Pancreatic Cancer

Surgical Aspects in Targeted Therapy for Pancreatic Cancer

Interventional Radiology - Important Aspects

Progress in Liver Surgery

Influence of Dental Implant Surface Modifications on Osse- and Periointegration

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المطلبية في الطريقة الجراحية

الاعتبارات الجراحية في المعالجة المطلوبة لسرطان البنكرياس

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Interventional Radiology - Important Aspects

متقدم في جراحة الكبد

Influence of Dental Implant Surface Modifications on Osse- and Periointegration

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Germany takes a leading position in medicine.

German hospitals, clinics and medical doctors enjoy an excellent reputation. The continuously rising number of patients, who come to Germany to receive medical treatment and support, strongly confirms this fact.

Patients from the Gulf States gladly come to Germany to receive medical treatment because they regard Germany as a safe place and rely on German clinics and physicians. They feel welcome as guests and enjoy that they are encountered in an open-minded and friendly way.

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يكون مرجعًا.
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Keywords: Pancreatic cancer, surgical therapy

Introduction

The majority of periampullary tumors originate from the pancreas. The pancreatic component that is responsible for most of the tumors is the duct-system [1]. Therefore, invasive ductal adenocarcinoma is the most common tumor of the pancreas [2]. Nowadays, pancreatic cancer has reached the fourth leading cause of cancer mortality in the USA and western europe, indicating the significance of committed efforts to fight this tumor [3]. Complete resection of the tumor, so called radical resection, remains the only potential curative option for patients confronted with the diagnosis of pancreatic cancer.

Whether technical improvements in pancreatic surgery during the last 30 years significantly decreased the perioperative morbidity and mortality, several surgical aspects are not clear yet and still open for discussion. Especially, the role of surgical approaches in the context of new adjuvant treatment options and effective interdisciplinary interactions are challenges to pancreatic surgeons. The following manuscript tries to give a short survey on the spectrum of current surgical standards, perspectives and limits (Fig. 1).

Appropriate Preoperative Diagnostic Work Up

Because most pancreatic cancers arise in the right side of the pancreatic gland, the cardinal symptom is jaundice, resulting from obstruction of the intrapancreatic part of the common bile duct. However, due to the often delayed occurrence of clinical symptoms, for the majority of patients curative resection is not feasible at the time of diagnosis [4]. Especially in patients with pancreatic cancer arising from the left side of the pancreatic gland, jaundice generally is missing. Therefore, the disease often is not diagnosed until the tumor is locally advanced or metastatic. Today, preoperative clarification of localisation and expansion of the tumor by computed tomography is the

خلال النص التالي نعطي تصفح قصير للفحص التشخيصي الجراحية الحالية. ومستقبلها وحدودها (شكل 1).

الإجراءات التشخيصية المناسبة التي تسبق العمل الجراحي

نظراً لحدود أغلب سرطانات البنكرياس في الجهة اليمنى من البنكرياس فإن الأعراض الرئيسية هي اليرق الناجم عن انسداد قسم القناة الصفراوية الجامعة والموجودة ضمن البنكرياس. مع ذلك و بسبب تأخر حدوث الأعراض السريرية فإن القطع الجراحي الشفافي غير ممكن عند التشخيص (4). خاصة لدى مرضى سرطان البنكرياس الناجمة عن القسم الأيسر من الغدة، حيث لا يشاهد بشكل عام اليرق، لذلك لا يتم تشخيص المرض حتى يحدث تطور الورم موضعياً أو حدوث الانتقالات. حالياً أفضل وسيلة تشخيصية هو استخدام التصوير الطبيق المحوري الذي يحدث قبل الجراحة موضع الورم وانتشاراته. ومن الهمام في هذا المضمور أن نؤكد تقييم إمكانية القطع الجراحي

المقدمة

تتنوع معظم الأورام في منطقة ماحول المجل من البنكرياس. إن الجزء من البنكرياس المسؤول عن أغلب الأورام نتجم عن نظام الأقنعة (1). لذلك فإن أكثر أورام البنكرياس شيوعاً هو سرطان الأقنعة الغدية الغازية (2). حالياً أصبح سرطان البنكرياس رابع سبب في مقدمة أسباب الوفيات للسرطان في الولايات المتحدة وأوروبا الغربية (3). ويبقى الاستئصال التام للورم، أو ما يدعى الاستئصال الجدي، هو الخيار الشافي الممكن الوحيد للمرضي المشخيص لديه سرطان البنكرياس. ونقرأ للتطبيقات التقنية في جراحة البنكرياس خلال الثلاثين سنة الماضية أدت إلى إقفال نسبة المرضة الوفي. ماحول الجراحة ولكن هناك اعتبارات جراحية متعددة ماتزال غير واضحة ومفتوحة للنقاش. و خاصة دور العلاج البديل في منح استعمال خيارات المعالجة المراقبة والجديدة والتفاعلات الفعالة ضمن فرق المعالجة هي تحديات لجراح البنكرياس ومن
preferred imaging modality. In this context it is important to emphasize that assessment of resectability should be only performed via laparotomy. Radiological (CT/MRI) signs of local inoperability, such as involvement of the mesenteric portal axis or visceral arteries should not be interpreted in general as contraindication for surgical exploration. In such cases surgical exploration may indicated to confirm inoperability. However, laparoscopic exploration only excludes potential peritoneal carcinomatosis or liver metastasis, therefore gives incomplete information regarding the local resectability and can not be recommended to clarify the local situation [5].

The role of endoscopic retrograde cholangiopancreatography (ERCP), as a invasive procedure, in patients with clinical and radiological suspicion of a pancreatic malignoma is negligible nowadays. Precise visualisation of the peripancreatic region including ductal structures should be performed using MRI-imaging. In selected cases, as in patients with severe jaundice, preoperative biliary stenting prior to pancreatic resection may be reasonable . Malignant biliary tract obstruction can cause severe cholangitis leading to cholangiosepsis [6]. Nevertheless preoperative stenting is still under discussion. On the one hand a correlation between obstructive jaundice and operative morbidity and mortality could be demonstrated [7]. On the other hand recent studies showed that short-term preoperative biliary decompression does not improve surgical results after pancreatic head resection [8]. Prospective trials have failed to show either significant reduction of in-hospital time nor decreasing morbidity after preoperative drainage [9, 10]. Recent findings indicate that preoperative stenting seems to increase the rate of wound infections and possibly contaminate bile after instrumentation of the bile duct [9]. For that preoperative biliary stenting can not be recommended generally in jaundiced patients due to malignant distal bile duct occlusion, and therefore should only be used very selectively.

**Contraindications for Pancreatic Resection**

Because of the agressive nature of the tumor and due to early metastases in only 20% of patients curative resection is feasible at time of physician first contact [4]. However, the only curative intent is a radical resection of the tumor. A strong contraindication for pancreaticoduodenectomy is the presence of distant metastasis including peritoneal carcinomatosis. A metastatic stage of the disease is known as a significant predictor of short expected survival. Further contraindications for radical surgery are: Tumor invasion of the mesenterical root and/or invasion of visceral arteries (superior mesenteric artery (SMA), celiac axis or hepatic artery). Nowadays, cancer invasion of the superior mesenteric-portal venous confluence (SMPCV) should no longer be considered as a contraindication for pancreatic resection [11].

**Contraindications for Endoscopic Retroduodenoplasty**

Due to the agressive nature of the tumor and cancer invasion of the mesenterial root and/or invasion of visceral arteries (superior mesenteric artery (SMA), celiac axis or hepatic artery). Nowadays, cancer invasion of the superior mesenteric-portal venous confluence (SMPCV) should no longer be considered as a contraindication for pancreatic resection [11].

**Contraindications for Preoperative Drainage**

Due to the agressive nature of the tumor and cancer invasion of the mesenterial root and/or invasion of visceral arteries (superior mesenteric artery (SMA), celiac axis or hepatic artery). Nowadays, cancer invasion of the superior mesenteric-portal venous confluence (SMPCV) should no longer be considered as a contraindication for pancreatic resection [11].

Conclusions:

- **Early Metastases:** Early metastases in only 20% of patients affects the resectability of the tumor.
- **Local Inoperability:** Radiological (CT/MRI) signs of local inoperability should be interpreted as confirmatory findings and not as absolute contraindications.
- **Preoperative Stenting:** Preoperative stenting is not recommended generally in jaundiced patients due to malignant distal bile duct occlusion, and therefore should only be used very selectively.
- **Contraindications:** Contraindications for pancreatic resection include distant metastasis, peritoneal carcinomatosis, and involvement of the mesenterial root and/or invasion of visceral arteries (superior mesenteric artery (SMA), celiac axis or hepatic artery).
- **Preoperative Drainage:** Preoperative drainage is not recommended generally in jaundiced patients due to malignant distal bile duct occlusion, and therefore should only be used very selectively.

**Hospital:**

1. The German Medical Journal is a peer-reviewed medical journal published by the German Medical Association. It covers a wide range of topics in medicine and surgery, with a focus on cancer research.
2. The article discusses the role of endoscopic retrograde cholangiopancreatography (ERCP) in the assessment of resectability in pancreatic cancer.
3. The authors argue that ERCP is not a suitable method for assessing resectability due to its low sensitivity in detecting local inoperability.
4. The article recommends a more invasive approach, such as laparotomy, for assessing resectability.
5. The authors conclude that preoperative stenting is not recommended due to its potential complications and lack of evidence for improved outcomes.
6. The article highlights the importance of multidisciplinary assessment and decision-making in determining resectability.
7. The authors suggest that further research is needed to develop more accurate methods for assessing resectability in pancreatic cancer.

**References:**


to the significant increased mortality risk for patients with concomitant severe disease indication for pancreaticoduodenectomy should be carefully evaluated in such patients. Because of declining surgical mortality rates after pancreatic resection, the significance of palliative resections has been discussed more and more in recent years. Especially, the question whether a palliative resection should be offered to patients with hepatic metastases is still unanswered.

Standard Surgical Procedures

Today, the standard resection procedure for periampullary malignancies is the pylorus-preserving pancreaticoduodenectomy (PPPD). In contrast to the standard Kausch-Whipple operation this technique preserves the entire stomach, including the pylorus, cutting the duodenum usually about 2-3cm distal from the pyloric ring. The discussion regarding oncological radicality of the pylorus-preserving technique should belong to the past yet [12,13]. The pylorus-preserving pancreaticoduodenectomy is a safe and radical operation which, does not affect the prognosis [14].

The surgical treatment of left sided carcinomas (pancreatic body or pancreatic tail) is the so-called pancreatic left resection. Such resections should

Fig.1: Ductal adenocarcinoma of the pancreatic head. The tumor is clearly circumscribed and surrounded by soft, tan lobulated pancreatic tissue without signs of pancreatitis.
be performed, also based on the principles of surgical oncology, as no-touch-technique and standard en-bloc dissection of the peripancreatic lymph nodes and in general combined with splenectomy. Depending on the dimension of a left sided carcinoma, the resection has to be extended towards the pancreatic head to reach tumor free resection margins (subtotal left-sided pancreatectomy).

The pancreatic-enteric anastomosis is the weak point of pancreatic surgery. Devastating clinical courses after development of a pancreatic leak are a common feared complication. The operative resection of pancreatic cancer includes cautious handling of the pancreatic remnant [15]. One of the most commonly employed techniques is a pancreatico-jejunal anastomosis. However, to prevent a leakage from the pancreatico-jejunal anastomosis, different anastomotic techniques have been published during recent years. Which technique of pancreatico-jejunal anastomosis, whether end-to-side or end-to-end, and whether duct-to-mucosa, does not seem to influence the anastomotic leak incidence significantly [16-18]. Several strategies have been established in the past to improve the safety of the pancreatic-enteric anastomosis. One alternative reconstruction technique after pancreatic head resection is the introduction of a pancreaticogastrostomy [19]. Three different principles to achieve pancreaticogastrostomy are in use today: The implantation of the pancreatic remnant into the stomach, the implantation of only the pancreatic duct into the stomach, or an anastomosis between the pancreatic duct and the gastric mucosa. (Fig. 2, 3). A view through the literature shows that the surgical results after pancreaticogastrostomy are similar to those presented after pancreaticogastrostomy [20-22]. There is still the discussion that long-term pancreatic secretion into the stomach causes alkaline juice, which affect the gastric mucosa. To date there is no substantial data showing a correlation between an increased risk of peptic ulcers and pancreato-gastric anastomosis [23]. In summary, rather than the choice of the variant used, however, the successful management of the pancreatic anastomosis depends more on the surgeon’s concentration and whether duct-to-mucosa, end-to-side or end-to-end, different anastomoses—end-to-end or duct-to-mucosa, whether duct-to-mucosa, whether duct-to-mucosa, whether duct-to-mucosa, different anastomoses—end-to-end or duct-to-mucosa.

Anastomoses establishment in the past several strategies for improvement of prognosis have been established. One approach was the introduction of total pancreatoduodenectomy [25]. The idea was that the removal of the entire pancreas can eliminate multifocal disease, achieve broad resection margins and allows the avoidance of as pancreatic leakage, pancreatitis or pancreatic fistula. However, several studies showed that the median survival for patients after total pancreatoduodenectomy was significantly lower compared to patients undergoing partial pancreatoduodenectomy [26]. The removal of the pancreatic gland can cause severe metabolic dysfunctions as a consequence to the loss of pancre-
Lymph Node Dissection

Affection of lymph nodes are reported to be found in more than 70% of patients after resection [28]. The standard lymph node dissection is defined as radical lymphadenectomy along the hepatoduodenal ligament, the celiac trunk and superior mesenteric artery, the mesenteric vein and portal vein.

The rationale for the so called extended lymphadenectomy is, that lymph node studies have shown positive lymph nodes beyond the bound of the standard dissection [29]. Nagakawa et al. could demonstrate metastatic lymph nodes of the paraaortic region, between the celiac trunk and the origin of the inferior mesenteric artery [30]. These findings led to the suggestion, that these lymph nodes should be removed en bloc during radical resection. The extended lymph node dissection therefore includes the resection of bilateral paraaortic lymphatic tissue from the transverse colon to the diaphragm.

Fig. 2: View into the opened stomach. The pancreatic stump has been placed through the dorsal gastric wall and sutured in mattress technique. Additionally, a short tube has been inserted into the pancreatic duct of the remnant.

The extended lymph node dissection during radical resection.

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diaphragm down to the inferior mesenteric artery and laterally to the hilum of the right kidney [31]. Several recent studies indicated a variability in results regarding the influence of an extended lymph node dissection. Nimura et al. compared 51 patients after standard lymphadenectomy versus 50 patients after extended lymph node dissection in a prospective randomized trial. No differences could be detected in overall survival, survival for pN0/ pN1, tumor recurrence, body weight, quality of live and bowel movements [32, 33]. Neoptolemos et al. demonstrated that metastatic involvement of lymph node 8a (located at the common hepatic artery) is an independent prognostic factor after pylorus-preserving resection [34]. Two further randomized studies from Baltimore reported a similar overall morbidity, although the study indicated an increased rate of delayed gastric emptying after extended lymph node dissection [35, 36]. The current standard of surgery for pancreatic head tumors therefore is a pancreatic head resection without extended lymphadenectomy [37](Table1).

Vascular Resection

Tumor invasion of portal or superior mesenteric vein has always been a controversial issue in pancreatic surgery. Fuhrmann and colleagues found that tumors adherent to the hilum of the right kidney (mesenteric artery and laterally the diaphragm down to the inferior mesenteric artery) is an independent prognostic factor after pylorus-preserving resection [34]. Two further randomized studies from Baltimore reported a similar overall morbidity, although the study indicated an increased rate of delayed gastric emptying after extended lymph node dissection [35, 36]. The current standard of surgery for pancreatic head tumors therefore is a pancreatic head resection without extended lymphadenectomy [37](Table1).

Fig. 3: Pancreatic remnant after implantation into the stomach (a: Stomach, b: Pancreatic remnant, c: Portal vein, d: Hepatic artery)
the superior mesenteric vein-portal vein trunk did not display eminent aggressiv biology [38]. They concluded that venous adherence was more a function of tumor localisation rather than an indicator of aggressiveness. Furthermore, pathological assessments of resected veins confirmed cancerous venous invasion in about 20 - 70% of resected specimens [39, 40]. This data indicates, that a significant percentage of patients with suspected venous tumor invasion only show an inflammatory adherence. For that, portal vein invasion should not lead to an absolute contraindication for pancreatic resection. New data indicate that the need for portal resection does not affect overall patient survival. Lygidakis et al. showed that patients with portal-mesenteric venous invasion had far better 5 - year survival compared with patients who were randomized to only palliative bypass [41]. Several surgical techniques in case of venous involvement are common: Tangential resection and venous patch-plastic, segmental resection with splenic vein ligation and primary anastomosis or splenic vein ligation and graft interposition. Further techniques are the segmental resection with splenic vein preservation either with primary anastomosis or again with graft interposition [42, 43](Table 2).

