = 50) underwent the procedure without such registration. Figure 3 shows a fusion image of PET and CT. There was no difference between
the two groups with respect to the patient age, sex, the tumor size, and the tumor location.

When a malignant tumor was diagnosed by biopsy in group 2 patients, PET/CT scans were obtained thereafter. The clinical characteristics of the two groups are presented in Table 1.
Table 1. Clinical characteristics of the 106 patients

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<th>Group 2</th>
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<tr>
<td>Age (years)</td>
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<td>58.5</td>
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<td>Sex (male/female)</td>
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<td>25/28</td>
<td>0.77</td>
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<tr>
<td>Tumor size (mean, cm)</td>
<td>5.5</td>
<td>5.3</td>
<td>0.67</td>
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<tr>
<td>Tumor location</td>
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<td>Anterior mediastinum</td>
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<td>Posterior mediastinum</td>
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<td>Middle mediastinum</td>
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<tr>
<td>Tumor characteristics</td>
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<tr>
<td>Tumor border regular</td>
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<td>31</td>
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<tr>
<td>Tumor border irregular</td>
<td>24</td>
<td>9</td>
<td></td>
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<tr>
<td>Cystic tumor</td>
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Group 1: CT-guided percutaneous biopsy with registration of prior PET/CT images
Group 2: CT-guided percutaneous biopsy without registration of prior PET/CT images
Figure 3. A 72-year-old male with squamous cell lung cancer

a  Enhanced CT shows solid homogenous masses with an irregular tumor border in the middle and posterior mediastinum
b  Uptake is visible on the PET image but it is difficult to distinguish neighboring organs
c  Fusion image of PET and CT. The tumor location is clear
d  CT-guided biopsy
PET/CT-guided Biopsy Procedure

All biopsy procedures were performed by two members of the abdominal IR staff; both had 20 years of experience. For all interventional procedures we used an IVR-CT unit comprised of an angiographic suite and a CT scanner (AXIOM Artis dTA/ VB30E; Siemens, Erlangen, Germany). All biopsy specimens were acquired with a coaxial core-needle biopsy technique; the needles were 15- or 17-gauge co-axial introducer needles and 16- or 18-gauge co-axial needles (Tru-Core™ II, Angiotech, Vancouver, BC, Canada).

Before the biopsy, group 1 patients were subjected to FDG PET/CT scanning. A needle path was defined on the monitor that simultaneously displayed CT fluoroscopic- and PET/CT images (Figure 4). The patients were immobilized in the proper position depending on the location of the lesion and the biopsy approach.
Figure 4. A 65-year-old male with malignant pleural mesothelioma

a  Plain CT image
b  Fusion image of PET and CT. FDG uptake is clear
c  PET/CT-guided biopsy. The uptake point is punctured
The skin entry site was marked and prepared and sterile drapes were applied. For moderate sedation we used midazolam (1 - 2 mg, iv) and fentanyl (50 - 200 mg, iv) in all patients plus local anesthesia with 2% lidocaine.

A suitable coaxial needle was inserted at the previously identified puncture site. Under CT fluoroscopic imaging guidance the angle and direction of the 15- and 17-gauge co-axial introducer needles were chosen to accommodate the position of the suspicious lesion.

The tip of the coaxial needle was placed at the border of the suspected lesion and default PET/CT images were acquired to confirm its correct position. The needles were then pulled out and a 16- or 18-gauge co-axial needle was inserted. Satisfactory puncture was confirmed on the CT scan, the biopsy site was recorded, and 3 or 4 specimens measuring 1- or 2 cm were obtained. When the lesion was small or difficult to differentiate from important structures such as peripheral vessels, contrast-enhanced CT scans were used to optimize the images. The co-axial needle was withdrawn and manual compression was applied for 2 - 3 minutes at the puncture site. The specimens were fixed in 10% formalin and submitted for histopathologic study.

After the biopsy procedure all patients were monitored for at least 3 hours to ensure hemodynamic and respiratory stability. CT scans were acquired immediately- and
3 hours after the biopsy procedure.

**Statistical Analysis**

Biopsies were considered inadequate if they did not provide sufficient pathological material for diagnostic evaluation due to necrotic debris or blood only, and excluded from further analysis. The biopsy results were later compared with the final diagnosis returned by surgical histopathological findings or clinicoradiologic follow-up. We compared the diagnostic value of CT-guided percutaneous biopsies with and without the registration of prior PET/CT images.

Complications related to the IR techniques including pneumothorax, hematoma, hemoptysis, and death were classified as major and minor according to the reporting standards of the Society of Interventional Radiology. We also compared the incidence of complications encountered in CT-guided percutaneous biopsies with and without the registration of prior PET/CT images.

For analysis we applied the Pearson χ2 test; to determine the diagnostic accuracy of the two methods we used the Fisher exact test for final outcomes.
4. Results

Our overall results are summarized in Table 2. CT-guided percutaneous needle biopsy yielded adequate samples in 101 of 106 patients (95.3%; group 1, n = 53; group 2, n = 48). Sample errors occurred in the other 5 patients; on pre-biopsy CT- and MRI scans their lesions appeared to be cystic tumors. The difference in sample errors was not statistically significant (group 1, n = 5.4%; group 2, n = 4%; p = 0.47) (Table 2).