In a subgroup of patients curative resection is denied as a result of the direct invasion of major visceral arteries, often in the absence of distant disease. On the one hand the involvement of major vessels, such as the celiac axis, is a clear contraindication for resection for most surgeons. On the other hand, radical vascular resection in such cases can potentially implicate complete tumor removal leading long-term survival. The Appleby operation proposed en-bloc resection of the celiac trunk with distal pancreactectomy a the treatment of patients with locally invasive carcinomas of the body and tail of the pancreas. The anatomic and physiological premises for this approach is the presence of collateral circulation between the superior mesenteric artery (SMA) and the hepatobiliary system by way of an intact pancreaticoduodenal arcade [44, 45]. However, such surgical approaches have not yet been established as a standard technique and therefore are only indicated in highly selected patients.

Significance of Extended Pancreatectomy

In efforts to improve the long-term results after pancreatic resection, the palliative bypass [41] to only palliative bypass [41].

Table 1

<table>
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<tr>
<th>LN Group</th>
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<th>LN-positive patients %</th>
<th>Involved LN (mean)</th>
<th>Involved LN (median)</th>
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<td>paraortic</td>
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<td>3,40</td>
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<td>common hepatic artery</td>
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<td>0,60</td>
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<td>infrapyloric</td>
<td>7</td>
<td>0,10</td>
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Tangen- estudied - showed that the result of the direct invasion of the pancreas. The anomalous adherence of the arteries and veins is a significant factor in the long-term survival of patients with locally invasive carcinomas of the body and tail of the pancreas. The anatomic and physiological premises for this approach is the presence of collateral circulation between the superior mesenteric artery (SMA) and the hepatobiliary system by way of an intact pancreaticoduodenal arcade [44, 45]. However, such surgical approaches have not yet been established as a standard technique and therefore are only indicated in highly selected patients.

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Palliative Pancreatic Head Resection

The goal of palliative therapy is to prolong life by relieving life threatening biliary and duodenal obstruction to improve quality of life by eliminating local tumor associated problems. This does not mean, that only surgery offers the best possible palliation, but no effective alternative therapies are available and only resection of the tumor offers a chance for long-term survival. For that, the goal of modern pancreatic cancer surgery should not be the selection of patients with the greatest chance for cure. Contrarily, the selection of patients in whom resection provides a chance for longer survival and better quality of life should be considered for pancreatic resection. Increasing the rates of resection might also include M1 resections in selected patients. Further arguments for extending the resectability criteria are supported by the results of recent multicenter trials in adjuvant chemotherapy after R0 and R1 resections for pancreatic head carcinoma indicating that even the patients with R1 resection showed a benefit from postoperative adjuvant resection [50]. To date no prospective data are available in which a palliative resection was investigated in a randomized fashion. To elucidate the role of palliative pancreatic head resection we conducted a prospective randomised study. We derived a protocol in which patients with carcinomas of the pancreatic head and synchronous liver metastasis were rand-

<table>
<thead>
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<th>Author</th>
<th>Histological portal vein invasion (%)</th>
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<th>3-year survival (%)</th>
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Table 2

أهمية الاستئصال الواسع

ليس من خلال الجهود لتحسين النتائج على المدى البعيد بعد استئصال السرطان، فإن الاستئصال الجراحية لسرطان البانكرياس الفجع من خلال خارج السيرير السرطاني، أصبح أكثر شدة.

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all data show that resection for recurrent adenocarcinoma of the pancreas does not significantly increase survival [55]. The aim of further studies should be to identify subgroups of patients potentially benefit from reoperation. For that, re-resection for recurrent pancreatic cancer cannot be recommended outside randomized controlled trials yet.

**Summary**

Today, surgical resection of localized adenocarcinoma of the pancreas still remains the only potentially curative option for these patients. Advances in surgical techniques and perioperative care have improved significantly during last twenty years, causing an extension of indications for surgical intervention. As a standard resection procedure for periampullary malignancies the pylorus-preserving pancreatoduodenectomy (PPPD) has been established in recent years. Resections of advanced tumors including portal vein resections can be carried out safely nowadays with low perioperative mortality rates. Although new diagnostic techniques are established, surgical exploration is still very important for the final assessment of resectability. However, laparoscopic exploration only gives incomplete information regarding the local resectability and can not be recommended to clarify the local situation. Contraindications for pancreatic resection are distant metastasis, peritoneal metastasis and tumor infiltration of visceral arteries. But, nowadays, cancer invasion of the mesenteric-

**Resection for Recurrent Pancreatic Cancer**

Although the significant progress in pancreatic surgery over the last 20 years the 5-year survival rate of resected patients are still between 15-20% [51]. One reason for this phenomena is that, even after curative resection, tumor cells are detectable on the edge of resected samples in up to 50% of cases [52]. A further reason seems to be the presence of systematic occult disease at the time of diagnosis leading to liver metastasis and peritoneal carcinomatosis in up to 50% patients [53, 54]. In case of tumor recurrence, there are no established surgical strategies. In other words: The significance of re-resection for pancreatic carcinoma is completely unclear. In a recent paper Kleef et al. reported on the outcome of patients re-operated for recurrent pancreatic cancer. They found an increased median survival in patients undergoing resection compared with patients undergoing exploration or palliative bypass. Interestingly, they found an increased median survival for patients with a prolonged interval from resection to recurrence. Over

احتعلت المرضى الذين سوف يقدموهم للقطع فرصة أفضل للحياة. وبتفاهم أفضل للحياة يجب أن يتم اختيارهم لإجراءات قطع المدة. إن ازدياد معدل القطع من الممكن من ازدياد قطع M1 في بعض الوقت أو ازدياد مراقبة قطع من أجل توضيح معايير القطع من قبل نتائج الدورات المتعددة المراكز

للعلماء الكيميائية الممارسة بعد قطع R1 لسرطان الأندروفا للدورة الانتقائية لسرطان الأندروفا والتي تشير إلى مدى максимально المتضمن في M1 إلى أن قطع R1 لدى المرضى أظهر فوائد من القطع المفقود (50). وإلى الآن لا يوجد معلومات استثمارية والتي فيها يتم الدماء المعوقة من أجل القطع التلطيفي.

وإلا يضاعف دور قطع لأندروفا للدورة التلطيفي لتوصل إجراء دراسة

عشوائية استقصائية. وقد تم وضع بروتوكول لدى المرضى المصابين بسرطان أندروفا للدورة للانتقائيات الجينية مسلمة حيث تم توقيع المرضى عشوائيا إلى المجموعتين abine

بقيادة المتخصصين: gemicitinbserver نونو مثل و R0. في و R1 المرضى لم تظه مزج مع الفوائد، ولا يوجد من الأنواع الأخرى قطع أندروفا مثبتاً للمعالجة القياسية لـ gemicitinbserver و

لم يتم إعطاء المجموعة الأخرى قطع أندروفا مثبتاً بالمعالجة القياسية abine gemicitinbserver.

وبشكل عام تظهر النتائج بأن الاستئصال من أجل معالجة الأدوية أو الشعور في الانتقائيات لدورة أندروفا في الناقش لا ت.didn’t أندروفا مثبتاً من معدل الحياة (55). لذلك فإن الفوائد من الاستئصال الأخرى يجب أن تكون المجموعات الجزئية من المرضى الذين من الممكن أن يستفيدوا من إعادة العملية. لذلك فإن إعادة القطع

من الممكن أن يؤثر التطور الملحوظ في جراحة الأندروفا خلال العشر سنوات على نتائج هذه الجراحة. كما أن التطورات الجراحية غير المسبوقة في القص الانتقائيات مثل التوسيع الجاهز من أورام الأندروفا، و Tết هيئة من الممكن أن يؤثر التطور الملحوظ في جراحة الأندروفا خلال العشر سنوات على نتائج هذه الجراحة. كما أن التطورات الجراحية غير المسبوقة في القص الانتقائيات مثل التوسيع الجاهز من أورام الأندروفا، و
Serum vascular confluence should no longer be considered as a contraindication. In regard to lymph node dissection the current standard resection is defined as a radical lymphadenectomy along the hepato-duodenal ligament, the celiac trunk and superior mesenteric artery, the mesenteric vein and portal vein with or without extended lymph node dissection. Palliative pancreatic head resections and re-resections for recurrent pancreatic cancer are not indicated to date beyond accepted study protocols.

References
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New Treatment Option that Opens Up New Avenues in the Treatment of Resistant Hypertension — Renal Sympathetic Denervation

Background
Hypertension is a major global public health concern and widespread disease number one. Especially, in the industrialized countries its prevalence will increase in the years ahead. Some 30-40% of the world’s adult population suffer from hypertension, and, of these, 10-15% suffer truly resistant hypertension. Several hypertensive patients are faced with lifelong intake of medicines for reducing their chances of suffering from heart attacks, renal insufficiency or stroke. Despite the daily intake of many antihypertensive drugs, nearly half of these patients continue to have inadequately controlled blood pressure. Many patients do not achieve adequate blood pressure control despite the use of multiple medications as well as dietary and lifestyle modifications. Many pharmacological therapies have been tried. But still, when blood pressure is not controlled, there is a very high burden of stroke, heart attack and cardiovascular death. Mechanistically, hyperactivity of the sympathetic nervous system activates norepinephrine release from the kidneys and seems to be an important contributor for maintaining hypertension and its progression [1]. In previous studies in Homburg and Australia patients were intensively evaluated to exclude secondary forms of hypertension. In particular, renal artery stenosis was excluded.

The Procedure
The renal denervation procedure itself involves endovascular catheter base approach to disrupt renal sympathetic nerves using radiofrequency (RF) ablation applied at an electrode at the catheter tip (Fig. 1).

The catheter is placed via the femoral artery and the aorta to the lumen of the main renal artery. A guiding catheter is used to insert the Symplicity catheter (Adrian Inc., USA) in the renal artery and is connected to a RF generator. The catheter tip is placed before the first junction in the main trunk of the renal artery. Multiple RF treatments are applied. The developed key is controlled by the generator and several points of RF application was excluded.

The Denervation Process
The renal denervation procedure was initially performed in 16 patients with resistant hypertension at the Clinical Research Center in Homburg, Germany. The clinical effect was assessed by a core laboratory that received medical records. The initial study showed that the procedure reduced blood pressure by more than 1,000 mmHg in most patients. However, the long-term effect was not fully evaluated.

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are chosen circumferentially by pulling back the catheter tip into the proximal renal artery. Four to six treatments are applied in each individual renal artery in order to apply denervation to the full circumference of the vessel (Fig. 2). The ablations are separated both longitudinally and rotationally with a spacing of >5 mm. Each RF energy depletion takes about 2 minutes.

The first results have shown that blood pressure reduction is pronounced mounting to 20-35 mmHg systolic and 10-15 mmHg diastolic [2]. There is evidence that the blood pressure reflects stable over the available observation period, i.e. 24 months. Accordingly, there are no evidences of re-inervation. In addition to profound blood pressure reduction and high normalization rates in many patients, patients subjectively feel better, report better sleep and experience less headaches and symptoms of hypertension and sympathetic overactivity.

Furthermore, Mahfoud et al. [3] recently reported a marked improvement of metabolic parameters of glucose metabolism, improvement of insulin resistance and diabetes mellitus type 2. The later finding is of particular importance because resistant hypertension is frequently associated with impaired glucose metabolism and type 2 diabetes adding to the cardiovascular risk which is already imposed by hypertension.

This new catheter-based interventional approach has the potential to achieve blood pressure control in many patients who are not at levels which optimally prevents the occurrence of cardiovascular death, stroke and heart attack. Furthermore, there is a chance that drug exposure in the treated individuals can be reduced avoiding side effects like dizziness, orthostatic symptoms, metabolic disorders and erectile dysfunction. Long term studies are planned in order to assess how expressed the reduction of cardiovascular endpoints are.

Summary
Catheter-based renal denervation is a new and very promising therapy option for patients with resistant hypertension. During the minimally invasive procedure, the tip of the catheter is directed into the distal renal artery and two minutes of RF energy is applied. The tip

Fig. 1: Symplicity treatment catheter for interventional renal denervation.

Fig. 2: Close-up of the equipment and lead insertion during renal denervation.

Osteohrulistaq Data

Recent studies have shown that renal denervation can significantly reduce blood pressure in patients with resistant hypertension. This is achieved by reducing sympathetic overactivity, which is thought to be a key factor in the development of resistant hypertension. The procedure is performed using a catheter that is inserted into the renal artery and the tip is placed in the renal parenchyma. The sympathetic nerves are then ablated using radiofrequency energy, thereby reducing the sympathetic drive to the kidneys. This results in a decrease in renin secretion and, subsequently, a reduction in angiotensin II levels, which leads to a decrease in blood pressure.

This new approach to treating resistant hypertension offers several potential benefits compared to traditional pharmacological treatments. It is a minimally invasive procedure, with no need for surgery or hospitalization. It also avoids the side effects associated with long-term use of medication. Additionally, it can be delivered in a single session and does not require any additional medications.

Conclusion
Renal denervation is a promising new treatment option for patients with resistant hypertension. Further studies are needed to fully evaluate its effectiveness and safety, and to determine the optimal patient selection criteria. Despite these limitations, renal denervation offers a non-pharmacological approach to treating this challenging condition, and may represent an important addition to the therapeutic armamentarium.
is withdrawn, circumferentially rotated within the artery, and a further two minutes of energy is applied, and so on all the way back through the renal artery. Prof. M. Böhm, Dr. F. Mahfoud and their team treated most patients in Europe using the novel technique. Since 2008 the division is appointed as a Hypertension Excellence Centre of the European Society of Hypertension (ESH). Prof. Böhm works in close cooperation with the Baker Institute in Melbourne, Australia. “After denervation we see an immediate and sustained reduction in blood pressure of 30-35 mmHg, which sustained over 12 months, without any long-term adverse events,” he explained. The procedure only takes about 30-45 minutes and patients can be discharged very early after the intervention.

Interestingly, beside a dramatic blood pressure reduction, renal denervation influences also glucose metabolism. The research group from Homburg demonstrated for the first time, that interventional renal denervation improves insulin sensitivity and glucose metabolism in patients with resistant hypertension [3].

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Concept for the Treatment of Pelvic Ring Injuries in Elderly Patients – a Challenge

Summary
Whereas pelvic injuries in patients during their 20’s and 30’s are typically caused by high-energy traumas, another group suffering this type of injury are elderly patients between the age of seventy and eighty. Due to osteoporosis and comorbidity, particularly the female gender is affected by low-energy traumas. After taking medical history, a physical examination of the pelvis is performed. If necessary, this is followed by imaging with X-ray and CT-scan with 3D reconstruction. If there are concomitant injuries, additional diagnostic measures are essential (sonoagraphy, MRI, retrograde ureterography, cystography, excretion urogram).

The standard AO/ASIF classification (Arbeitsgemeinschaft für Osteosynthesefragen / Association for the Study of Internal Fixation) has proved well and does not depend on the age of the patient. A distinction is made between three different types of fractures (type A, B and C). This classification in combination with the description of the affected anatomical region (transsymphysious, transpubic, etc.) is in daily clinical practice sufficient to decide in favour of the necessary treatment.

There are frequent diagnostic problems in elderly patients (so-called differentiation of A-B problem). At first a type A fracture is diagnosed and treated by non-surgical measures. In case of persistent pain, the imaging is repeated and an additional (insufficiency-) fracture is shown. The therapeutic regime has to be changed using this new information.

The reconstruction of the pelvic ring is of major significance especially for elderly patients. This reduces the pain and the primary objective, the earliest possible rehabilitation without prolonged immobilisation, can be achieved. In elderly patients, the external fixation with supraacetabular screw positioning is an effective procedure. As a result, secondary insufficiency-instability (mostly dorsal) can be avoided. Whereas type A fractures can almost exclusively be treated by means of non-surgical measures, type B and C usually need surgery.

Patients – A Challenge

A review based on the data provided by the Study Group Pelvis III of the DGU (German Association for Trauma Surgery) (2004 – 2009; 4532 cases with 3410 pelvic ring injuries)

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Like in young patients, B fractures are stabilized ventrally and C fractures dorsoventrally. In case of emergency, the supracetabular external fixation, and where required, extraperitoneal tamponade have been established in Germany as the standard treatment methods for elderly patients. For the definite surgical management, standard procedures are used but they often have to be modified depending on the bone structure.

**Aetiology and Epidemiology**

The incidence of pelvic ring injuries amounts to 3% of all fractures. A concomitant pelvic ring injury is expected in 25% of all patients with multiple injuries or polytraumas. From the epidemiologic point of view, there are two peaks of incidence: on the one hand, in young, typically male patients (25 – 35 years), on the other, in elderly patients (80 years and over), in this case predominantly in women. Whereas in younger patients pelvic injuries very often occur only in combination with a high-energy trauma, a pelvic ring fracture in elderly patients can already be expected through a significantly lower energy impact (low-energy trauma caused by domestic accident). In this case, fractures can be regarded as the manifestation of a deficient bone structure. The sacroiliac joint in elderly patients is often ankylosic, which is the reason why transiliac fractures or direct sacrum fractures occur with special frequency in this group of patients (21% = 171 / 811 patients with type C injury > 65 years (Figures obtained from the data register of the Study Group Pelvis III of the DGU/AO, period 2004 – 2009 with altogether 4532 cases, thereof 75% (3410) of pelvic ring injuries)). Because of the low energy impact during the accident, however, the fracture frequency does not tend to significant dislocation and can thus be easily overlooked during conventional diagnostics. Chipping of the transverse processes of the lumbar vertebral body 5, clear persistence of complaints in the posterior pelvic ring region and “deep back pain” lasting for more than one week should thus always be an indication for the existence of a posterior pelvic ring injury requiring treatment and entail further diagnostic measures (incl. CT).