Of the 101 successful biopsies, 95 (94.1%; group 1, n = 51; group 2, n=44) yielded a correct diagnosis that coincided with specific histological typing (Table 3). In the other 6 patients (5.9%) the lesions were diagnosed based on CT-guided percutaneous biopsy as thymic cysts (n = 2), granuloma, reactive lymph nodes, unknown carcinoma, and thymoma (n = 1 each). However, surgical histopathologic study and/or clinicoradiologic follow-up identified thymic carcinoma (n = 2) and B-cell lymphoma, Castleman disease (plasma cell type), lung cancer, and thyroid carcinoma in one case each. Nonetheless, the difference in diagnostic accuracy between group 1 and group 2 (91.1% and 88.0%) was not statistically significant (p = 0.32) (Table 2) (Figs. 5 & 6).
Table 2. Overall results of the 106 CT-guided percutaneous biopsies

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases</td>
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<td>50</td>
<td></td>
</tr>
<tr>
<td>Sampling error</td>
<td>3/56</td>
<td>2/50</td>
<td>0.47</td>
</tr>
<tr>
<td>Correct diagnosis</td>
<td>51/53</td>
<td>44/48</td>
<td>0.32</td>
</tr>
</tbody>
</table>

Group 1: CT-guided percutaneous biopsy with registration of prior PET/CT images
Group 2: CT-guided percutaneous biopsy without registration of prior PET/CT images
Table 3. Overall correct diagnosis with specific histological typing

<table>
<thead>
<tr>
<th>Diagnosis</th>
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<tr>
<td>Correct diagnosis (cases)</td>
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<td>44</td>
</tr>
<tr>
<td>Malignant tumor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hodgkin's lymphoma</td>
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<td>9</td>
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<tr>
<td>Metastatic tumor</td>
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<td>5</td>
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<tr>
<td>Thymic carcinoma</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Lung cancer</td>
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<td>2</td>
</tr>
<tr>
<td>Hodgkin's lymphoma</td>
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<td>1</td>
</tr>
<tr>
<td>Malignant mesothelioma</td>
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<td>1</td>
</tr>
<tr>
<td>Germ cell tumor</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Neuroendocrine carcinoma</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Leukemia</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Benign tumor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thymoma</td>
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</tr>
<tr>
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<td></td>
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<tr>
<td>Granuloma</td>
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<td>4</td>
</tr>
<tr>
<td>Castleman’s disease</td>
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<td>4</td>
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<tr>
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<tr>
<td>Thymic cyst</td>
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<td></td>
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<tr>
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<td></td>
</tr>
<tr>
<td>Amyloidosis</td>
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<td></td>
</tr>
<tr>
<td>Pericardial cyst</td>
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<tr>
<td>Extramedullary hemopoeisis lesion</td>
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</tbody>
</table>

Group 1: CT-guided percutaneous biopsy with registration of prior PET/CT images
Group 2: CT-guided percutaneous biopsy without registration of prior PET/CT images
Figure 5. A 27-year-old male with mediastinal seminoma who underwent PET/CT-guided biopsy

a  Enhanced CT shows solid homogenous masses with a regular tumor border in the anterior mediastinum
b  The PET/CT fusion image acquired one week before CT-guided biopsy shows the location of the metabolic lesion
c  The image acquired during CT-guided biopsy shows the placement of the coaxial needle in the metabolic lesion on the PET/CT fusion image
d  Pathological examination of the lesion confirmed mediastinal seminoma (hematoxylin-eosin staining x 400)
Figure 6. A 20-year-old male with mediastinal choriocarcinoma who did not undergo PET/CT-guided biopsy

- a Enhanced CT shows heterogeneous masses with a regular tumor border in the anterior mediastinum
- b The image acquired during CT-guided biopsy shows the placement of the coaxial needle in the anterior mediastinum
- c The PET/CT fusion image acquired two days after CT-guided biopsy shows the location of the metabolic lesion. At CT-guided biopsy the metabolic lesion was missed
- d Pathological examination of the lesion confirmed mediastinal choriocarcinoma (hematoxylin-eosin staining x 400)
Complications encountered in this series were pneumothorax and hemothorax (n = 4 each), mediastinal hematoma (n = 3), and hemopneumothorax, mediastinal emphysema, and hemoptysis below grade 2 (n = 1 each). Chest drainage or degassing was required in 5 patients with pneumothorax and one who presented with grade 3 hemopneumothorax. The difference in the complication rate between group 1 (19.6%) and group 2 (18.0%) was not statistically significant (p = 0.81) (Table 4).
Table 4. Complications

<table>
<thead>
<tr>
<th></th>
<th>group 1</th>
<th>group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases</td>
<td>56</td>
<td>50</td>
</tr>
<tr>
<td>Complications</td>
<td>11/56</td>
<td>9/50</td>
</tr>
<tr>
<td></td>
<td>&lt; Grade 2</td>
<td>Grade 3</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Hemothorax</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Mediastinal hematoma</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Hemopneumothorax</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Mediastinal emphysema</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Hemoptysis</td>
<td></td>
<td>1</td>
</tr>
</tbody>
</table>

Group1: CT-guided percutaneous biopsy with registration of prior PET/CT images
Group2: CT-guided percutaneous biopsy without registration of prior PET/CT images
5. Discussion

As PET/CT can demonstrate malignancy even before morphologic changes are evident, at image-guided biopsy, this information may facilitate the early histologic diagnosis and staging of malignancies. Furthermore, the metabolic information provided by PET/CT on viable malignant tissue in masses containing non-malignant-, e.g. necrotic- or fibrotic tissue, may improve the diagnostic accuracy of image-guided biopsy (13-19). Ours is the first investigation to compare the value of CT-guided percutaneous biopsy with and without registration of prior PET/CT images for the diagnosis of mediastinal tumors.

We found that PET/CT-guided biopsy of mediastinal tumors offered no special advantages. The uptake of FDG is not specific to cancer cells, not all cancers are detected with FDG PET/CT, and the reasons for false-positive and false-negative FDG uptake findings must be considered especially when there is a discrepancy between the biopsy result and the associated PET/CT interpretation (13-19). Considerable overlap between the standardized uptake value of malignant and benign lesions renders it devoid of intrinsic diagnostic importance without integration into the proper clinical context and without a correlation with anatomic imaging findings[1, 14, 60-64].

If a mass is not well visualized on non-enhanced CT images, contrast material can be administered iv during CT-guided biopsy. However, the usefulness of this method is
limited because contrast enhancement of some masses (e.g. HCC) may be transient and insufficient and thus not available for guidance throughout the duration of the procedure [65]. While US or MRI guidance can be used at the biopsy of masses that are not visible on non-enhanced CT images, not all masses are detected by US; MRI requires special wide-bore or open-configuration imaging units. Furthermore, these modalities may still be limited in their depiction of the neoplastic part of masses that also contain non-neoplastic portions. PET/CT-guidance may be particularly helpful for biopsies of abdominal masses that are FDG avid but not well visualized on non-enhanced CT images [1]. However, as most mediastinal tumors are clearly visualized and differentiated from normal organs on non-contrast enhanced CT images, PET/CT-guided needle biopsy is more useful in patients with lesions in other intra-abdominal organs.

Our study has some limitations. First, our study population was small and the patients presented with similar kinds of tumor and tumor locations. This precluded meaningful statistical analysis of the tumors and their location. Second, in both types of PET/CT-guided percutaneous biopsy we used a PET/CT scanner while in earlier reports the PET/CT images registered with intraprocedural CT images were acquired with computer software [14, 62, 63, 66]. When a PET/CT scanner is used, biopsy guidance is performed by using the CT elements of the integrated PET/CT system. Needle placement
in the targeted area of the FDG uptake is confirmed on fused PET/CT images acquired at the same table position used for both unenhanced CT- and PET scans [14, 62, 63, 66]. In another technique that employs previously acquired PET/CT images, diagnostic PET/CT images obtained before the procedure and CT images acquired intraprocedurally are transferred in the digital imaging and communications in medicine format to a computer via a local area network connection and the images are fused with the aid of medical image processing [62]. Although we used previously acquired PET/CT images at CT-guided percutaneous biopsy, the images were displayed side-by-side on the same monitor rather than fused.

In conclusion, CT-guided percutaneous biopsy is an easy and safe procedure that can yield a precise diagnosis in the majority of mediastinal tumors. Although we did not find that PET/CT-guided biopsy of mediastinal tumors offered specific advantages, further evaluation of its clinical impact and cost-effectiveness requires larger trials.
Chapter III

Evaluating the usefulness of continuous intravenous fentanyl delivery in patients with hepatocellular carcinoma (HCC) treated by percutaneous radiofrequency ablation (RFA)

1. Introduction

1-1. CT-guided percutaneous RFA for HCC

1-2. Outcome of RFA for HCC

1-3. Significance of pain control during percutaneous RFA in HCC patients

2. Purpose

3. Materials and Methods

4. Results

5. Discussion
1. Introduction

1-1. CT-guided percutaneous RFA for HCC

HCC is the fifth most common type of cancer worldwide, it predominantly arises in patients with liver cirrhosis, and its incidence is increasing [21, 67, 68]. The Barcelona Clinic Liver Cancer (BCLC) staging system (Figure 7) is the most widely accepted model as it integrates both tumor characteristics and the general health status with hepatic function to provide a clinical algorithm to help guide treatment decision-making according to the disease stage [21, 69-71].
Figure 7. Barcelona Clinic Liver Cancer (BCLC) staging system and treatment strategies.
RFA is one of the best curative treatment options for malignant liver tumors; it can be an alternative to resection. With advances in diagnostic modalities for HCC that meet the Milan criteria, defined as a single HCC ≤5 cm in maximum diameter or up to three nodules <3 cm, the relevance ratio and detection of early-stage HCC have improved significantly [72, 73]. The BCLC staging system stipulates that RFA is the standard of care for patients with early HCC. RFA of liver cancers can be performed safely using image-guided percutaneous-, laparoscopic-, or open surgical techniques, and RFA has remarkably changed the treatment strategy for small HCC. Image-guided percutaneous RFA can be performed with a variety of imaging modalities (US, CT, MRI, fluoroscopy) [74, 75]. CT guidance has advantages over US guidance in patients where the index tumors, for example lesions located in the dome, are not identifiable by US. Furthermore, in patients who had previously undergone TACE, residual or recurrent marginal tumors are sometimes difficult to differentiate on US images from areas with compact iodized oil retention [22, 76]. When RFA is performed under CT guidance, iodized oil retained from the prior TACE is commonly used as a targeting marker. The images used for CT guidance are non-contrast and they do not visualize enhanced arterial index tumors well; thus, the iodized oil remaining from an earlier procedure is useful as a targeting marker [22, 77].
On the other hand, laparoscopic and open surgical RFA procedures are more invasive than percutaneous RFA and need to be performed under general anesthesia. Image-guided percutaneous RFA, on the other hand, can be carried out under local anesthesia.