Most of the patients of this age group rarely survive pelvic injuries caused by a massive trauma. According to a study of the Study Group Pelvis III of the German Association for Trauma Surgery, patients who reach the clinic alive due to a overlooked fracture of the sacrum has a high frequency (about 75%).

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modern rescue network are predicted to have a high risk of yet not surviving this injury in the long term because of their age alone (comorbidity, sepsis, multiple organ failure).

Classification

Type A Fractures: These are stable anterior pelvic ring lesions without injury of the osteoligamentous structures of the biomechanically important posterior pelvic ring. According to the investigations of the Study Group Pelvis III of the DGU, these are with an incidence of 42% of all fractures still the most frequently occurring group of pelvic ring fractures; in patients > 65 years, this type of fracture occurs in 63% of all cases (comp: in patients < 65 years, this figure is 37%).

Type B Fractures: These are pelvic ring interruptions on the vertical axis of the pelvis. They may develop either through external or internal rotational movements. The ventral ligament sections of the sacroiliac joint are ruptured (external rotational injury) or the ventral edge

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Type C Fractures: Due to a corresponding trauma, excessive rotation and concomitant (mostly craniocaudal) translation of the pelvis occurs. Thus, full translational and rotational instability of the pelvis occurs; the continuity of the dorsal pelvic structures is completely interrupted. In case of elderly patients, a low energy impact is sufficient for this type of fracture to occur. Dorsal transforaminal sacrum fractures are frequently present (no posterior sacroiliac ligament bridging of the fracture in contrast to ala

Fig. 1c: After removing the fixation, an increasing ventral dislocation with migration of the S1 screw becomes evident.

Fig. 1d: Another fall, this time onto the left side; new left-lateral type B fracture.

Fig. 1e: Same procedure, this time left-laterally with iliosacral, navigation-supported screws and reapplication of a ventral external fixation. The somewhat caudally located entrance points of the first fixation are still recognizable in the clinical picture.

10: The ala sacralis is impressed (internal rotational injury). The dorsal pelvic ring structure is thus interrupted (rotationally unstable). This type of fracture occurs in 34% of all pelvic ring injuries (Study Group Pelvis iii). In patients > 65 years, this type of fracture occurs in 39% of all cases. Caused by lateral fall, the internal rotational injury in patients > 65 years is the most frequent cause for a type B injury (74%); by comparison, it only makes up 57% of the type B injuries in patients < 65 years.

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pelvic register of the Study Group Pelvis III, these can be found in only 5% of all patients > 65 years with type C injuries (171/811 type C fractures [21%]). By comparison, this figure is 79% in patients < 65 years (707/811 cases). Transiliac fractures or sacroiliac luxations occur less frequently but are just as unstable. If these fractures take a semilunar path out of the sacroiliac gap and run laterally into the iliac bone, these are referred to as “crescent or semilunar fractures”. This type of fracture may easily be overlooked during primary diagnostics but constitutes a special risk for a secondary dislocation with painful pseudoarthroses (so-called differentiation of B-C problem).

Complex Pelvic Injuries: A “complex pelvic injury” is understood to be a pelvic ring fracture with concomitant peripelvic soft-tissue damage, i.e. an additional injury of nerves, vessels, muscles or the pelvic viscerae [1]. Haemorrhages, an increased sepsis rate (contamination of extensive, retroperitoneal haematomata and necroses at large-scale decollements) and the multiple organ failure as a result of mostly long-term depression of the blood circulation make the complex pelvic injury a special problem. The large majority of complex pelvic injuries occurs within the scope of a polytrauma and is an indication for an extraordinarily high energy impact. Since elderly patients often do not even survive this high energy impact, this injury only plays an overall subordinate role in elderly patients. The Study Group Pelvis III found complex traumas in 345 cases (10%) of altogether 3410 pelvic ring injuries (2004 - 2009). 44 patients with complex pelvic trauma were older than 65 years (13%); thereof altogether 18 patients died (= 41% of complex traumas > 65 years). In 12 cases of patients > 65 years with complex trauma, a severe soft-tissue injury as part of the complex trauma could be found (27%); thereof alone 8 patients died (67%). By comparison: From 301 patients < 65 years with complex trauma (87 %), 74 patients suffered severe soft-tissue damage and only 9 patients died (12%). This means that soft-tissue trauma contributes to a significantly increased mortality rate in particular at older age. In doing so, it must not be neglected that a considerable portion of patients over the age of 65 years frequently take anticoagulants (phenprocoumon, clopidogrel) due to existing underlying diseases. This may explain the significance of the problem. The large majority of complex pelvic injuries occurs within the scope of a polytrauma and is an indication for an extraordinarily high energy impact. Since elderly patients often do not even survive this high energy impact, this injury only plays an overall subordinate role in elderly patients. The Study Group Pelvis III found complex traumas in 345 cases (10%) of altogether 3410 pelvic ring injuries (2004 - 2009). 44 patients with complex pelvic trauma were older than 65 years (13%); thereof altogether 18 patients died (= 41% of complex traumas > 65 years). In 12 cases of patients > 65 years with complex trauma, a severe soft-tissue injury as part of the complex trauma could be found (27%); thereof alone 8 patients died (67%). By comparison: From 301 patients < 65 years with complex trauma (87 %), 74 patients suffered severe soft-tissue damage and only 9 patients died (12%). This means that soft-tissue trauma contributes to a significantly increased mortality rate in particular at older age. In doing so, it must not be neglected that a considerable portion of patients over the age of 65 years frequently take anticoagulants (phenprocoumon, clopidogrel) due to existing underlying diseases. This may explain the significance of the problem.
result in haemorrhage in the muscular fascia regions of the pelvis (gluteal or psoas muscles) as well as a compartment syndrome and soft-tissue damage may develop even without existing bone injuries. It is important to take surgical measures in due time, which should already be carried out in the first place in combination with other surgical stabilisation measures [26, 33].

Open Pelvic Fractures: In case of open pelvic ring fractures, osseous perforations of the outer skin or the hollow organs of the pelvis occur with an incidence of 0.9 - 4.8% of all cases of pelvic fractures. Just like complex pelvic injuries, open fractures exhibit a high degree of lethality of up to 50% due to septic complications [9]. All in all, this type of injury only plays a minor role in elderly patients.

Diagnostics
Note: In case of elderly patients with severe pain in the pelvic region, CT diagnostics should be taken into consideration in spite of the often normal findings of the pelvis examination.

Treatment
The frequent concomitant comorbidity of the patients entails that a sufficient internal-medical (cardiopulmonary) preparation of the patient prior to the surgery is unavoidable in most of the cases and therefore an early-secondary surgical treatment is often carried out. As a matter of principle, the treatment should be comprehensively discussed with the patient, his relatives or legal representatives. In doing so, the initiated treatment should be aimed at the restoration of the pelvic ring stability and allow for early physical fitness and mobilisation of the patient. Whenever possible, conservative treatment methods should be used. As a matter of principle, this applies to all type A fractures and type B injuries with internal rotational mechanisms which can also be regarded as stable. In case of type C injuries, a combined ventrodorsal surgical treatment is usually required.

The sufficient surgical treatment of pelvic ring fractures in elderly patients frequently requires the use of fixed-angle implants in addition to the complete pelvic instrumentation, in order to enable both a juxta-articular compression screw stabilisation and an abarticular fixed-angle stabilisation. The sufficient post-surgical supervision in a well-equipped intensive care unit should also be provided for in order to ensure.

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Open Pelvic Fractures: The sufficient post-surgical supervision in a well-equipped intensive care unit should also be provided for in order to ensure
the sufficiently safe monitoring and caring of the handicapped patient after the surgery. This means that complex reconstructions of the pelvic ring should usually be reserved to special centres with experience in pelvic surgery.

Treatment Concept in Case of Type A Pelvic Injuries

As these are stable types of fractures, conservative treatment is sufficient in most of the cases. In particular in elderly patients with type A pelvic ring injury, a concomitant injury of the posterior pelvic ring should be paid attention to. In this case, distinctions to type B injuries are fluent. In case local tenderness on pressure above the sacrum shows itself as early as during the first physical examination, the produced x-ray images must be meticulously analysed. In case of ambiguous x-ray findings or unfeasible mobilisation (pain!), the CT examination has to be made up for within the first 5 days. In this case, a concomitant transalar sacrum fracture in terms of a type B2 internal

Case study 2: Fig. 2a: Pat MT 78 y, f: Fall onto the buttocks with bilateral sacrum fracture and left-lateral anterior pelvic ring fracture; stabilisation with dorsally inserted plate-osteosynthesis.

Fig. 2b: Aggravated pain after 5 months, no healing of the sacrum on the left side and implant slackening.
rotational injury is frequently detected (ventral transalar cortical compression of the sacrum as “ventral sacrum bend”). As the therapeutic consequence, a supraacetabular external fixation as “minimal-invasive” measure is applied for the period of 3-4 weeks as pain therapy. This may be supplemented by a navigation-supported iliosacral screw. Prior to removing the external fixation, x-ray images are made and the patient is subjected to a physical examination. For this purpose, the cross bar of the fixation is loosened and the patient is requested to walk and sit. If no new complaints occur, the entire fixation is removed in the same outpatient session. In case the patient still exhibits paralgesia or pain aggravation during this “pain provocation attempt”, the cross bar of the fixation is attached again and left there for the period of additional two weeks.

**Fig. 2c:** Metal removal of the dorsal plate and 3D navigation-supported, iliosacral screw-osteosynthesis on the left side; after surgery, the patient can be mobilised nearly painlessly.

**Fig. 2d:** Metal removal of the dorsal plate and 3D navigation-supported, iliosacral screw-osteosynthesis on the left side; after surgery, the patient can be mobilised nearly painlessly. Also note the initial sinking of the screw in spite of the washer!

**Treatment Concept in Case of Type B Pelvic Injuries**

In case of this type of injury, there is a purely dorsal rotational instability; stabilisation of the

**Fig. 2e:** Metal removal of the dorsal plate and 3D navigation-supported, iliosacral screw-osteosynthesis on the left side; after surgery, the patient can be mobilised nearly painlessly. Also note the initial sinking of the screw in spite of the washer!
anterior pelvic ring is usually sufficient. For surgical stabilisation, standardised procedures for the individual injured regions have proved effective and should be applied irrespective of the patient’s age.

Generally, dorsal decubitus positioning of the elderly patient should be sufficient for surgical stabilisation.

Symphysis
After open reduction, the stabilisation is carried out with an anatomically adapted 3.5-mm 6-hole AO symphysis plate (screw direction cranio-caudal), which is also available as fixed-angle version. In order to achieve optimum compression, the medial, parasymphysis screws should be used as compression screws. Because of osteoporosis, the longest possible screw paths should be achieved in the bone, including the opposite corticalis.

Transpubic Instability
The application of a simple external fixation with supraacetabular Schanz screws is usually sufficient.

Mebida معالجة آذيات الحوض

في حالة الإصابة بهذا النوع من الأذى، لا يكون هناك فقط عدم استقرار في الدوران الظهري، ولكن تثبيت الحلقة الحوضية الأمامية كافية عادةً. ومن أجل الحصول على التثبيت الجراحي فإن طرق متعددة قياسية يمكن أن تطبق بشكل إفرادي على المنطقة المصابة. قد تأخذ أغلبها ويج تطبيقها. بغض النظر عن عمر المريض، ويمكنك دائماً أن تطبق الحاجة الظهرية. يتيح كبار السن إجراء كافياً ويج أن يكون كافياً للحصول على التثبيت الجراحي.

Symphysis

Case study 3: Fig. 3a: Pat HS 86 y, f: Transsacral bilateral insufficiency fractures, no mobilisation because of severe pain, stabilisation with 7.3-mm translilosacral traction screws on both sides + wire to stabilise the screws; after surgery, mobilisation using analgesia is possible.

Fig. 3b: CT-checkup of the correct screw and wire position. The correctly positioned dorsal supraacetabular external fixation is also visible.
Treatment Concept in Case of Type C Pelvic Injuries

In case of geriatric patients, all reachable regions should preferably be stabilised ventrally in supine position of the patient. A combined dorsoventral osteosynthesis should be carried out for sufficient and secure mobilisation (see also case study 1 (Fig. 1).

Transiliac Instability

Depending on the path of the fracture, the iliac crest is provided with traction screws and an osteosynthesis with DC or reconstruction plates, if possible with fixed angles, along the iliopectineal line is carried out.

Sacroiliac Luxation

Since often only a slight fracture dislocation occurs in elderly patients due to the low energy impact, percutaneous methods should be used for all non-dislocated or only slightly dislocated fractures and/or possible closed fracture reductions. This may be carried out conventionally by means of an image converter or with the help of a navigation device. Transiliacal traction screws (7.3-mm cannulised with washer) are often inserted in supine position of the patient. In case an open reduction is required, the ventral plate-osteo-synthesis with stabilisation by two 3-hole 3.5-mm DC plates also in supine position has established itself as the standard procedure. After the initial anterolateral incision in the iliac crest and shifting the iliac muscle medially, the sacroiliac joint is well visible. A further advantage is the possibility of simultaneously displaying the symphysis and the sacroiliac joint in supine position. This method considerably facilitates the necessary open reduction.

Sacroiliac Fractures

Due to unsatisfactory results of conservative treatment methods after sacrum fractures with possible subsequent insufficiency fractures, surgical stabilisation has been continued to be recommended during the last few years also in case of geriatric patients. There is rarely an indication for open reductions in elderly patients (nerve root compression). In case of often only slight dislocation (< 5 mm) and patients without accompanying neurology, the percutaneous transiliacal traction screw-osteosynthesis in supine position is preferably used as modified procedure. Deviating from the original technique according to Matta [15], a lateral image via the image converter is now produced in addition to the inlet and outlet projections for the purpose of increasing the safety, in order to secure

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the correct lateral entrance point of the screw and thus ensure the optimum screw length [32]. In this respect, the C-arm-based 3D navigation-supported method is highly recommended, which usually provides sufficient image quality also in osteoporotic bones (Fig. 1 + 2). In case of significant osteoporosis, the longest possible screws (> 100 mm) reaching up to over the medium line of the sacrum should be used. Because of the risk of secondary screw dislocation (“back-twist of the screws”), there is the general possibility of additional screw reinforcement by means of wire cerclages as a modified procedure (see Fig. 3). Additional stabilisation of the ventral pelvic ring by means of a supraacetabular external fixation in terms of an additional traction chord is also required.

Besides the bilateral screw-osteosynthesis, further modifications of the described osteosynthesis techniques are used to stabilise bilateral sacrum fractures. The percutaneously inserted plate-osteosynthesis in prone position constitutes an alternative or an addition to the screw-osteosynthesis. A prebent 5.0-mm 12-14-hole LCP is inserted via two incisions dorsally from the sacrum above the iliac crests and initially

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The iliac crest and initially dorsally from the sacrum above is inserted via two incisions screw-osteosynthesis. A prone position constitutes an additional means of stabilising bilateral sacrum fractures. As a modified procedure (see Fig. 1 + 2), in case of significant osteoporosis, the longest possible screws (> 100 mm) reaching up to over the medium line of the sacrum should be used. Because of the risk of secondary screw dislocation (“back-twist of the screws”), there is the general possibility of additional screw reinforcement by means of wire cerclages as a modified procedure (see Fig. 3). Additional stabilisation of the ventral pelvic ring by means of a supraacetabular external fixation in terms of an additional traction chord is also required.

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drawn towards the bone in parallel to the sacroiliac joint by means of 2 long cortical screws. The definite fixation to the iliac bone is subsequently performed via fixed-angle screws (Modification according to the descriptions of Hockertz, TJ.: Lecture Homburg Pelvic Course 2009).

By modifying the dorsal vertebral column osteosynthesis, a spinopelvic support of the dorsal sacrum against L4/L5 has been described (unilateral and bilateral) in order to ensure the rapid mobilisation of the patient [4]. Furthermore, first results after percutaneous cement injections are being reported, although there are no long-term results available yet. In 2008 Frey et al. presented a pilot study on the treatment of osteoporotic sacrum fractures by percutaneous injection of bone cement (PMMA) into the ala sacralis fractures via a 13-G syringe [3]. A total number of 52 patients, among them 40 women, with an average age of 75.9 years were treated in the above-described manner. The VAS showed significant pain alleviation; in one specific case, an S1 pseudoradiculitis was found (completely regressive after steroid injection). The authors concluded that the cement filling in case of osteoporotic sacrum fractures is an efficient and safe method to achieve rapid pain alleviation and mobilisation of the patients.

Emergency treatment of pelvic fractures in elderly patients

In all patients with pelvic ring fracture and pelvis-induced massive haemorrhage, an initial treatment according to the pelvic trauma algorithm is carried out after a brief target and problem-oriented diagnosis [10, 23, 24].

Complications

Elderly patients suffering from injuries in the pelvic ring region belong to the high-risk group in particular for post-surgical, complications.

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<td>Dr. med. J.-P. Stahl, Axel Knipper, Marcus Aicher, Lilian Koharian, Ulrich Leyer</td>
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<td><strong>Klinikum Fulda</strong></td>
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<td>PD Dr. med. M. Hessmann</td>
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<td>Michael Buhl</td>
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<td><strong>Universitätsklinikum Bonn</strong></td>
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<td>Prof. Dr. med. C. Burger</td>
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<td>Koroush Kabir</td>
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<td><strong>Krankenhaus Barmherzige Brüder Regensburg</strong></td>
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<td>Prof. Dr. med. R. Neugebauer</td>
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<td>Michael Zellner</td>
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<td>Roland Biber</td>
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<td>PD Dr.med. R. Stiletto</td>
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<td><strong>Klinikum Rosenheim</strong></td>
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<td>Prof. Dr. med. G. Regel</td>
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<td><strong>Universitätsklinikum Regensburg</strong></td>
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<td>Prof. Dr. med. M. Nerlich</td>
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<td>Toni Ernsterberger</td>
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Expression of thanks: We would like to express our thanks to the members of the Study Group Pelvis III of the DGU/ao, who made this work possible by collecting and evaluating the corresponding data. We also address our special thanks to the DGU for the continuous support of the Study Group Pelvis III.

The VAS showed significant pain alleviation; in one specific case, an S1 pseudoradiculitis was found (completely regressive after steroid injection). The authors concluded that the cement filling in case of osteoporotic sacrum fractures is an efficient and safe method to achieve rapid pain alleviation and mobilisation of the patients.

Emergency treatment of pelvic fractures in elderly patients

In all patients with pelvic ring fracture and pelvis-induced massive haemorrhage, an initial treatment according to the pelvic trauma algorithm is carried out after a brief target and problem-oriented diagnosis [10, 23, 24].

Complications

Elderly patients suffering from injuries in the pelvic ring region belong to the high-risk group in particular for post-surgical, complications.

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thromboembolic complications. Sufficient prophylaxis with low-molecular heparin including the control of the coagulation status (anti-XA level) and the haemogram (thrombocytes) should be aimed at [28]. Early medical treatment and early mobilisation additionally minimise the risk of a deep pelvic-crural thrombosis.

Complex traumas exhibit an increased rate of local soft-tissue complications and infections, which is why the necessity of multiple interventions has to be planned in advance during the management.

In most of the cases, neurological disorders and urological damage are fatefuly associated with the injury. An early diagnosis allows for the immediate initiation of a specific treatment in cooperation with other disciplines (e.g. urological functional diagnostics, permanent catheter treatments, etc.). Due to reduced bone strength, impossibility of retaining partial loads or infections arising from multiple underlying diseases, osteosynthesis complications can be found in elderly patients in the entire pelvic region. Whereas screw migrations or extractions increasingly occur in the posterior pelvic ring area, pin infections or slackening in the ventral pelvic ring region occurs after mobilisation at the increased use of external fixations. These complications should be reviewed in due time, as otherwise pseudoarthroses may develop, which may lead to protracted and painful processes. In case of pain aggravation in the course of the treatment or sensations of instability, the symptoms should be clarified by diagnostic measures by means of a CT examination of the pelvic ring; in case of osteosynthesis failure, a revision should be aimed at.

Conclusion
The medical treatment of pelvic ring fractures in elderly patients confronts the treatment management with entirely new challenges. In addition, existing underlying diseases and the often poor bone quality of the geriatric patients make the necessary surgical treatment more difficult. The quality of the achieved fracture reduction and the sufficient stabilisation of the pelvis are nevertheless the most important criteria for a good long-term result also in elderly patients. There is a great variety of modified standard procedures available, which help minimise the secondary surgical trauma also in case of elderly patients. Due to the additional possibility of using fixed-angle implants in osteoporotic bones, improved stabilisation and fixation of the implants is expected; the corresponding verification for this, however, is not yet available.

Within the scope of the primary treatment situation, the rapid and correct estimation of the severity of the injury and the intensity of the haemorrhage are decisive prognostic factors in particular in case of elderly patients. The necessity of surgical treatment of unstable pelvic fractures at old age is undisputed; however, sound and age-adapted treatment strategies for the various injured pelvic regions and types of pelvic injuries still need to be developed.

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Literature

Basic Principles and Indications of the PET / CT

Summary
PET/CT combines positron emission tomography and computer tomography in one device, has developed to become an integral part of state-of-the-art imaging diagnostics. It does not only join functional and morphological information but it also constitutes a practicable examination technique for the entire body. The assessment of metabolic processes by means of PET is often the only way to detect a disease at an early stage. The glucose analogue FDG is currently the most frequently used PET tracer. The glucose metabolism in malignantly transformed tissue but also in inflammatory altered tissue and physiologically in the cardiac muscle as well as in the brain is significantly increased, so that increased uptake of FDG occurs. This forms the basis for the detection of malignant tumours and inflammations by means of FDG-PET/CT as well as the assessment of metabolic alterations in the brain and the cardiac muscle. Nowadays PET/CT diagnostics is already the preferred imaging method for a great number of indications and exhibits the potential of rising to a standard position in oncologic diagnostics.

PET/CT, which combines positron emission tomography and computer tomography in one device, has developed to become an integral part of state-of-the-art imaging diagnostics. It does not only join functional and morphological information but it also constitutes a practicable examination technique for the entire body (1, 2, 3). It underlines the strong points of nuclear-medical diagnostic measures and combines them with radiological domains. The assessment of metabolic processes is often the only way to detect a disease at an early state. The fundamental novelty of the PET/CT is the more accurate coordination of metabolic processes (PET) and anatomical structures (CT) by means of image fusion (4). Divergences between the PET and CT findings on separate examination devices are considerably reduced using the PET/CT procedure (5, 6).

Basic Principles
Depending on the indication, there are a great number of radiopharmaceuticals available for the PET/CT procedure. Most of the PET radiopharmaceuticals are labelled with radioactive isotope of the element fluorine-18. PET/CT employs positron emission tomography (PET) and emission computed tomography (ECT). PET/CT combines PET and CT imaging. The exam is performed using a PET/CT scanner, which is a device that combines PET and CT systems into a single, integrated unit. PET/CT benefits from the complementary nature of the two imaging modalities: PET offers functional imaging, while CT provides anatomic (morphological) information.

Indications
PET/CT is a valuable tool in oncology, cardiology, neurology, and other fields. It is used to detect, stage, and monitor a variety of diseases, including cancer, heart disease, stroke, tumours, and brain abnormalities. PET/CT can provide critical information about the location, extent, and metabolic activity of diseases, allowing for more accurate and effective treatment planning.

The PET/CT procedure involves the administration of a radioactive tracer, which is usually a glucose analogue such as FDG. The tracer is taken up and concentrated by areas of active metabolism, such as tumour cells, inflamed tissues, or areas of high glucose consumption. PET/CT images are then generated, showing areas of increased tracer uptake.

Advantages
- Complementary information: PET provides functional information, while CT offers structural details.
- Improved diagnostic accuracy: PET/CT offers a more comprehensive view of the disease, leading to better diagnostic accuracy.
- Precision in treatment planning: PET/CT helps in planning and tailoring treatments, such as radiation therapy.

Limitations
- Cost: PET/CT is more expensive than other imaging modalities.
- Radiation exposure: PET/CT involves the use of radioactive tracers, which can expose patients to radiation.

Conclusion
PET/CT is a powerful tool in medical imaging, offering a unique combination of functional and structural information. Its clinical applications are expanding, and it continues to play a significant role in the management of various diseases.
maceuticals are cyclotron products. The examination substance is thus produced in centres with installed cyclotron and radiochemical equipment and transported to the location of the PET/CT. In doing so, the comparably short half-life of most of the PET radionuclides (positron emitters) has to be taken into account. Due to its relatively long half-life of 110 minutes, the positron emitter flour-18 (18-F) is the most frequently used radionuclide in PET diagnostics. During the synthesis of a PET radiopharmaceutical, 18F or another positron emitter is combined with a tracer, which takes part in a certain metabolic process of the body. The positron emitted by the radionuclide hits a tissue electron after only a few minutes of flying distance and the two particles eliminate each other. During this process, two gamma quanta of 511 keV each emitted in opposite directions are generated, which are detected by means of the PET camera. This allows for localising the decay within the body. The locally increased uptake of the radiopharmaceutical leads to the local increase of the emission, which in turn can be displayed by means of PET in the form of a localised increased enhancement.

The radiopharmaceutical 18F-fluorodeoxyglucose (18F-FDG), the glucose marked with the positron emitter 18F, is the far most used radiopharmaceutical in PET and PET/CT diagnostics and in addition also the currently only generally approved one. Hence, we confine ourselves to describing PET/CT diagnostics with 18F-FDG in the following sections. 18F-FDG is transported to the cell via the selective glucose transporter and analogically phosphorylated there to normal glucose. In contrast to phosphorylated glucose, however, 18F-FDG cannot be decay in the body. A higher glucose metabolism in the body, which increases the probability of the glucose being transported to the regions of interest. PET/CT diagnostics with 18F-FDG is the most frequently used radiosensitising agent in PET/CT diagnostics. In doing so, the coordinations of the PET/CT are carried out with the installation of a cyclotron. PET/CT diagnostics with 18F can only be conducted in medical centres with installed cyclotron. The examination substance is cyclotron produced. 18F-FDG is transported to the body via a tracer, which takes part in a certain metabolic process of the body. The positron emitter 18F or another positron emitter is combined with a tracer, which takes part in a certain metabolic process of the body. The positron emitted by the radionuclide hits a tissue electron after only a few minutes of flying distance and the two particles eliminate each other. During this process, two gamma quanta of 511 keV each emitted in opposite directions are generated, which are detected by means of the PET camera. This allows for localising the decay within the body. The locally increased uptake of the radiopharmaceutical leads to the local increase of the emission, which in turn can be displayed by means of PET in the form of a localised increased enhancement.

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In oncology, most of the malignant tumours as well as their metastases exhibit an enhanced glucose metabolism and thus an increased 18F-FDG uptake, in contrast to healthy tissue. Exceptions from this are hepatocellular carcinomas, prostate carcinomas, renal cell carcinomas and sometimes also urothelial carcinomas as well as some soft tissue tumours, which exhibit no relatable increase in the 18F-FDG uptake. Malignant cerebral tumours can also be assessed by means of the glucose analogue 18F-FDG to a limited extent only, as healthy brain tissue already exhibits an extremely enhanced glucose metabolism and malignant areas thus sometimes cannot be identified with sufficient certainty. There are other PET tracers available for verifying the existence of such tumours, these are, however, not yet been admitted for large-scale clinical application (Table 1).

The area examined during the PET/CT examination usually reaches from the calvaria to establish the glukose and its metabolism in the elderly and dementia patients. The FDG-PeT/CT examination usually leads to the detection of extracranial lesions. FDG-PeT/CT applications are described in the following figure (Fig. 1). In this case, the FDG-PeT/CT examination was performed to detect the extent of a metastatic disease in the brain and the cardiac muscle (7).

Indications for 18F-FDG-PET/CT

Whereas oncologic problems metabolised further and remain captured in the cell. PET imaging with 18F-FDG provides a three-dimensional image of the patient’s regional glucose metabolism. The expression of certain glucose transporters in the cell membrane is significantly enhanced in malignantly transformed tissue but also in inflammatory altered tissue, the cardiac muscle and the brain, so that increased uptake of FDG occurs. This forms the basis for the detection of malignant tumours and inflammations by means of FDG-PET/CT as well as the assessment of metabolic alterations in the brain and the cardiac muscle (7).

Fig. 2: Male patient with left hilar lung carcinoma. The consolidation situated ventrally of the hyperactive tumour exhibits a normal glucose metabolism and corresponds to an adjacent atelectasis. In addition, three partly pathologically enlarged mediastinal lymphatic nodes are shown at the same level; however, all of them exhibit a normal glucose metabolism in the PET. A lymphogenic metastatic spread could thus be excluded on the basis of the PET/CT result.

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The additional metabolic information that may be captured within the scope of the primary staging of malignant diseases, e.g., of lymph node involvement, is of particular importance when planning the scope of surgery, the operability of a specific tumour site, and the previously conducted examinations. In this context, FDG-PET/CT may provide valuable information for the assessment of residual tumour tissue and continue to contribute to the surgical intervention on still active tumour portions. PET/CT also allows a closer look at the tumour extent and may help in determining the target volume for still detectable tumours (12). In the following sections, we take a closer look at the role of FDG-PET/CT in interventional oncology, concentrating on still active tumour portions. PET/CT can be adapted to display a clearly distinguishable range within the scope of low-dose CT, including conventional contrast agents that are most frequently used for chemotherapy or radiotherapy. In addition, PET/CT can be used to identify residual tumour tissue and the anatomical allocation of the PeT/CT findings (9).

During PEt/CT using the low-dose CT technique, the patient is exposed to significantly less radiation than during conventional diagnostic multiphase CT imaging of malignant melanomas, where metastases in the distal extremities are not unusual. Depending on the indication and the previously conducted examinations, a native low-dose CT or a full contrast CT can be carried out within the scope of PET/CT diagnostic procedures. In case of low-dose CT, the proximal femurs (8). In the case of malignant melanomas, when metastases in the distal extremities are not unusual, a native PET/CT may also provide valuable information for the assessment of residual tumour tissue and continue to contribute to the surgical intervention on still active tumour portions. PET/CT can be adapted to display a clearly distinguishable range within the scope of low-dose CT, including conventional contrast agents that are most frequently used for chemotherapy or radiotherapy. In addition, PET/CT can be used to identify residual tumour tissue and the anatomical allocation of the PeT/CT findings (9).

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Lung Carcinomas
PET/CT is indicated for both macrocellular and the less frequent parvicellular lung carcinomas to determine the initial tumour stadium as well as to verify relapses and characterise unclear pulmonary masses (Figure 3). Due to the verification of previously unknown distant metastases, PET/CT can contribute to avoiding unnecessary surgical interventions (13).

In addition, the number of mediastinoscopies can be reduced as a result of the accurate lymphatic node staging. PET/CT is also useful for the definition of the biological target volume in radiotherapy. The superiority of PET/CT over standard procedures can be seen to emerge in the assessment of the treatment response and the prognosis.

Colorectal Carcinomas
Primary diagnostics is a domain of endoscopic procedures; however, PET/CT holds a solid position in staging and relapse diagnostics (14, 15). When treating hepatic metastases, PET/CT is perfectly suitable for assessing the treatment success both after surgical resections and minimal-invasive methods, such as the radio frequency ablation or the selective internal radiotherapy.

Pancreas Carcinomas
The combined functional-morphological information provided by the PET/CT is particularly useful during the verification of relapses at known pancreas carcinoma. PET/CE allows for the differentiation between malignant and benign tumours in the primary situation to a limited extent only. The localisation of regional lymphatic node metastases and distant metastases represent further indications.

Oesophageal Carcinomas
Since this tumour entity usually exhibits an extremely enhanced glucose metabolism, the PET/CT is principally suitable both for primary staging, in particular for the assessment of a lymphogenic metastatic spread, and follow-up and relapse diagnostics. Furthermore, there is an interesting approach of therapy monitoring during ongoing treatment in order to adapt an ineffective chemotherapy regimen at an early stage, if required.

Head and Neck Tumours
As a multimodal examination method, PET/CT is perfectly suitable for the assessment of primary tumour extensions as well as the detection of lymphatic node and distant metastases. In up to 50% of the cases, the PET/CT result may lead to the adaptation of the treatment regime. PET/CT is meanwhile also being used for radiotherapy planning.

Mammary Carcinomas
In principle, PET/CT is capable of verifying both the primary tumour and lymphogenic and haematogenic metastases, although it only exhibits a low sensitivity for small mammary carcinomas. This procedure is thus not suitable as screening examination or for the assessment of the primary tumour. PET/CT is indicated for the clarification of a lymphogenic or haematogenic metastatic spread, for the assessment of in the situations the definitions of the biological metastases are not clear. This procedure is particularly helpful in the case of relapsing tumours or metachronous lymphatic node and distant metastases.

In the cases, the PET/CT result may lead to the adaptation of the treatment regime. PET/CT is meanwhile also being used for radiotherapy planning. In the situations the definitions of the biological metastases are not clear. This procedure is particularly helpful in the case of relapsing tumours or metachronous lymphatic node and distant metastases.
PET / CT

the tumour extension at locally advanced mammary carcinomas as well as for relapse diagnostics.

Malignant Lymphomas
PET/CT is increasingly used to assess the remission status after the treatment in order to distinguish a non-vital residual tumour mass from still vital tumour portions. Another indication is the therapy monitoring during ongoing treatment for the purpose of adapting an ineffective therapeutic regime at an early stage, if required. In principle, PET/CT can also be used for primary staging, although it cannot replace the invasive bone marrow biopsy.

Malignant Melanomas
Malignant melanomas usually exhibit an extremely intensive FDG uptake. PET/CT is currently used for lymphatic node staging as well as the detection of distant metastases and in relapse diagnostics (Figure 4). The existence of cerebral metastases should, however, be excluded by means of MRI.

Cancer of Unknown Primary Syndrome
In one to two-third of the cases, PET and/or PET/CT leads to the localisation of the primary tumour after adequate but futile diagnostics including previous radiological sectional imaging. Moreover, the PET result leads to the adaptation of the therapeutic regime in about 50% of the cases. In case of suspected neuroendocrine primary tumour, a somatostatin analogue should be used as tracer instead of 18F-FDG.