The accurate evaluation of the RFA treatment response is very important and a sufficient safety margin (at least 0.5 cm) is needed to prevent local tumor recurrence [78]. A characteristic of RFA is its cooling effect on the blood flow; this has a considerable effect on the outcome of RFA treatment [79, 80]. The reduced efficacy of RFA with respect to large tumors reflects the in vivo biophysiological limitations imposed by perfusion-mediated vascular cooling; this limits heat-induced coagulation necrosis. In animal models, it was possible to increase RF-induced coagulation necrosis by occluding the blood flow to the liver during ablation procedures [79, 81-83]. Nakasone et al. [17] reported that in normal pig kidneys, RFA with balloon occlusion of the renal artery increased the volume of coagulation necrosis at a shorter ablation time than RFA alone. The mean coagulation diameter was 31 mm when they used a 17-gauge, 2.0-cm expandable electrode. Under hepatic arterial occlusion it may be possible to determine the appropriate ablation area for RFA in humans.

Rare but potential complications after RFA for liver tumors include subcapsular
hematoma, abscess, hepatic infarction, injury to the gallbladder, bile duct stenosis and biloma, hemobilia, injury to the gastrointestinal tract, pleural effusion, pneumothorax and hemothorax, tumor seeding, and skin burn [74, 84].

In a review of 1,000 RFA procedures addressing 2,140 lesions in 664 patients, the rate of major complications was 1.9%; it was 0.82% for minor complications per individual treatment session [84]. To minimize complications, familiarity with the imaging features of each type of complication is needed and the appropriate management of complications is essential for the success of RFA [78].
1-2. **Outcome of RFA for HCC**

Hepatic resection is a conventional treatment for HCC; however, most primary liver cancers cannot be resected curatively at the time of diagnosis. Difficulties with surgical resection may be related to the size, site, and number of tumors, to vascular and extrahepatic involvement, and to liver function [85-88]. Percutaneous RFA does not elicit some of the side effects of other ablative techniques [89] and it is performed widely due to its ease of use, safety, reasonable cost, and minimal invasiveness [78].

When the HCC is small and at a favorable location, RFA alone can yield local control rates equivalent to hepatic resection [78]. In tumors larger than 3 cm, the efficacy of RFA decreases as the tumor size increases. A complete response has been reported in lesions with a 3-5 cm diameter [10, 90, 91]. In a randomized trial of RFA versus surgical resection in patients with a solitary HCC less than 5 cm in diameter, no difference was found in the overall- and the cumulative recurrence-free survival rates [10, 32]. One, 3-, and 5-year overall survival rates after RFA are shown in Table 5 [10, 32, 72, 92-101].

Due to its high treatment efficacy and low complication risk, RFA is widely accepted as a first-line interventional oncology approach for HCC [102].
Table 5. Overall survival rate after RFA

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients</th>
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<th>3 years</th>
<th>5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen 2006 [32]</td>
<td>71</td>
<td>68(96%)</td>
<td>50(70%)</td>
<td>-</td>
</tr>
<tr>
<td>Cho 2005 [92]</td>
<td>99</td>
<td>95(96%)</td>
<td>79(80%)</td>
<td>-</td>
</tr>
<tr>
<td>Guglielmi 2008 [93]</td>
<td>109</td>
<td>90(83%)</td>
<td>45(41%)</td>
<td>21(19%)</td>
</tr>
<tr>
<td>Guo 2013 [94]</td>
<td>94</td>
<td>89(95%)</td>
<td>70(74%)</td>
<td>47(50%)</td>
</tr>
<tr>
<td>Hiraoka 2008 [95]</td>
<td>105</td>
<td>99(94%)</td>
<td>92(88%)</td>
<td>62(59%)</td>
</tr>
<tr>
<td>Hong 2005 [96]</td>
<td>55</td>
<td>55(100%)</td>
<td>40(73%)</td>
<td>-</td>
</tr>
<tr>
<td>Huang 2011 [97]</td>
<td>413</td>
<td>355(86%)</td>
<td>261(63%)</td>
<td>236(57%)</td>
</tr>
<tr>
<td>Lu 2006 [98]</td>
<td>48</td>
<td>48(100%)</td>
<td>44(92%)</td>
<td>-</td>
</tr>
<tr>
<td>Lupo 2007 [99]</td>
<td>42</td>
<td>40(95%)</td>
<td>22(52%)</td>
<td>-</td>
</tr>
<tr>
<td>Ueno 2009 [100]</td>
<td>155</td>
<td>152(98%)</td>
<td>142(92%)</td>
<td>97(63%)</td>
</tr>
<tr>
<td>Vivarelli 2004 [101]</td>
<td>79</td>
<td>62(78%)</td>
<td>26(33%)</td>
<td>-</td>
</tr>
<tr>
<td>Ghanaati 2012 [10]</td>
<td>52</td>
<td>52(100%)</td>
<td>-</td>
<td>-</td>
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</tbody>
</table>