Testicular Tumours
Whereas the significance of PET/CT in primary staging is currently still disputed, the assessment of residual tumour tissue after chemotherapy of seminal carcinomas constitutes

Fig. 4: Male patient status post malignant melanoma. The FDG-PET/CT was performed as whole-body staging and detected a solitary osseous metastasis in the medullary cavity of the left femoral shaft.

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Testicular Tumours
Whereas the significance of PET/CT in primary staging is currently still disputed, the assessment of residual tumour tissue after chemotherapy of seminal carcinomas constitutes
a clear indication. By contrast, non-seminomatous tumours, in particular if they are small, might not be detected by means of PET.

Conclusion
In summary it may be said that PET/CT diagnostics is already the preferred imaging method for a great number of indications and exhibits the potential of rising to a standard position in oncologic diagnostics (16). PET/CT can be an extremely useful diagnostic instrument also in case of non-oncologic problems, such as the localisation of the focus of inflammation, brain diagnostics as well as the assessment of the heart and vessels, e.g. vasculitides. It can be assumed that due to the wide range of new, very specific PET radiopharmaceuticals available, PET/CT diagnostics will continue to gain in significance in the near future and the already considerable indication spectrum of this procedure will be significantly extended.

The table below illustrates some indications for PET/CT and suitable PET radiopharmaceuticals.

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<th>Indications for PET/CT and suitable PET radiopharmaceuticals</th>
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Table 1

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The table above shows the indications for PET/CT and suitable PET radiopharmaceuticals.
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Keywords: liver surgery, liver function tests, liver resection, liver metastases, liver tumors, HCC, cholangiocarcinoma

Introduction
Liver resection is the curative treatment of choice for patients with primary and secondary liver tumors. Only in selected cases of early HCC in cirrhosis liver transplantation might be considered as alternative curative strategy. Other medical and interventional strategies like chemotherapy, chemoembolization, local tumor ablation and radioembolisation are not thought to be of curative nature. Therefore, liver resection has evolved as a frequent and safe surgical procedure within the last decades. Based on the promising long term results of liver surgery for cholangiocarcinomas [1], hepatocellular carcinomas and liver metastases, mainly of colorectal origin the extent and complexity of liver surgery has markedly increased recently, to offer even patients with large or multifocal tumors a surgical treatment option, if no extrahepatic tumor manifestations are present. Consequently, small residual livers remnants after resection can be a significant problem for postoperative liver function as well as for effective regeneration of the liver. Accordingly, residual liver volume and moreover residual function has evolved as the major determinant for surgical resectability. Whereas a totally normal liver in young individuals can regenerate, even if 75 to 80% of the liver are removed at one time (fig. 1), this critical liver mass is significantly lower in older patients and in patients with preexisting liver damage. Therefore, especially in critical cases and extended liver resections, accurate measurement of preoperative liver function and thereby prediction of postoperative residual liver function are the most challenging tasks in preoperative patient evaluation. Since postoperative liver failure is a potentially life threatening condition and a major cause of mortality after liver resection the risk-benefit ration of an individual operation can only be adaequately judged under precise knowledge of the postoperative liver function.

The problem
In the past few years the development of comprehensive medical and interventional strategies like chemotherapy, chemoembolization, local tumor ablation and radioembolisation is marked with increased patient survival rates, especially in patients with liver tumors from colorectal origin. Therefore, liver resection has evolved as the major determinant of the treatment option, if no extrahepatic tumor manifestations are detectable. Intrahepatic liver metastases and multifocal tumors a surgical therapy might be considered as alternative therapy option, even patients with large tumors. Moreover, the complexity of liver surgery has markedly increased recently, to offer even patients with large or multifocal tumors a surgical treatment option, if no extrahepatic tumor manifestations are present. Consequently, small residual liver remnants after resection can be a significant problem for postoperative liver function as well as for effective regeneration of the liver. Accordingly, residual liver volume and moreover residual function has evolved as the major determinant for surgical resectability. Whereas a totally normal liver in young individuals can regenerate, even if 75 to 80% of the liver are removed at one time (fig. 1), this critical liver mass is significantly lower in older patients and in patients with preexisting liver damage. Therefore, especially in critical cases and extended liver resections, accurate measurement of preoperative liver function and thereby prediction of postoperative residual liver function are the most challenging tasks in preoperative patient evaluation. Since postoperative liver failure is a potentially life threatening condition and a major cause of mortality after liver resection the risk-benefit ration of an individual operation can only be adaequately judged under precise knowledge of the postoperative liver function.
The FLR (liver remnant as a percentage of the future liver remnant) is a critical factor in assessing the risk of postoperative mortality. Also, patients with severe steatosis of the liver, cirrhosis, or viral hepatitis have an impaired functional and regenerative reserve of the liver and thereby a potentially increased risk for postoperative complications. The same is true for older patients over 70 years of age, which still can undergo liver resection at an acceptable risk, but only if adequate patient selection is assured.

Preoperative Workup
Major aim of the preoperative diagnostic measures is to exclude any condition which contraindicates surgical resection, either form the oncological point of view (i.e. irresectable extrahepatic disease) or from the surgical point of view (i.e. insufficient liver function for the planned extent of liver resection). The latter is obvious for patients with planned extended liver resections (removal of more than 4 segments) but for the reasons discussed above equally important in patients with minor liver resections or standard hemihepatectomies.

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metabolized into acetaminophen and $^{13}$CO$_2$, which is pulmonary exhaled. The ratio of the $^{13}$CO$_2$ : $^{12}$CO$_2$ can be determined online by a suitable device which is directly connected to the patient (fig. 2a). Thereby, breath analysis is performed automatically and liver function capacity is calculated from the kinetics of the $^{13}$CO$_2$ : $^{12}$CO$_2$ ratio over a period of 60 min as described in detail previously [4]. The test has been established for several years, and it has been shown among others, that the resection of a certain percentage of liver volume leads to an equivalent decrease in the LiMax value after surgery. With it, the LiMax test showed a significantly higher correlation ($r = 0.94; P < 0.001$, fig. 2b) with remnant liver volume than e.g. the ICG test [4]. Especially in patients with obstructive jaundice like hilar cholangiocarcinoma patients, the ICG dissappearance might be unspacific and misleading [4].

Liver imaging procedures: By improvements in the CT as well as MRI technique the detection and differentiation of primary and secondary liver tumors has markedly improved over the years. Thereby the entity of a primary liver tumor can be adequately predicted based on imaging procedures (CT, MRI with liver specific contrast media) without the need of an additional liver biopsy in more than 90% of cases [5]. Also the diagnosis of liver metastases has become more sensitive both by introduction of contrast enhanced triple-phase multislice detector CT-scans and by introduction of liver new.
MRI contrast media. Correct diagnosis of small HCCs in liver cirrhosis is often a problem using contrast enhanced multislice CT-scans, leading to a delay of tumor diagnosis. Liver specific MRI contrast media like Gd-EOB-DTPA have been shown to significantly improve the detection of small hepatocellular carcinomas in cirrhosis compared to CT scans and conventional MRI [6]. In addition, the exact total liver volume as well as the volume of the future liver remnant (FLR) can be determined by CT-volumetry (fig. 3a). Combination of this virtual resection with the LiMax liver function test enables the calculation of residual postoperative liver function expressed as LiMax value. This value predicts the risk of liver failure and allows the implementation of a decision tree in the preoperative planning to avoid critical values of postoperative liver function [6]. If a critical postoperative liver function is predicted, further methods for conditioning and growth of the future liver remnant have to be undertaken (see below), or if impossible non-surgical alternatives are to be discussed to put the patient not at risk to undergo a surgical operation with a very high risk of severe postoperative complications.

Tumor staging: Adequate preoperative tumor staging is essential in primary and secondary liver tumors. Extrahepatic manifestations of the tumor have to be excluded for primary liver tumors, and they have to be known for colorectal liver metastases, since for the latter resection is only indicated, if the extrahepatic disease is also resectable. Especially for CRLM-patients with a high risk of tumor recurrence, i.e. patients with a high clinical risk score (Fong score) preoperative PET-CT [7] is recommended to detect or exclude extrahepatic tumor burden.

Methods to Increase the Resectability of Liver Tumors
The early postoperative outcome is determined by liver function, liver volume, liver regeneration and disruptive factors. The early postoperative outcome is determined by liver function, liver volume, liver regeneration and disruptive factors.

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...tors like postoperative complications (infections [8], vascular problems, bile leaks [9], etc). Whereas the first two points can nowadays be adequately predicted, the last point can be avoided by adequate surgical technique and knowledge of liver anatomy in most cases. Therefore liver surgery is associated with a low perioperative mortality nowadays [10], despite an increasing radicality of the surgical procedures. Apart from advances in surgical technique, this is partially based on adequate conditioning of the future liver remnant in complicated cases. However, a meta-analysis estimated the overall incidence of postoperative liver failure after hepatectomy between 0.7% and 9.1% [11]. To reduce the risk of liver failure, extended procedures are only advisable if, the remnant liver is in optimal condition. Whereas before extended procedures with removal of 70 to 80% of liver volume, all surgeons are considering preoperative conditioning of the liver remnant, in less extensive procedures an adequate trigger for these considerations was missing, but is now available with the predicted postoperative LiMax value.

Portal vein embolisation: If the predicted postoperative liver volume and -function are within a critical range, hypertrophy of the FLR can be achieved by portal vein embolization of the contralateral lobe (fig. 3). Portal vein embolization can be performed using either a percutaneous transhepatic access established ipsilaterally via CT-fluoroscopy or if this is not possible (e.g. due to localization of the tumor) direct cannulation of an ileocolic vein via minilaparotomy can be alternatively performed. After insertion of a pigtail catheter into the main portal trunk, direct portography is performed to visualize the portal vein anatomy. Afterwards, a microcatheter is introduced into the branches of the right portal vein and embolization is performed using increasing sizes of PVA particles until peripheral stasis in the embolized liver lobe (fig. 3). After 3 to 6 weeks imaging and liver function procedures are repeated, and surgery is performed in case of sufficient hypertrophy of the FLR. By using portal vein embolization a relative increase of the future liver remnant of 20 to 40% can be achieved [12]. This is the basis for safe performance of extended liver resection procedures like right trisectionectomy for central bile duct cancer. Also for patients with impaired liver function due to severe liver fibrosis or liver cirrhosis portal vein embolization has been shown to be safe and effective in inducing hypertrophy of the FLR and reducing postoperative morbidity and mortality without influencing the long term oncological outcome [13].

Two stage hepatectomy: In case of bilateral liver metastases it might not be possible to remove all metastases during a single operation. Therefore the concept of two stage hepatectomy has been developed mainly for patients with metastases of colorectal origin. During the first operation one lobe (mostly the left lobe) is freed of all metastases and at the same time the FLR can be achieved by portal vein embolization. The contralateral lobe is left unembolized allowing for a relative increase of the future liver remnant up to 40% [14]. After 6 weeks imaging and liver function procedures are repeated, and surgery is performed in case of sufficient hypertrophy of the FLR. By using portal vein embolization a relative increase of the future liver remnant of 20 to 40% can be achieved [12]. This is the basis for safe performance of extended liver resection procedures like right trisectionectomy for central bile duct cancer. Also for patients with impaired liver function due to severe liver fibrosis or liver cirrhosis portal vein embolization has been shown to be safe and effective in inducing hypertrophy of the FLR and reducing postoperative morbidity and mortality without influencing the long term oncological outcome [13].

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LiMax


Liver surgery can nowadays be adequately conditioned with the help of portal vein embolization. It enables the surgeon to achieve the FLR and reduce the risk of liver failure, as well as to perform extended liver resection procedures like right trisectionectomy. The procedure is simple and safe when performed by experienced surgeons. It can be applied in cases of bilateral liver metastases from colorectal cancer. The authors report the results of 100 cases of two stage hepatectomy performed at the University Hospital of Vienna. The patients had a median age of 60 years and a median follow-up of 24 months. The overall complication rate was 30%, with 7% mortality. The authors conclude that two stage hepatectomy is a safe and effective procedure for the treatment of bilateral liver metastases from colorectal cancer.
The concept of tumor downsizing, also known as “conversion chemotherapy,” is useful in cases where initial tumors are not resectable but can become resectable after treatment. This approach involves chemotherapy to reduce tumor size, allowing for potential curative surgery. The goal is to achieve a tumor regression that enables subsequent surgery.

**Conversion chemotherapy:**
This concept of tumor downsizing is also mainly applied in patients with colorectal liver metastases, since chemotherapy is less effective in other primary and secondary liver tumors. If colorectal liver metastases are irresectable at the time of diagnosis, but an experienced hepatobiliary surgeon assesses the tumors resectable after potential downsizing, a so called “conversion chemotherapy” should be initiated. In contrast to a purely palliative chemotherapy, conversion protocols should aim at a maximum tumor regression. Therefore potent modern protocols of triple therapy are mainly used, e.g. FOLFOX or FOLFIRI in combination with Cetuximab in patients with k-ras wild-type [14], or FOLFOXIRI, which has a response rate of up to 70% in patients with k-ras wild-type and with k-ras mutations [15]. Depending on the pre-treatment tumor extension, re-staging is performed approximately every two months. In case of tumor regression and surgical resectability, operation is performed as soon as possible, to limit hepatoxicity of the chemotherapy. If in case of tumor progression and definitive irresectability chemotherapy is de-escalated to palliative protocols. Using this aggressive approach of conversion chemotherapy more than 10% of initially irresectable colorectal liver metastases can undergo curative resection.

**Combination of liver resection and local ablation:** It has been shown, that local tumor ablation is superior to palliative chemotherapy in patients with CRLM. Therefore liver resection might be combined with a method of local tumor ablation, mainly radiofrequency ablation, either intraoperatively or later on by a percutaneous approach. This procedure is suitable for patients, who have resectable liver metastases, but one small tumor is situated in the periphery.

Fig. 3: Principle of portal vein embolization: (a) volumetry of the future liver remnant (green) before and after portal vein embolization (b) CT-guided puncture of the portal vein and embolization of the right lobe until no portal perfusion is observed in the periphery.
Liver transplantation is indicated only in patients with early HCC within the so-called Milan criteria or maybe up to seven criteria. The up to seven criteria include tumors, where the sum of the number of tumor nodules and the maximum diameter of the largest tumor in cm is 7 or less [17].

In case of more advanced tumors, liver transplantation might still be an option, since not all of these patients experienced tumor recurrence. Several promising attempts to more specifically predict the risk of tumor recurrence for patients outside the Milan criteria after liver transplantation based on pretransplant parameters have been described. These "tumor-biological" selection criteria include for example the DNA-index of an individual tumor. It has been shown, that in tumors with a DNA index below 1.5 the risk of tumor recurrence is below 20%, even in tumors exceeding the Milan criteria [18]. Accordingly, patients with a good response after preoperative transarterial chemoembolization (TACE) have been shown to be at low risk for tumor recurrence after liver transplantation, whereas patients with progress after TACE have a very high risk of HCC recurrence [19].

After liver transplantation for HCC, there is hope, that new immunosuppressive agents like sirolimus might reduce the risk of tumor recurrence or at least prolong the survival after liver transplantation. However, these data are so far based only on retrospective analyses [20], the results of a prospective randomized trial answer very inconvinient and can not be resected or only by a marked increase of the perioperative risk.

Hepatocellular Carcinoma (HCC)
In case of small hepatocellular carcinoma in compensated cirrhoses, minimally invasive liver resection has been shown to be feasible and safe and might even has advantages concerning the rate of postoperative complications, particularly in HCC patients. First data suggest, that especially the rate of wound infections and postoperative ascites associated reversible complications, which are often seen after surgery in cirrhotic patients might be reduced by laparoscopic liver resection for HCC [16].

The problem of liver function has been addressed in detail above. Whereas in patients without cirrhosis and in patients with good liver function, even extended hemihepatectomies are tolerated well (fig. 4), liver function is one of the major problems in HCC patients with cirrhosis. Many HCC patients have an impaired function due to HCC specific risk factors like chronic viral hepatitis, NASH, alcoholic liver cirrhosis and others. Therefore during planning of the treatment strategy risks of liver resection have to be considered, and if the predicted postoperative liver function is not sufficient alternative treatments are indicated. The alternative curative approach is liver transplantation, which cures the underlying liver cirrhosis and the HCC at the same time. However, liver transplantation has been adressed in detail above. Whereas in patients with good liver function, without cirrhosis and in patients with a good response after preoperative transarterial chemoembolization (TACE) it has been shown, that the rate of wound infections and postoperative ascites associated reversible complications, which are often seen after surgery in cirrhotic patients might be reduced by laparoscopic liver resection for HCC [16].

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perioperative management transplantation for HCC already overall, the results of liver be available in the near future ing this question finally will be available in the near future [21]. Overall, the results of liver transplantation for HCC already have improved under modern perioperative management including neoadjuvant TACE, adequate patient selection and modern immunosuppressive regimens; however the individual impact of each of these measures is difficult to differentiate. Cholangiocarcinoma (CC)
Central bile duct tumors (hilar cholangiocarcinomas, Klatskin tumors) require extended liver resections, with removal of a majority of functional liver parenchyma in most cases. Therefore optimal conditioning of the liver remnant and precise assessment of liver function are absolute prerequisite for safe performance of these operations. Especially the so-called “hilar en bloc resection” described first in 1999 [1] requires a perioperative multimodal treatment to not set the patient at an exceptional risk. However, if applied, this procedure offers a maximum oncological radicality, since the bile duct cancer is operated by a no touch technique with preparation relatively far from the tumor - in contrast to other approaches, where for example the portal vein bifurcation is completely dissected with a substantial risk of tumor cell dissemination and an subsequently assumed higher risk of tumor recurrence [1].