Summarized from Duan 2013 [72]
1-3. **Significance of pain control during percutaneous RFA in HCC patients**

Although hepatic percutaneous RFA is usually performed with the patient under deep iv sedation or local anesthesia, the tumor ablation area may be insufficient because many patients experience pain during and/or after the procedure [103]. Referred pain due to thermal injury is often the main problem during RFA procedures performed under local anesthesia [104, 105]. Severe pain occasionally induces pain shock or bradycardia; this may force the operator to shorten the duration of ablation, decrease the current intensity, or reduce the amount of overlapping ablations [104, 106]. The local recurrence rate can differ significantly between patients with a sufficient and an insufficient ablation area [104, 107, 108]. Therefore, ensuring sufficient tumor ablation during RFA is crucial for an optimal treatment effect [104]. Some anesthetic techniques, including total iv anesthesia with fentanyl, yielded favorable results [109, 110].
2. Purpose

Several anesthesia methods, e.g. local-, epidural-, and general anesthesia can be used to control pain in HCC patients undergoing RFA. The chosen method depends on the clinician’s recommendation and the patient’s preference. Epidural anesthesia is a partial solution to reduce the pain experienced during RFA procedures; however, it is an invasive technique and the skill required for thoracic spinal puncture can limit its use.

Anesthesia with high-dose fentanyl rather than morphine does not affect cardiovascular stability during induction or in the course of the procedure in patients with normal or abnormal left ventricular function [111]. Continuous epidural anesthesia and analgesia may be considered in liver resection, but is often avoided because of the potential development of coagulopathies and the risk of epidural hematoma [110].

We performed a retrospective study of pain control provided by single-shot iv fentanyl injections and by the continuous iv infusion of fentanyl during percutaneous RFA in HCC patients.
3. Materials and Methods

Patients

Between April 2007 and March 2010, 83 patients with 98 HCCs underwent percutaneous RFA. The diagnosis of HCC was based on nodular staining, dynamic CT, dynamic MRI, angiography or CT during CT-assisted hepatic arteriography, the presence of a nodular perfusion defect on conventional CT scans acquired during arterial portography, and elevated tumor marker levels. All HCCs were addressed by CT-guided percutaneous RFA performed within 5 hours after embolization of the tumor vessels with iodized oil and gelatin sponges.

Table 6 shows a summary of the 83 patients. For conscious sedation, group 1 patients (n=41) were injected iv with 100 mg of fentanyl before and 100 mg of fentanyl 30 min after percutaneous RFA. In group 2 (n=42) we delivered fentanyl by continuous iv infusion at 100 mg/h during RFA. All had a history of chronic liver disease; 58 (70%) had hepatitis C or B, 9 (10.8%) had hepatitis B and C; 6 patients (7.2%) manifested no hepatitis virus. The hepatic function reserve was evaluated using the Child-Pugh classification (32); 62 (74.7%) patients were recorded as Child-Pugh A and 21 (25.3%) as Child-Pugh B [112]. The median serum alpha fetoprotein level was 353.4 ng/ml (range 3.0 - 13,141 ng/ml. The median maximum diameter of the main tumor was 15.8 mm (range 7 - 39 mm). The tumor location was
classified into 4 regions, i.e. the liver surface, a major vascular structure, the parietal peritoneum, and the central liver parenchyma; 45 tumors were on the liver surface, 2 were on major vascular structures, 18 in the parietal peritoneum, and 18 on the central liver parenchyma. The median distance to the diaphragm was 2.5 cm (range 0.4 - 10.8 cm).
Table 6. Summary of the patients

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
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<tbody>
<tr>
<td>Patients</td>
<td>41</td>
<td>42</td>
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<tr>
<td>Age (y)</td>
<td>72.2±8.2</td>
<td>70.7±9.0</td>
<td>0.41</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>29:12</td>
<td>29:13</td>
<td>0.86</td>
</tr>
<tr>
<td>Etiology</td>
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<tr>
<td>non hepatitis</td>
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<td>5</td>
<td></td>
</tr>
<tr>
<td>hepatitis C</td>
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<td>32</td>
<td></td>
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<tr>
<td>hepatitis B</td>
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<tr>
<td>hepatitis B and C</td>
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<td>Child-Pugh class</td>
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<td></td>
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<tr>
<td>A</td>
<td>34</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>7</td>
<td>14</td>
<td></td>
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<tr>
<td>α-Fetoprotein (ng/ml)</td>
<td>300.4±942.9</td>
<td>406.3±2033.2</td>
<td>0.76</td>
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<td>Platelet count (x10⁴/µl)</td>
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<td>10.6±4.9</td>
<td>0.03</td>
</tr>
<tr>
<td>Previous treatment</td>
<td></td>
<td></td>
<td>0.44</td>
</tr>
<tr>
<td>Liver surgery</td>
<td>3</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>RFA</td>
<td>10</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>PEIT</td>
<td>2</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Tumor size (mm)</td>
<td>14.7±4.6</td>
<td>16.8±4.2</td>
<td>0.08</td>
</tr>
<tr>
<td>Number of tumors</td>
<td></td>
<td></td>
<td>0.78</td>
</tr>
<tr>
<td>One</td>
<td>31</td>
<td>31</td>
<td></td>
</tr>
<tr>
<td>Two</td>
<td>8</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Three</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Distance to the diaphragm (cm)</td>
<td>3.1±2.1</td>
<td>2.5±2.2</td>
<td>0.16</td>
</tr>
<tr>
<td>Tumor location</td>
<td></td>
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<td>0.43</td>
</tr>
<tr>
<td>Liver surface</td>
<td>24</td>
<td>30</td>
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</tr>
<tr>
<td>Major vascular structures</td>
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<td></td>
</tr>
<tr>
<td>Parietal peritoneum</td>
<td>18</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Liver parenchyma</td>
<td>8</td>
<td>10</td>
<td></td>
</tr>
</tbody>
</table>

Group 1; One-shot intravenous fentanyl delivery
Group 2; Continuous Intravenous fentanyl delivery
Criteria for the Treatment of HCC

RFA was performed when the HCC lesions met the Milan criteria, i.e. the presence of a single 5-cm diameter HCC or of up to 3 HCCs with none larger than 3 cm, and the absence of metastasis or vascular invasion [113]. Liver transplantation was not performed due to refusal by the patient, economic issues, cardiopulmonary dysfunction, or lack of a liver donor. The initial treatment was RFA combined with transcatheter arterial embolization (TAE). In patients with multiple nodules, all nodules were treated with the same method.

TAE

All tumors were percutaneously ablated within 5 hours of embolization of the tumor vessels with iodized oil and gelatin sponges (Figure 8). First we performed digital subtraction angiography of the superior mesenteric- and celiac artery using a 4-Fr RC2 catheter (Medikit Co. Ltd, Tokyo, Japan), 25 ml of iomeprol (Iopamiron 300; Bayer, Osaka Japan; 300 mg I/ml); the flow rate was 5 ml/sec. The catheter was replaced with an identical 4-Fr catheter (RC2; Medikit) and an angiogram of the proper hepatic artery was obtained using 20 ml of iomeprol (Iopamiron 300; Bayer; 300 mg I/ml); the flow rate was 3 ml/sec. Finally, a 2.5-Fr microcatheter (Renegade-18, Boston Scientific, Watertown, MA) was inserted into the tumor vessels. Embolization was achieved by injecting iodized oil (Lipiodol Ultrafluid, Laboratorie
Guerbet, Aulnay-Sons-Bois, France) followed by gelatin sponge particles (Gelfoam; Upjohn, Kalamazoo, MI, USA). All agents were administered via the tumor vessels and enhancement of the whole tumor was determined by CT-assisted renal arteriography. The endpoint of embolization was retention of the contrast medium in the feeding vessels.
Figure 8. A 76-year-old male with HCC who underwent TAE and RFA

a  Plain CT. The tumor is invisible.
b  Early-phase of contrast-enhanced CT. The HCC is observed as an enhanced lesion.
c  An image acquired after TAE. The lipiodol-retaining HCC is observed.
d  The HCC is punctured by aiming at the area of lipiodol retention.
e  An image acquired 3 months after RFA. Lipiodol is seen in the ablation zone.
Total Intravenous Anesthesia

The 83 patients treated between April 2007 and September 2009 were divided into 2 groups. Standard anesthesia consisted of 10 ml of 1% lidocaine injected locally; conscious sedation was with fentanyl administered iv before (100 μg) and 30 min after (100 μg) percutaneous RFA (group 1, n=41). Group 2 (n=42) received a continuous iv infusion of fentanyl (Phentanest, Sankyo, Tokyo, Japan) delivered at 100 μg/hr during the RFA procedure. Upon request, patients in both groups received 5 mg of diazepam, iv, for pain during percutaneous RFA.

Percutaneous RFA

All RFA procedures were performed 5 hours after TAE. We used a 460-kHz monopolar RF generator (RF3000; Boston Scientific) with a maximum power output of 100W and a coaxial 14-gauge LeVeen needle electrode (Boston Scientific, San Jose, CA, USA) featuring a 2-, 3-, and 3.5-cm array.

The needle electrode was placed under CT-fluoroscopic guidance using iodized oil as a puncture marker. After satisfactory deployment, a 2-, 3-, and 3.5-cm needle was connected to the RF generator and ablation was started at 20-, 30-, and 40W; the energy was increased by 5-, 7-, and 10W at one-minute intervals. Tissue impedance was continuously monitored.
and ablation was stopped when there was a sharp rise in tissue impedance (roll-off). After a one-minute cool down, we performed a 2nd ablation session [114]. To obtain the ablative margin we created multiple overlapping ablation zones when using electrodes whose array diameter or noninsulated tip length was equal to or smaller than the tumor diameter.