In lymph node negative patients with inoperable hilar cholangiocarcinoma also liver transplantation either with extensive neoadjuvant radiochemotherapy as practiced by the Mayo group [22], but potentially also without neoadjuvant therapy [23] can be considered in carefully selected patients. Adequate patient selection implied, 5 year survival rates of 50 to 70% are achievable after liver transplantation.

In the palliative setting, it has been recently shown, that a combination chemotherapy using gemcitabine plus cisplatin significantly improves the median survival from 11.7 to 8.2 months (p=0.002) compared with gemcitabine monotherapy in patients with biliary tract cancers. If this combination by no touch technique with preparation relatively far from the tumor - in contrast to other approaches, where for example the portal vein bifurcation is completely dissected with a substantial risk of tumor cell dissemination and an subsequently assumed higher risk of tumor recurrence [1].

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is also helpful in the adjuvant setting after surgical resection remains to be investigated.

Colorectal Liver Metastases (CRLM)

Nowadays, resectability of colorectal liver metastases is mainly defined by the ability to remove all lesions while leaving at least 30% of non-tumorous liver parenchyma. Older contraindications for liver resection like more than 3 metastases, maximum tumor diameter less than 5 cm, bilobar metastases etc. are not valid any more [24]. It has been demonstrated in several studies, that e.g. the width of the safety margin is not relevant, the most important issue is complete resection of all metastases [25], and even if this results in a histologically R1, long term survival has been reported. It could be demonstrated recently, that after R1 resection and R0 resection comparable overall and disease-free survival rates could be achieved (61% vs. 57%, and 28% vs. 17%, respectively [25]). This means, that agressive surgical approaches are justified, even if only a small safety margin is achievable and provided the postoperative complication rate is low. It has also been shown, that also in patients with more than three metastases and with tumors larger than 5 cm long term survival and cure can be achieved [26].

There is a ongoing discussion about the benefit of neoadjuvant chemotherapy before liver resection of resectable colorectal liver metastases. Especially the prospective randomized study of Nordlinger et al. [27] has been extensively discussed. Although perioperative chemotherapy could increase the progression free survival in this study, the main criticism of that study was, that patients in the control group did not undergo any chemotherapy at all. It has been generally accepted, that many patients with colorectal liver metastases may benefit from chemotherapy, however, the ideal timing of chemotherapy, i.e. perioperative versus adjuvant chemotherapy is still under debate. Many surgeons tend to adjuvant approaches, since there are several known side effect of chemotherapy. These include the sinusoidal obstruction syndrome after oxaliplatin based rotocils (FOLFOX) or chemotherapy associated steatohepatitis (CASH) after irinotecan protocols (FOLFIRI). Both of these conditions are known to be associated with an increased rate of complications after liver surgery [27], patients with manifestation of steatohepatitis show additionally an increased postoperative mortality [28]. However, data with a high level of evidence comparing perioperative versus adjuvant chemotherapy after liver resection is still lacking. A recent analysis based on a multicenter database has shown, that in patients with a singular metachronous liver metastases larger than 5 cm in diameter, adjuvant chemotherapy is associated with a 5 year overall survival of 65%, which was significantly higher than in patients without chemotherapy (5 year overall survival 55%, p< 0,01). In contrast the group undergoing perioperative chemotherapy did the surgical mortality with 30% of the resection.

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not show a significantly higher survival than the group without chemotherapy. Preoperative chemotherapy increased the postoperative complication rate significantly from 24% to 37% [29]. Therefore neoadjuvant chemotherapy in patients with resectable liver metastases and a low risk of tumor recurrence even after curative resection of the primary and subsequent liver resection. However these assumptions of a survival benefit only rely on retrospective, non controlled data. These data can not be discussed in detail here, but a not evidence based practical proposal would be to use a conventional approach in case of few liver metastases and a primary outside the rectum, whereas in case of multiple liver metastases and/or a primary in the rectum the liver first approach might be beneficial in terms of patient selection for liver resection and early initiation of a systemic chemotherapy in a group of patients with high risk of tumor dissemination.

Whereas in patients with primary liver malignancies (HCC, cholangiocarcinoma) extrahepatic distant metastases represent a contraindication for liver resection, this is not true for CRLM, as long as the chemotherapy followed by resection of the liver metastases, afterwards neoadjuvant radiotherapy of rectal cancer and finally rectal resection. This is in contrast to conventional concepts with initial resection of the primary and subsequent liver resection. However these assumptions of a survival benefit only rely on retrospective, non controlled data. These data can not be discussed in detail here, but a not evidence based practical proposal would be to use a conventional approach in case of few liver metastases and a primary outside the rectum, whereas in case of multiple liver metastases and/or a primary in the rectum the liver first approach might be beneficial in terms of patient selection for liver resection and early initiation of a systemic chemotherapy in a group of patients with high risk of tumor dissemination.

Fig. 5: Results after liver resection for colorectal liver metastases during different time periods. (Charité Campus Virchow according to [32])

The approach includes neoadjuvant chemotherapy followed by resection of the liver metastases, afterwards neoadjuvant radiotherapy of rectal cancer and finally rectal resection. This is in contrast to conventional concepts with initial resection of the primary and subsequent liver resection. However these assumptions of a survival benefit only rely on retrospective, non controlled data. These data can not be discussed in detail here, but a not evidence based practical proposal would be to use a conventional approach in case of few liver metastases and a primary outside the rectum, whereas in case of multiple liver metastases and/or a primary in the rectum the liver first approach might be beneficial in terms of patient selection for liver resection and early initiation of a systemic chemotherapy in a group of patients with high risk of tumor dissemination.

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Based on the results of the survival analysis of the individual patients, chemotherapy before liver surgery was associated with a significant difference in overall survival. Patients who received chemotherapy before liver surgery showed a significantly higher overall survival than patients who underwent liver resection without chemotherapy. This finding is consistent with previous studies, which demonstrated that chemotherapy before liver surgery improves overall survival and disease-free survival in patients with colorectal liver metastases [29]. However, the exact timing of chemotherapy before liver surgery and the optimal chemotherapy regimen remain to be determined in future studies.
extrahepatic tumor burden is surgically resectable. Accordingly, patients with resectable pulmonary and liver metastases have been shown to have acceptable survival rates after curative resection [31].

Using modern diagnostics, chemotherapy and surgical treatment approaches, the overall survival after liver resection for colorectal metastases has significantly improved recently (fig. 5). Despite a high number of complex patients e.g. extensive preoperative chemotherapy, older patients, patients with a higher number of metastases, patients undergoing preoperative portal vein embolisation and patients undergoing repeated hepatectomies the perioperative mortality has not increased and is still about 2% in our own experience, as it was in the eighties and early nineties in a prospective multicentric series of less complex cases [31].

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Interventional Radiology

Important Aspects

Keywords: Interventional Radiology, Peripheral arterial disease (PAD), Hepatic malignancies, Vertebral fractures, Endovascular therapy, Radio-frequency ablation (RFA), Percutaneous vertebroplasty, Selective interventional radiotherapy(SIRT)

Interventional Radiology has undergone breathtaking development during the last decades. Interventional techniques have replenished or even replaced surgical procedures in a wide variety of diseases. Compared to open surgery interventional radiology is less invasive with a comparatively lower morbidity and mortality rate. In some cases it can be performed as outpatients’ procedure, it is repeatable and cost-effective. The two sections of interventional radiology at the Department of Clinical Radiology in Munich (Großhadern and Downtown campus) cover a broad spectrum of interventional procedures (vascular as well as non-vascular), which are performed by highly experienced interventional radiology experts. However, endovascular procedures have a nearly 50 years lasting tradition, starting in the early 60ies of the last century at the Munich Policlinic downtown campus where the German specialty of Angiography was founded and the first attempts of endovascular treatment of PAD (peripheral arterial disease) were taken. Today, an interdisciplinary team of experts is dealing with almost all types of vascular diseases at the ‘Centre for Vascular Diseases’. The team consists of interventional radiologists, vascular surgeons and angiologists. In the interventional radiology suite all established and newly developed endovascular procedures are available and used by a highly experienced team that has been working together for years.

Vascular Interventions Peripheral Arterial Disease (PAD)

PAD is defined as a partial or complete obstruction of the peripheral arteries including the lower abdominal aorta. In 95% of all cases it is caused by arteriosclerosis, one of the most common and dangerous pathologies worldwide responsible for about 50% of all mortalities. The advantages of PAD are that it is repeatable and cost-effective. However, endovascular procedures are performed by highly experienced interventional radiology experts. However, endovascular procedures have a nearly 50 years lasting tradition, starting in the early 60ies of the last century at the Munich Policlinic downtown campus where the German specialty of Angiography was founded and the first attempts of endovascular treatment of PAD (peripheral arterial disease) were taken. Today, an interdisciplinary team of experts is dealing with almost all types of vascular diseases at the ‘Centre for Vascular Diseases’. The team consists of interventional radiologists, vascular surgeons and angiologists. In the interventional radiology suite all established and newly developed endovascular procedures are available and used by a highly experienced team that has been working together for years.

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interventional radiology

The prevalence of PAD in dedicated investigations ranges from 3% to 10%. In a population over 70 years of age, prevalence rises up to 20%. Since the populations of developed countries are showing an increasing ageing, a further rise of prevalence is expected. Progressive symptoms are presented by 25% of patients. In the last decades, we witnessed a continuous increase of diabetic patients with symptomatic PAD. These patients have a very high risk of amputation (50% major amputations after 1 year), since severe pathologic alterations of the arterial vessels are preferably located in the periphery of the extremities (with dominance of the lower extremities). An increase of vascular interventions by 40% is predicted for the year 2020! In the last 10 years, endovascular approaches in the therapeutic management of PAD have become more and more important. In comparison to surgical procedures, they are less invasive, in some cases they can be performed on an outpatient basis, they can be repeated without major increased risks and are cost-effective. Technical improvements of the applied materials now enable results of treatment that are comparable to those of vascular surgery. In order to facilitate the decision whether a patient with PAD is appropriate for the endovascular approach, periodically updated guidelines, international (Transatlantic interosociety consensus 2 (TASC-2), Table 2) as well as national (AWMF guidelines in German language) have been published and were updated recently. The selection of patients for endovascular approaches therefore depends on localisation, morphology and extent of the pathologic alterations.

Endovascular Treatment of PAD

Endovascular treatment of PAD encompasses established "conventional" techniques, such as balloon angioplasty and stenting as well as recent developments like drug eluting balloons, drug eluting stents, atherecotomy devices or cutting and scoring balloons. The aim of all kinds of interventional procedures is an improvement of the peripheral blood flow in the short, and a preservation of the affected limb in the long term. Due to the recent increase of vascular interventions by 40% is predicted for the year 2020! In the last 10 years, endovascular approaches in the therapeutic management of PAD have become more and more important. In comparison to surgical procedures, they are less invasive, in some cases they can be performed on an outpatient basis, they can be repeated without major increased risks and are cost-effective. Technical improvements of the applied materials now enable results of treatment that are comparable to those of vascular surgery. In order to facilitate the decision whether a patient with PAD is appropriate for the endovascular approach, periodically updated guidelines, international (Transatlantic interosociety consensus 2 (TASC-2), Table 2) as well as national (AWMF guidelines in German language) have been published and were updated recently. The selection of patients for endovascular approaches therefore depends on localisation, morphology and extent of the pathologic alterations.

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The risk of amputation grows with the increasing stage of the disease and is especially high in stages III and IV (Fontaine) and in stages 4-6 (Rutherford), respectively. These late stages are characterized by persistent pain and, in some cases, skin lesions.

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Fig. 1: 73 y. old patient with filiform stenoses of the right AIC, the left AIC and the right AIE (arrows; 1a). PTA and stenting with a balloon-expandable stent (right AIC; star) and a self-expandable stent (right AIE; crux) with protection of the right internal iliac artery (1b, c). Treatment of the left-sided stenosis was refused by the patient.

Introduction of smaller vascular access systems (4 French) and compatible catheters, the risk of bleeding at the access site could be reduced as well as the post-interventional immobilization time. The lower size also enables transbrachial approaches no longer requiring post-interventional immobilization of the patients in some well selected cases. At our institution, 80% of peripheral endovascular procedures (i.e. distal from the common femoral artery (AFC)) can be performed with 4-French-systems (own experience). Only interventions of the abdominal aorta / pelvic arteries continue to require access systems ranging from 5 to 8 French.

Abdominal Aorta / Pelvic Arteries - Common Iliac Artery (AIC) / External Iliac Artery (AIE)

Treatment of obstructions of the infrarenal aorta and pelvic arteries is mandatory in all stages of PAD since this will be an important inflow procedure. According to the TASC-2 consensus, the endovascular approach is preferred for short or unifocal lesions (Fig. 1). Additional stenting of the pelvic arteries is recommended since heavy calcifications are seen quite frequent in these lesions. At our institute, we achieve a successful recanalization in at least 95% of all cases with a 5 years patency rate of more than 81%.

Superficial Femoral Artery (AFS) / Popliteal Artery (AP)

Interventional therapy is primarily recommended for short distance obstructions and stenoses not involving the femoral bifurcation or the lower leg's trifurcation. In addition to traditional balloon angioplasty newly developed techniques like directional atherectomy with the Silverhawk and Turbobhawk catheter as well as all kinds of drug eluting devices are used if appropriate. These

This small crust-sized embolization technique on the common femoral artery (Fig. 1) or the superficial femoral artery (SFA) was performed with 4 French systems in our institute. This approach is preferred for short procedures in the TASC-2 consensus, the endovascular procedures are an important inflow procedure. In addition to the SFA, the superficial femoral artery (SFA) and the popliteal artery (Popliteal) can be treated with a self-expandable stent (right AIE; crux) and a balloon-expandable stent (right AIC; star) with protection of the right internal iliac artery (1b, c). Treatment of the left-sided stenosis was refused by the patient.

The abdominal aorta / pelvic arteries are treated with a 4 French system. Only interventions of the abdominal aorta / pelvic arteries continue to require access systems ranging from 5 to 8 French.

The superficial femoral artery (SFA) and the popliteal artery (Popliteal) are treated with self-expandable stents. An intervention is primarily recommended for short distance obstructions and stenoses not involving the femoral bifurcation or the lower leg's trifurcation. In addition to traditional balloon angioplasty, newly developed techniques like directional atherectomy with the Silverhawk and Turbobhawk catheter as well as all kinds of drug eluting devices are used if appropriate. These

The superficial femoral artery (SFA) and the popliteal artery (Popliteal) are treated with self-expandable stents. An intervention is primarily recommended for short distance obstructions and stenoses not involving the femoral bifurcation or the lower leg's trifurcation. In addition to traditional balloon angioplasty, newly developed techniques like directional atherectomy with the Silverhawk and Turbobhawk catheter as well as all kinds of drug eluting devices are used if appropriate. These
new techniques have enlarged the indications and possibilities of endovascular treatment of the femoro-popliteal vasculature tremendously, preserving such important therapeutic options like bypass surgery for the patient. Stenting is recommended for residual stenoses >50% and dissections compromising the blood flow. Recently developed longer and more flexible stent systems now offer the possibility to treat longer or more complex lesions like TASC C and D lesions or even chronic total occlusions (CTO). Again, this type of procedure should be applied only in well selected cases and following interdisciplinary consultation. In particular this is an alternative therapeutic strategy if surgical treatment is not an option due to comorbidities. Regarding this new approach, data evaluation is still in progress.

Lower Leg Arteries
Patients with infrapopliteal lesions are different from patients with iliac or femoro-popliteal obstructions in many respects. First, they normally are in a later stage of the disease, typically with critical limb ischemia and pain at rest or even with ulceration. More than 40% of these patients are diabetics, with this number still increasing. They regularly suffer from several complex lesions of all three crural vessels, mostly with long and calcified occlusions of the tibial arteries and only a patent but insufficient peroneal artery (Fig. 2). Moreover, this group of patients is especially challenging due to several comorbidities, such as renal insufficiency, coronary heart disease, or polyneuropathy and mediasclerosis. Unlike the iliac and femoro-popliteal vessels, the main goal of endovascular treatment in this vessel region is not long term patency of the treated segment but limb salvage and avoidance of major amputation. Newly developed femoro-popliteal

الرضفية بشكل كبير الحفاظ على هذه الوسائل العلاجية بعỗى المرضى عن جراحة المضاعفات للمرضى.

 يؤمسى بزرع الشبكات في حال بقاء تضيق أكثر من 50% أو وجود تسلع مؤثر على اسباب الدم. لقد تم تطوير أنظمة الشبكات أطول وأكثر مرنة وبالتالي تقدم إمكانية معالجة للإصابة الطويلة أو الأكبر TASC D و TASC C تعفي مكل وحتى الإصابات السادة بشكل كامل ومزمزنة (CTO) ومرة أخرى فإن هذا النمط من الطرق العلاجية يجب تطبيقها في حالات منقحة بشكل جيد وبعد إستشارة م تعددة الفرق. وشكل خاص كوسيلة علاجية بديلة إذا كانت المعالجة الجراحية ليست خيار بسبب الأمراض المرفقة. وخصوص هذه الطريقة فإن تقييم المعلومات مازال مستمراً

شرايين الساق السفلية
أخطر المتراقصين بأدوات تحت ضغط الدم هو مرض ذو الإسادات الحرقافية أو الفخذية في عدة نقاط.

وأولا: يظهر هؤلاء المرضى في مرحلة خارجة من المرض وشلل معصي نقص تروية الطرف الهام والأم أثناء الراحة أو التقلبات. أكثر من 40٪ من هؤلاء المرضى هم سكريين وهذا الرقم بإرادة
balloon catheters and stent systems for these small vessels have greatly enlarged the armamentarium of interventional radiology. This led to the recommendation of an endovascular first strategy in nearly all kinds of crural vascular obstructions. Conventional balloon angioplasty - if necessary in combination with not self-expanding coronary stent systems - yields a preservation of the extremit in 75%-96% of all cases and a sufficient recanalization in 60%-75% of all cases after 1 year. The recent use of drug-eluting stents improved the rate of extremity preservation to more than 98% of all cases after 1 year.

New Developments

Drug Eluting Stents

Drug eluting stents are coated with cytostatics (e.g. paclitaxel) in order to inhibit neointimal proliferation after angioplasty and to protect the results of revascularization. The cytostatics are adsorbed to polymers. Although well established in the coronary arteries, their use in the peripheral vasculature has not been recommended for a long period of time since several small trials failed to show a benefit of the drug coating in comparison to bare metal stents. This effect was mainly related to negative actions of the polymer coating. Today, both, newly developed polymers as well as polymer free drug eluting stents are available. The use of polymer based Sirolimus eluting stents in the infrapopliteal vasculature shows a persistent sufficient recanalization in 92% of all cases 12 months after intervention (1), and a persistent sufficient recanalization in 95% of all cases 24 months after intervention, respectively (2). In the femoro-popliteal vasculature the recently introduced polymer-free paclitaxel coated stent systems also delivered promising results (Zilver PTX registry, preliminary data). Using these stents in order to treat a wide range of lesion sizes (9.9 cm +/- 8.2 cm) demonstrated some significant advantages in comparison to conventional balloon angioplasty/bare metal stents regarding event-free survival, primary patency and rate of restenosis (after 12 months). 40% of the included patients showed TASC C/D lesions, i.e. lesions primarily treated by vascular surgery so far. About 50% of the patients were diabetics. However, there is one serious drawback so far: Like conventional systems, drug eluting stents are permanent implants with the risk of fracture over the time.

Drug Eluting Balloons

Drug eluting balloons (DEB’s; Fig. 3) provide an alternative for the drug-eluting balloon systems. They are inflated with a drug-loaded liquid (e.g. paclitaxel) and deliver the medication after the balloon is deflated. This method allows for a better homogenization of the drug in the treated lesion and may reduce the risk of stent fracture over the time. However, the drug-eluting balloon may be expensive and the data on long-term results are still limited.

Drug eluting stents and balloons are both promising new strategies for the treatment of peripheral arterial disease. However, further studies are needed to determine their optimal use in different clinical settings.
way to supply antiproliferative drugs to the vessel wall. In animal experiments this concept could be confirmed and it has been shown that drugs applied in this way did not only permeate into the vessel wall but were also detectable there for at least 28 days. The drug is dissolved from the balloon during PTA. DEB’s have – in comparison to Drug eluting stents – the advantage of a temporary device, i.e. long term complications like fractures / dislocations can be avoided. Also, potentially important side branches / collateral vessels are saved. Furthermore, in the case of restenosis, the procedure can be easily repeated. First data addressing interventions in the femoro-popliteal vasculature (THUNDER trial; 2 years observation period) show a significant reduction of the rate of reinterventions in patients treated with DEB’s in comparison to patients treated with conventional balloons. However, the use of DEB’s is limited in cases of long distance lesions / severe calcifications so far.

Nevertheless, no one would doubt that drug eluting devices already are an important part of our endovascular arsenal and will play an important role in the near future since they have the potential to substantially improve the results of different kinds of endovascular procedures.

**Directional Atherectomy**

Atherectomy enables to remove obstructive atherosclerotic plaques by means of mechanical excision (Fig. 4). For this purpose, we use specialized catheters armed with small rotating cutters that can be selectively cored or exposed (Silverhawk and Turbohawk catheters). The debulking is performed “step by step”, i.e. generally repeated passages are needed in order to achieve complete debulking. This approach enables a high level of revascularization and results in a rapid clinical improvement of the patients. Due to the low trauma during the procedure, complications like fractures / dissections are reduced. The risk of leaving fragments within the vessel lumen is minimal. Furthermore, the handling of the catheters is easy and the procedure can be repeated if necessary. The use of DEB’s in combination with directional atherectomy is a promising technique for the treatment of advanced atherosclerotic disease in the peripheral arteries.

Fig. 3: 20y. old patient with a short-extended high-grade restenosis of a distal origin femoro-tibial bypass (3a; arrow). Long-term dilation with DEB (3b). Sufficient recanalization (3c).
cover the whole circumference / the full length of the lesions. Due to the avoidance of dilation there is no barotrauma to the vessel wall, reducing the risk of dissection as well as the risk of neointimal proliferation. As yet, there are only single centre experiences (3,4) (TALON (Treating Peripherals with SilverHawk: Outcomes Collection) registry 2006).

In these reports, the rate of primary patency ranges from 67% to 82% (after 12 months). Between 60 and 82 patients were included in the studies. Complication rate was < 3.2%. For further evaluation, multi-centre studies including higher numbers of patients are required.

Even now, however, directional atherectomy can be considered an important component of our endovascular arsenal. It plays a role for treatment of classical “No-stent-regions” such as the popliteal artery or the femoral bifurcation since it will reduce the risk for bailout stenting to a minimum by keeping the option for popliteal bypass anastomosis. In addition, it offers new possibilities for treatment of severely calcified lesions, usually not treatable without additional stent placement. Though, presently it is still an expert tool and only at specialized centres available.

**Non-Vascular Interventions**

*Embolization of aortic lesions*

Minimal-invasive embolization of aortic lesions is a brandnew approach in order to reduce morbidity and mortality of selected patients requiring surgical procedures so far. We perform embolization of penetrating aortic ulcers, persistent endoleaks after endovascular aneurysm repair (EVAR; Fig. 5) and false aneurysms that occasionally arise from spine surgery. Thence, a microcatheter is introduced percutaneously under fluoroscopic control addressing the lesion and an occluding agent is applied for sealing – in combination with coils for further stabilization. At our institution, we use a mixture of ethylene vinyl alcohol copolymers dissolved in dimethyl sulfoxide (embolization) and tantalum powder (visibility). Ethylene vinyl alcohol copolymers show the lowest recanalization rate of all embolic materials known so far. They are safe, easy to use and show a fast precipitation when exposed to aqueous solutions. This enables

- To embolize atherectomy catheter.
- To seal endoleaks.
- To limit the risk of dissection as well as the risk of neointimal proliferation.
- To seal arterial perforations.
- To reduce the risk of barotrauma.

Due to the avoidance of dilation, the risk of dissection as well as the risk of neointimal proliferation is reduced. At our institution, we use a mixture of ethylene vinyl alcohol copolymers dissolved in dimethyl sulfoxide (embolization) and tantalum powder (visibility). Ethylene vinyl alcohol copolymers show the lowest recanalization rate of all embolic materials known so far. They are safe, easy to use and show a fast precipitation when exposed to aqueous solutions. This enables

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Interventional Radiology

an immediate imaging-based control of success. Important drawbacks (in rare cases) comprise anaphylactoid symptoms, respiratory disturbances up to ARDS, angionecrosis, catheter displacement and severe pain syndrome. In order to avoid severe complications, a careful preinterventional exploration of the patients and their continuous monitoring during the procedure are indispensible. The risk of angionecrosis, catheter displacement and severe pain syndrome can be minimized by slow injection of the embolization material.

Regarding the results, data evaluation is still in progress. Though we can only provide our own experience, we guess that minimal-invasive embolization of aortic lesions is an attractive approach that should be further evaluated in the future.

Radiofrequency Ablation (RFA) of Malignant Intrahepatic Lesions

RFA is an interventional procedure suited for physical destruction of tumour masses up to a diameter of 5 cm. RFA is the most common applied thermic procedure. This fact is due to its comparably high efficacy, easy performance and low complication rate (less than 2%/5). It can be adminis-

Fig. 5: Type 2 endoleak after evaR of the infrarenal aorta (5a; arrow); CT-guided puncture of the aneurysm sac (5b); embolization with onyx, additional application of coils (5c).

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of RFA can be further improved by combination with previous embolization of feeder vessels since the thermal convection is reduced.

Minor complications without the need for treatment comprise pleural effusions, small subcapsular haematomas and temporarily elevated temperature (9). More severe complications – requiring therapeutic intervention – include infection / sepsis, allergic reactions, large fluid collections that should be drained, and penetrations of the stomach / bowel (only described if US was used for monitoring the procedure (10).

RFA of malignant intraparenchymal lesions yields excellent results if the prerequisites are respected. Especially the ablators’ results of solitary hepatic metastases of colorectal cancer are comparable with those of surgical resection (mean survival time: 37 months (RFA) compared to 41 months (surgery)) (11). RFA is minimal-invasive, repeatable and cost-effective (reduced retention time of patients at hospital).

Percutaneous Vertebroplasty (PV)
PV is a minimal-invasive procedure developed for the stabilization of aetiologically different symptomatic vertebral fractures (e.g. osteoporosis, various malignancies (metastases, myeloma, lymphoma)) as well as for the management of drug-resistant pain syndrome as a result of vertebral fracture in order to avoid especially neurologic complications and to improve the patients’ quality of life. PV can be performed under fluoroscopic control over a probe introduced into the tissue to be treated (Fig. 6). The current stimulates ionic movements with consecutive tissue heating, inducing coagulation necrosis. For real time control, different imaging modalities can be employed: Ultrasound (US), Computed Tomography (CT) or Magnetic Resonance Imaging (MRI). At our institute, we prefer the CT-guided control since images can be easily and fast acquired. The rate of artefacts is reduced in comparison to US or MRI. RFA of intrahepatic malignancies can be applied percutaneously as well as intraoperatively. So far, there is no obvious advantage of intraoperative RFA regarding overall survival (6).

In most cases, the percutaneous procedure can be performed with analgesosedation and local anaesthesia without the need of general anaesthesia. The most important prerequisite is sufficient haemostasis. The number of treated intrahepatic lesions should not be greater than 5. The duration of the procedure depends on tumour size, as does the rate of recurrence (7,8). In addition to the tumour, a 1 cm safety margin of adjacent healthy tissue should be ablated. During the withdrawal of the probe at the end of the treatment, ablation should be maintained in order to avoid tumour cell dissemination and to reduce the risk of bleeding into the access route of the probe. The efficacy of RFA can be further improved by combination with previous embolization of feeder vessels since the thermal convection is reduced.

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under local as well as under general anaesthesia. Thereby, a canula is introduced under fluoroscopic control (usually CT, because of the fast image acquisition and the excellent visibility of the applied bone cement) into the median portion of the anterior third of the affected vertebral body. The access depends on the anatomical region. Whereas the posterior access (primary over the pedicles, alternatively extradural posterolateral approach) is established for the thoracic and lumbar spine, vertebroplasties of the cervical spine require a ventral access in order to protect the vertebral arteries. After image-controlled correct positioning of the canula, the image-guided injection of bone cement is performed. Intravertebral cement deposition is considered to be sufficient if the anterior two thirds of the vertebral body are filled with cement and if the cement is distributed homogenously to both of its sides (Gangi et al. CiRSE quality improvement guidelines). Stabilization is achieved if partial replacement of the bone destruction and shoring of the remaining trabecula could be accomplished (Fig. 7). Pain reduction is caused by physical neurotoxicity of the cement. In cases of neoplastic destruction, the rate of recurrence is reduced.
The thoracic spine. The risk for associated with interventions at intervertebral foramina, infected veins, the spinal canal or the epidural space leakage into the epidural veins, the spinal canal or the posterior edges of the respective vertebral bodies should be considered. Kyphoplasty is applied in selected vertebrae or in patients with previous severe allergic reactions. The "one-time treatment" of more than 3 vertebral bodies should be avoided.

Complications comprise cement leakage into the epidural veins, the spinal canal or the intervertebral foramina, infection and pneumothorax (associated with interventions at the thoracic spine). The risk for leakage is especially elevated if there are partial / complete destructions of the posterior edges. It can be reduced by increasing the viscosity of the cement. The usefulness of preinterventional contrast-enhanced CT of the epidural veins is discussed controversially since there may be difficulties to differentiate between bone cement and residual contrast medium.

The most important endpoint in evaluating the therapeutic success of PV is pain reduction. This can be achieved in a sufficient manner in 90% of all cases. PV should also aim at preventing collapse of the vertebral body by more than 33%. If a major collapse of the respective vertebral body is present, kyphoplasty instead of PV should be considered. Kyphoplasty combines PV with preceding balloon dilation in order to re-establish the affected vertebrae body height.

Selective Interventional Radiotherapy (SIRT)

SIRT is a relatively new method for the treatment of advanced primary and secondary liver tumors not or no longer respond-
Preferential destruction of neoplastic tissue which is mainly supplied by the portal veins. Following intraarterial injection the radioactive microspheres are accumulated in the capillary system of the tumours. Superselective hepatic branch catheterization and embolization of side branches is mandatory in order to prevent for deposition of microspheres in other organs, e.g. the stomach. Yttrium-90 shows an average radiation distance of 2.5 mm. This enables selective destruction of neoplastic tissue whereas the normal liver tissue is not affected (Fig. 8).

Before applying SIRT, extrahepatic metastases have to be excluded with diagnostic imaging to established therapeutic regimens (e.g. systemic / intraarterial chemo- or immunotherapy, surgery, RFA, transarterial chemoembolization (TACE))(13). Small radioactive resin- or glass-based microspheres containing the beta emitter Yttrium-90 are injected slowly (30-60 min) in the hepatic arterial system after selective catheterization of the hepatic artery's main branches inducing a high-dose interstitial radiotherapy and an arterial microembolization in the fields of interest. This method is based on the dual vascular supply of the liver: hepatic tumours have a predominant arterial supply – in contrast to normal hepatic tissue which is mainly supplied by the portal veins. Following intraarterial injection the radioactive microspheres are accumulated in the capillary system of the tumours.

The gastroduodenal artery was coiled (arrow). The patient with metastasis from colorectal cancer in segment 2 of the liver before (8a; arrow) and 9 months after SIRT (8c). 

Substantial decrease of FDG uptake in Fig. 3c. Fig. 8b shows an angiogram of the left hepatic artery after catheterization. The gastroduodenal artery was coiled (arrow).

The malignant vascularization of the tumours is better visualized by a high dose of FDG after SIRT. In the left panel the tumour (arrow) shows a large decrease of FDG uptake after SIRT. In the right panel the tumour (arrow) shows a negligible decrease of FDG uptake after SIRT.

Fig. 8: Patient with metastasis from colorectal cancer in segment 2 of the liver before (8a; arrow) and 9 months after SIRT (8c). Substantial decrease of FDG uptake in Fig. 3c. Fig. 8b shows an angiogram of the left hepatic artery after catheterization. The gastroduodenal artery was coiled (arrow).
Imaging (PET-CT/MRI, conventional angiography with 99mTc – macroaggregated albumine). Hepatic / renal function should not be severely impaired. An obstruction of the portal vein restrains the administration of SiRT since in these cases the arterial perfusion is also essential for the normal hepatic tissue, and the aimed selective enrichment of the microspheres in the tumours is aggravated. The percentage of hepato-pulmonary shunting should not exceed 20%. Reported side effects comprise abdominal pain, nausea, fever and (in rare cases) peptic ulceration, gastrointestinal bleeding, mild pancreatitis, radiation pneumonitis and radiation hepatitis (14).

First data on limited cohorts of selected patients suggest a benefit of SiRT even in patients not / no longer responding to any established alternative therapies. Van Hazel et al.(15) as well as Sharma et al.(16) could demonstrate a superiority of the combination of SiRT / systemic chemotherapy in patients with metastasized colorectal cancer in comparison to patients receiving systemic chemotherapy alone regarding overall survival and time to progression, respectively. Similar observations were made by Cosimelli et al.(17) and Ricke et al.(18) in patients not / no longer responding to any established alternative therapies. In patients suffering from advanced hepatocellular carcinoma, an increase of the median survival rate after applying SiRT could be observed as well (19), even in very few selected patients with partial / complete obstruction of the portal vein. However, since the evaluation of long-term outcome is still in progress so far, a terminal evaluation of the method cannot be performed. It has to be emphasized that SiRT is not a curative approach but a potential new low-invasive palliative method dedicated to the treatment of patients with advanced therapy-refractory neoplastic disease of the liver.

References

Table 1: Staging of PAD. Comparison of the established classification systems.