**Evaluation**

We evaluated the degree of pain experienced by HCC patients undergoing RFA on the Visual Analogue Scale (VAS, Figure 9), a 100 mm-long horizontal line was anchored by word descriptors at each end. It measures characteristics or attitudes that range across a continuum of values that cannot be easily measured directly [115]. Patients placed marks along the line at points that reflect their perception of their current state and the distance between the left terminus of the line and the mark was measured. In this study we compared the VAS scores and anesthetic complications of both patient groups.
Figure 9. Visual Analogue Scale (VAS) 100mm

The visual analogue scale (VAS) is a horizontal straight line of 100 mm. Patients mark the degree of their pain along the line where the left and right termini indicate no- and maximum pain, respectively.
Fentanyl toxicity was graded according to the National Cancer Institute Common Toxicity criteria (version 4.0). Complications were assessed using previously described guidelines based on the number of ablation sessions [75, 116]. Events resulting in serious morbidity and/or disability or the need for a high level of care requiring hospitalization or a prolonged hospital stay were considered major complications. All other complications were recorded as minor.

The therapeutic effects of treatment were evaluated on contrast-enhanced dynamic CT- or MRI scans obtained within 3 months after RFA. We performed MR studies to exclude lipiodol artifacts in cases where unenhanced CT scans obtained immediately after RFA showed dense lipiodol deposits. Lesions with enhancement exceeding 10 Hounsfield units on CT images acquired after the injection of contrast medium were considered as untreated tumors. Tumor enhancement on MRI scans was evaluated qualitatively. The endpoint of RFA was the presence of an area of non-enhancing tissue that contained all of the treated tumor(s) on enhanced CT- or MRI scans.

**Statistical Analysis**

To assess the significance of differences between the background clinical characteristics and VAS scores of group 1 and 2 patients we used the X^2 test, the Fisher exact
probability test, and the Mann-Whitney \textit{U}-test. Differences in survival rates were evaluated with the generalized Wilcoxon test. Values of \( p < 0.05 \) were considered statistically significant.
4. Results

Technical success and therapeutic effects

Selective arterial embolization was technically successful in all 83 patients; angiograms confirmed the retention of contrast medium in vessels feeding the tumor. The average interval between selective arterial embolization and RFA was 5.2 hours (range 4 - 6 hours). On contrast-enhanced dynamic CT- or MR images obtained within 3 months after RFA, enhancement disappeared after two RF roll-offs in 39 of 41 group 1- (95.1%) and in 41 of 42 group 2 patients (97.6%). On contrast-enhanced CT images acquired 3 months after RFA, 2 group 1 (4.9%) and one group 2 patient (2.4%) manifested residual enhancement; these patients underwent additional treatments with same procedure. There was no significant difference in the rate of local recurrence between the two groups and no tumors required further treatments. There were no complications resulting in mortality in either treatment group.

Major complications occurred in 3 group 1- (7.3%) and 4 group 2 patients (9.5%). One group 2 patient developed hemorrhage; pneumothorax was observed in 3 patients from each group. All other complications were recorded as minor.

Treatment characteristics and toxicity

Table 7 shows the relationship between the VAS score and the treatment parameters.
The median VAS score was 4.0 ± 1.8 in group 1 and 3.4 ± 1.9 in group 2, the difference was not statistically significant (p=0.10). The median time for RFA, and the roll-off time were 74.0- and 4.2 min in group 1 and 70.6- and 4.4 min in group 2, the difference between the groups was not statistically significant (p=0.51 and p=0.75).

In Table 8 we present the relationship between the VAS score and the administered doses of diazepam and fentanyl. The median dose of additional diazepam was 7.8 mg in group 1 and 4.3 mg in group 2, the difference was statistically significant (p<0.01). The median fentanyl dose was 470 μg in group 1 and 490 μg in group 2; the difference between the two groups was not statistically significant (p=0.63).

Major fentanyl or diazepam toxicity was recorded in 11 group 1 (26.8%) and 2 group 2 patients (4.8%); it included apnea and respiratory depression with degraded oxygen saturation. The difference between the two groups was statistically significant (p<0.01).
Table 7. Relationship between the VAS score and treatment parameters

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>VAS score</td>
<td>4.0±1.8</td>
<td>3.4±1.9</td>
<td>0.10</td>
</tr>
<tr>
<td>Time for RFA (min)</td>
<td>74.0±22.7</td>
<td>70.6±24.7</td>
<td>0.51</td>
</tr>
<tr>
<td>Roll off time (min)</td>
<td>4.2±1.9</td>
<td>4.4±1.9</td>
<td>0.75</td>
</tr>
<tr>
<td>RFA session</td>
<td>3.3±1.5</td>
<td>3.0±1.3</td>
<td>0.28</td>
</tr>
</tbody>
</table>

Group 1 (n=41): One-shot iv fentanyl delivery  
Group 2 (n=42): Continuous iv fentanyl delivery

Table 8. Relationship between the VAS score and the diazepam and fentanyl dose

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>VAS score</td>
<td>4.0±1.8</td>
<td>3.4±1.9</td>
<td>0.10</td>
</tr>
<tr>
<td>Diazepam (mg)</td>
<td>7.8±5.8</td>
<td>4.3±5.2</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Fentanyl (μg)</td>
<td>470±14.0</td>
<td>490±15.6</td>
<td>0.63</td>
</tr>
</tbody>
</table>

Group 1 (n=41): One-shot iv fentanyl delivery  
Group 2 (n=42): Continuous iv fentanyl delivery
5. **Discussion**

The continuous infusion of fentanyl provided effective and safe analgesia in HCC patients undergoing percutaneous RFA. To achieve a good therapeutic response to percutaneous RFA, the precise placement of the RF electrodes is crucial. However, it can be difficult to identify the target tumor(s) by US, which is currently the main guidance modality used for targeting the tumors. US-guided percutaneous RFA was not feasible in 45% of the patients reported by Rhim [103]. Artificial pleural effusion, the ascites method, the use of US contrast agents, and image fusion are among the methods applied to overcome this problem [117-120]. The combined intra-arterial injection of iodized oil was another attempt to depict the target tumor(s) at the time of percutaneous RFA [121, 122]. In our study, all HCCs were depicted after the intra-arterial injection of iodized oil and CT-fluoroscopy-guided RFA was performed successfully.

A characteristic of RFA is its cooling effect on the blood flow; this has a considerable effect on the outcome of RFA treatment [79, 80]. The reduced efficacy of RFA with respect to large tumors reflects the *in vivo* biophysiological limitations imposed by perfusion-mediated vascular cooling; this limits heat-induced coagulation necrosis. In animal models it was possible to increase RF-induced coagulation necrosis by occluding the blood flow to the liver during ablation procedures [79, 81-83].
In our study the interval between arterial embolization and RFA was 5 hours rather than days; this decreased both the burden placed on our patients and the treatment costs. The length of hospitalization was shorter than in patients subjected to two-session intervention. We were able to use a temporary embolic material, gelatin sponge particles, for selective arterial embolization. Iodized oil served as a marker for CT-guided kidney puncture and our follow-up imaging studies confirmed that the treatment of even large tumors was successful.

Various types of anesthetic techniques have yielded favorable results [109]. The most common method was total iv anesthesia. Minor complications were uncommon. Nimmaanrat et al. [109] reported that among 120 percutaneous ethanol injection sessions, only one patient experienced cardiovascular collapse immediately after the injection was completed. Fentanyl tends to be used for total iv anesthesia, its onset is faster than of morphine [110].

An ultra-short-acting opioid such as remifentanil is preferable to long-acting opioids such as morphine because it does not exert significant adverse effects on the cardiovascular system and unlike other opioids, it does not accumulate in the body [123]. In addition, the intraoperative delivery of remifentanil induces less postoperative nausea and vomiting than the intraoperative injection of fentanyl [124]. According to Egan et al. [125] the bolus injection of remifentanil was safe and effective. However, some younger patients experienced respiratory depression at a relatively low dose of remifentanil and some suffered episodes of
apnea. In addition, after 25 μg of remifentanil were delivered, both young and older patients manifested respiratory depression. We encountered fentanyl-induced respiratory depression in 11 group 1- (26.8%) and 2 group 2 patients (4.8%); these adverse events included apnea and respiratory depression. The difference between the two groups was statistically significant (p<0.05).

Our study has some limitations. First, the need for strict inclusion criteria limited the number of enrolled patients; this precluded meaningful statistical data analysis and may have magnified selection bias. Second, we did not compare pain control in patients given morphine or diazepam. Third, as we administered diazepam in addition to fentanyl, we cannot rule out the possibility that the side effects were attributable to diazepam.

In conclusion, the continuous infusion of fentanyl provided effective and safe analgesia in HCC patients undergoing percutaneous RFA.
General Conclusions

CT-guided percutaneous biopsy is an easy and safe procedure that can yield a precise diagnosis in the majority of mediastinal tumors. Therefore, CT-guided mediastinal needle biopsy has been recommended as the initial diagnostic procedure in patients with mediastinal masses. Although we did not find that PET/CT-guided biopsy of mediastinal tumors offered specific advantages, further evaluation of its clinical impact and cost-effectiveness requires larger trials.

Percutaneous RFA does not elicit some of the side effects of other ablative techniques and it is performed widely due to its ease of use, safety, reasonable cost, and minimal invasiveness. Pain control during percutaneous RFA for HCC is important for a safe procedure.

Our findings suggest that the continuous infusion of fentanyl provides effective and safe analgesia in HCC patients undergoing percutaneous RFA.

CT-guided percutaneous mediastinal biopsy and RFA for HCC with the continuous infusion of fentanyl are useful and safe for use in clinical practice.
References


119. Miyamoto, N., et al., *Sonazoid-enhanced sonography for guiding radiofrequency ablation for hepatocellular carcinoma: better tumor visualization by Kupffer-phase*