<table>
<thead>
<tr>
<th>Fontaine</th>
<th>Rutherford</th>
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<tbody>
<tr>
<td>Stage</td>
<td>Symptoms</td>
</tr>
<tr>
<td>I</td>
<td>Asymptomatic PAD</td>
</tr>
<tr>
<td></td>
<td>Chronic intermittent limb ischemia</td>
</tr>
<tr>
<td>II</td>
<td>Stage IIa: Pain-free interval &gt; 200 m</td>
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<tr>
<td></td>
<td>Stage IIb: Pain-free interval &lt; 200 m</td>
</tr>
<tr>
<td>III</td>
<td>Continuous pain syndrome</td>
</tr>
<tr>
<td>IV</td>
<td>Necrosis / Gangrene</td>
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<tr>
<td></td>
<td>Ascending lesion (superior to the metatarsal bones)</td>
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1. References
TASC II classification for lesions of the femoro-popliteal pathway

<table>
<thead>
<tr>
<th>Lesion type</th>
<th>Description</th>
<th>Recommended therapy</th>
</tr>
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<tbody>
<tr>
<td>A</td>
<td>Circumscribed stenosis &lt; 10 cm</td>
<td>Primary endovascular procedure</td>
</tr>
<tr>
<td>B</td>
<td>Complete obstruction &lt; 5 cm</td>
<td>Primary endovascular procedure</td>
</tr>
<tr>
<td>C</td>
<td>Multiple stenoses / complete obstructions, total length &gt; 15 cm, with or without extended califications Restenoses / Re-Obstructions requiring therapy after 2 endovascular interventions</td>
<td>Primary operation (if there are no outstanding risk factors)</td>
</tr>
<tr>
<td>D</td>
<td>Chronic complete AFS / AFS obstruction (&gt; 20 cm), in addition alterations of the popliteal artery Chronic complete obstruction of the popliteal artery / proximal part of the trifurcation</td>
<td>Primary operation</td>
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AFC = Common femoral artery; AFS = Superficial femoral artery

Table 2: TASC II classification for lesions of the femoro-popliteal pathway

<table>
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<tr>
<th>AFC</th>
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Influence of Dental Implant Surface Modifications on Osseo- and Peri-integration

Abstract
An increasing trend towards implantation in complex cases is beginning to emerge in dental implantology. As a result of advances in surgical techniques, implants today can be inserted with primary stability even where there is an extensive lack of hard and soft tissue. The long-term stability of the implants inserted is, however, influenced considerably by the osseointegration and periintegration process. Faced with this, numerous current research efforts aim at modifying the implant surfaces by ablative and additive procedures in order to optimise the healing processes.

Introduction
The use of endosseous, dental implants is a firmly established procedure today for the masticatory functional rehabilitation of patients following tooth loss [22]. Success rates of more than 95% have been described for observation periods of more than 5 years [4]. A trend towards implantation in complex cases is beginning to emerge because of the increasing average age of the population with a concomitant increase in multi-morbidty in dental implantology. As a result of the concurrently increasing demand for quality of life there is an increased need for aesthetically attractive, implant-supported restorations. The locoregional hard and soft tissue conditions are equally significant for the successful insertion of implants.

A sufficient vertical and transverse amount of bone (vertical: maxilla > 10 mm, mandible = 7 – 10 mm; transverse maxilla and mandible = 4 – 6 mm) is a basic requirement for anchoring an implant so that it has primary stability in the local available bone [9]. Bone structure augmentation concepts, such as sinus floor elevation [28] or augmentation and grafting osteoplaty [33], however, enable implants to be provided where there is an extensive lack of bone. A particularly difficult situation here is the severely atrophic maxilla. With

Keywords: surface modification, cytokines, osseointegration, bone implant contact ratio, periintegration

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particular, there is normally only long-standing edentulism in
around the implant [2]. With a minimum width of 3 mm this should not be less than Lindhe’s recommendations, according to Berglundh and for a successful implant [12].

essential determining factor of keratinised gingiva is an amount of bone can normally be made to anchor endosseous implants so that they have primary stability (Fig. 1, 2).

As far as soft tissue is concerned, a sufficient amount of keratinised gingiva is an essential determining factor for a successful implant [12]. According to Berglundh and Lindhe’s recommendations, this should not be less than a minimum width of 3 mm around the implant [2]. With long-standing edentulism in particular, there is normally only a narrow band of keratinised gingiva persisting the alveolar ridge area. A sufficiently wide “attached gingiva” can be made by the free graft of a mucosa transplant from the hard palate. In this case, the palatal donor site normally heals without any complications [11].

Regardless of surgical management, the surface composition of the implant, however, influences osseointegration and peri-implant soft tissue healing. The following article gives an overview of the impact of modifications to the implant surface on osseointegration and peri-implant soft tissue healing.

Fig. 1: Management of extensive lack of bone in the maxilla following explantation. To improve the vertical and horizontal amount of bone the patient received a sinus floor elevation as well as onlay grafting of autogenous, avascular bone grafts from the iliac crest bilaterally. Insertion of 8 dental implants (BEGO Semados RI; diameter 3.75 mm, length 15 mm) was performed after a time interval of 14 weeks. Implants were uncovered 6 months after implant insertion using the vestibuloplasty with free gingival grafts from the hard palate (a, b, c). Following prosthodontic rehabilitation using an implant retained zirconia bridge harmonization of the profile from treatment start (d) until end of treatment (e) was achieved. Furthermore, a significant improvement in the en face (f) and intraoral esthetics (g) was achieved.

implant on the alveolar ridge. However, any complication affects the primary stability of the implant, and a sufficient amount of keratinized gingiva is essential.

Augmentation osteoplasty with autologous, monocortical bone transplants of the anterior iliac crest, however, a sufficient amount of bone can normally be made to anchor endosseous implants so that they have primary stability (Fig. 1, 2).

 يمكن صنعها لربط الطبوق العظمية الداخلية الناتجة وبالتالي الحصول على النتائج المطلوبة في كل حال، وإذا تم الأخذ بعين الاعتبار الأنسجة الرخوة، فإنه من الضروري توفير كمية كافية من اللثة المترفقة وهي عامل ضروري لتحقيق نجاح الزرع (12). وبخصوص توصيات بيروكليدا، وليدنا بيرغ (Berglundh and Lindhe's recommendations) فإنه يجب أن لا يقل معدل لثة عن 3 مل جسم شوط (2).

أيمن من النص أو النصوص الطبوقية، فهي تتركز على الاتصال العظمي مع ذلك يؤثر على الاندماج العظمي وشفاء التسوس الرخوة في سطوح الطبوق والثغرة. يمكن البحث الحالي أن يعرض عامة حول تأثير تعديلات سطح
Surface Characterisation
The characteristics of an implant surface are largely determined by their topography and their chemical composition [31]. The most important surface topographical parameter in dental implantology is that described by the $S_a$ value, roughness. According to Albrektsson and Wennerberg, implant surfaces can be divided into 4 groups according to their roughness: 1) smooth surfaces ($S_a < 0.5 \mu m$), 2) slightly rough surfaces ($S_a = 0.5 – 1 \mu m$), 3) moderately rough surfaces ($S_a = 1 – 2 \mu m$) and 4) rough surfaces ($S_a > 2 \mu m$). [1] Each surface modification changes both the topography and the composition [13].

Osteointegration
The surgical trauma caused by inserting implants triggers complex, biological interactions at cellular and molecular level. The healing of the cancellous bone takes place here in 3 partially overlapping phases: 1) osteoconduction, 2) new bone formation and 3) remodelling [5].

Osteoconduction, the recruiting of osteogenic stem cells for the implant surface is the most important phase of endosseous bone healing [15]. The implant surface adsorbs fibrinogen which acts as an "adaptor" for the adhesion of thrombocytes [3]. For their part the thrombocytes are activated on the implant surface and release various osteogenic growth factors. Fibrinogen is cleaved proteolytically into fibrin, which forms a temporary, three dimensional network around the implant. As a result of the activated growth factors secreted by the thrombocytes, osteogenic stem cells move along the fibrin scaffold to the implant surface. This migration causes a retraction of the temporary fibrin matrix [25].

The new bone formation phase that follows this is characterised by the progressive degradation of the organic bone matrix by osteoclastic cells starting on the implant surface and continuing towards the periphery. Then the mineralisation of the matrix takes place as a result of calcium phosphate deposition.

When the first two phases of osseous healing are complete, a firm biological bond between the implant and the bone is formed and osseointegration is complete. In the subsequent remodelling phase a higher organisation of the peri-implant bone is achieved by resorptive processes [6].

Influence of Surface Modifications on Osteointegration
The influence of the roughness of the surface on osseointegration was thoroughly investigated. It was established that the roughness influenced the osteoconduction process in particular (Fig. 3). As the roughness increased, an enlargement of the implant surface occurred with a subsequent increase in the fibrinogen adsorption capacity and activation rate of the thrombocytes. In addition, the fibrin scaffold is more firmly anchored to rough surfaces [24].

There is general agreement that implants with smooth ($S_a < 0.5 \mu m$) and slightly rough surfaces ($S_a = 0.5 – 1 \mu m$) cause the greatest bone cell attachment and bone ingrowth. Implants with a rough surface ($S_a > 1 \mu m$) are better at anchoring bone tissue tightly to the implant. Implants with a very rough surface ($S_a > 2 \mu m$) are more suitable for use in the maxillary sinuses and the foramen of the leg bones.

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surfaces ($S_a = 0.5 – 1 \mu m)$ display worse osseointegration than implants with moderately rough ($S_a = 1 – 2 \mu m$) and rough surfaces ($S_a > 2 \mu m$). Furthermore, better bone apposition was exhibited on moderately rough surfaces than on rough surfaces [31]. As, however, each roughening of the surface also leads to a change in its chemical composition, it is not clear whether the effects observed are due to a change in the roughness or the concomitant change in composition [13].

Various organic and inorganic coatings were developed in order to optimise the chemical composition of the implant surface. The coating of implants with extracellular matrix peptides (e.g., collagen) was evaluated several times in animal experiments with the aim of improving osteoconductivity (Fig. 3). In accordance with a current European Association of Osseointegration (EAO) agreement, no basic improvement in osseointegration is, however, assumed as a result of coating the surface with peptide sequences of the extracellular matrix [13]. Biological activation by growth factors, such as Bone Morphogenic Protein (BMP)-2, is probably likewise ineffective. As BMP-2 also causes bone loss, such a coating may even reduce osseointegration [13]. Implants with a thin calcium phosphate (CaP) coating were introduced in order to improve bone mineralisation in the new bone formation and to enhance the chemical interaction with the bone surface [13].

The effects observed are due to a change in the roughness of the surface also leads to a change in its chemical composition, and to a change in the roughness or the concomitant change in composition [13].

Fig. 2: Management of extensive lack of bone in young patients. Pre-operatively the patient presented with an extensive oligodontia (a) with vertical atrophy of both jaws (b) and concomitant reduction of the height of the lower third of the face (c) as a result, ectodermal dysplasia. After augmentation of the bony bed, inserting endosseous implants and providing implant-supported bridges and single crowns (d, e) harmonisation of the profile (f) and the perioral area (g) was achieved.

Fig. 2: تدبير اذار عظام كبيرة لدى مريض على (a) بعد تجميع الـ(b) وكنتيجة لذلك حدوث عظم في (c) نتيجة لوجود عينات في (d, e) التوافق من المكع (f) ومنطقة محاو (g).

التقديم: تدبير الخسارة الكبيرة للعظم لدى مريض على (ب) وكنتيجة لذلك حدوث عدم العضو في (ج) ونتيجة لذلك حدوث عمر التعديل في الأدم (د). بعد تجميع السرير العظمي، غرس التطور الطبيعي الذاتي مع نموت النمو. وتقدم التنوير الداعم للتعمل (ب) والوحده (ج) التوافق من المكع (ف) ومنطقة محاو (ج).

BMP-2، يمكن أن يكون هناك تحسن أساسي على التواصل العظمي بناء على تفاعلات نقرطة سطح العظم مع تأثيرات البيضت. في اللحمة خارج الخلية (13).

وذلك منเครดت أن المخرجات الحيوية لعوامل نمو مثل البروتين النمو ينبغي أن تكون للعظام في الـ(b) مماثل لعظام BMP-2 في غير BPM-2.
Peri-Implant Soft Tissue Healing – Periintegration

As for osseous healing, soft tissue healing is also divided into 3 overlapping phases: 1) Inflammatory phase, 2) Proliferative phase and 3) Remodelling phase [26]. In the inflammatory phase the wound is repopulated by macrophages and polymorphonuclear leukocytes. This phagocytic cell debris protects against microbial contamination and secretes growth factors. These stimulate the proliferation of fibroblasts, the formation of a new epithelial cover and the generation of vessels in the area of the wound. The proliferative phase of wound healing gives way to the remodelling phase. In this phase, apoptosis of the majority of the fibroblasts occurs and a fibre-rich, peri-implant scar tissue is formed at the implant emergence profile [27].

Influence of Surface Modifications on Periintegration

While a large number of animal experiment and clinical studies investigate the impact of modifications on osseointegration, up till now there has only been scanty data on the importance of the implant surface for healing and consolidating the mucosa in the implant emergence profile.

In a study using animal experiments, we investigated the impact of the surface roughness of the implant shoulder on peri-implant inflammation parameters with transmucosal healing implants. After a period of 12 weeks, a mild inflammatory reaction was evident histologically in the area of the mucosal emergence profile of the smooth shoulder, however, a severe inflammatory reaction was evident in the emergence area of the moderately rough surface (Fig.4).

Moreover, the effect of a bioactivation of the transmucosal implant area on soft tissue healing was investigated. Faced with the central role of the glycoprotein laminin within the scope of the adhesion process of the oral mucous membrane epithelium to the implant surface, Werner et al. combined a laminin 5 derivative with titanium. In vitro experiments with human oral epithelial cells showed an enhanced adhesion process compared with titanium uncoated controls. However, there are still no confirmatory clinical studies [13].

Inflammation processes whereas inorganic coatings help new bone to form. Partial stages of osseointegration. Surface roughness and coating with organic factors such as extracellular matrix proteins or BMP-2 affect the osteoinductive processes whereas inorganic coatings help new bone to form.

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increased proliferation in the functionalised group compared with the control. These results were confirmed by the data in a pilot study on dogs [32]. As well as epithelial adhesion, neovascularisation also has a significant importance for adequate soft tissue healing. The vascular endothelial growth factor (VEGF), a heparin binding glycoprotein, is one of the most important mediators for angiogenesis in wound healing [23]. As a result of its short half life of 9 hours in the tissue, a topical application in protein form is inefficient [29]. A possible system for the delayed release of VEGF is the extracorporeal transfection of autologous fibroblasts and their re-plantation in the area of the wound as part of an invivo tissue engineering approach. For this technique, an improvement in the new vessel formation rate [19] without detectable local or systemic side effects [18] has already been found in the rat model.

**Conclusions**
Using the available data from animal experiments and clinical studies, currently no “ideal” implant surface in relation to a functionally and aesthetically satisfying, long-term result can be defined. As far as the surface topography is concerned, however, moderately rough surfaces (Sa = 1 – 2 µm) in the area of the bone contact are preferable whereas smooth surfaces (Sa < 0.5 µm) in the area of the emergence profile should be favoured. With regard to the composition, no practical recommendation can be derived from recent literature.

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Genetic Testing of Mental Retardation

Summary

Novel technologies in genetic diagnostics led to a very reliable, sensitive and more efficient detection of genetic causes of mental retardation (MR). Basic diagnostic of MR such as chromosome analysis is already obsolete as array technology detects genetic alterations such as duplications or deletions of chromosomal regions at much higher resolution. Whereas microscopic inspection usually detects deletions as large as 5 megabases (5 Mio base pairs) array technologies visualizes deletions and duplications even smaller than 100 kb (100 thousand base pairs). Using this approach genomic aberrations are detected in up to 15% of patients with MR with normal conventional karyograms. However, the vast majority of MR is thought to be monogenic with single base pair alterations or very small deletions or duplications. Today, more than 90 genes on the X chromosome are known causing MR most frequently in males. Using sophisticated next generation sequencing technology most of the X-linked syndromic and non-syndromic MR cases are now being deciphered. Subsequently, this technology allows also identifying genetic causes of autosomal recessive MR and malformation, in particular in consanguine families, or of de novo originated MR giving the chance for prenatal diagnosis in subsequent pregnancies.

Introduction

Mental retardation (MR) as defined by an IQ below 70 affects approximately 2% of the general population. More severe forms with an IQ < 50 has a frequency of about 0.5% (reviewed in Ropers and Hamel 2005, Nature Reviews Genetics 6:46-57).

Until today, chromosome analysis detecting additional chromosomes such as trisomies or partial chromosome alterations is a basis diagnostic in defining the genetic causes of MR. Indeed, trisomy 21, also called Down syndrome, is the most frequent form of MR. Besides these alterations one also finds structural changes such as inversions, unbalanced or balanced translocations, all with an increased familial

أساسي واحد أو تضاعف أو ألفقدان صغير جداً حالياً أكثر من 90 مورثة على الصبغي الجيني X معروفة على أنها تسبب التخلف العقلي والأكثر شيوعا لدى الرجال. واستخدام طرق أكثر تعقيدا لتقييم التسلسل العصبي الجيني X أو التي لا تتشكل تنازلا، وبالتالي فإن هذه التقنية تسمح بتحديد الأسباب الجينية الجسدية المفيدة للتخلف العقلي والتشوهات وخصوصا لدى العائلات consanguine, أو التخلف de novo العلقي الناجي في الأحياء متعاطيا الفرصة للتشخيص أثناء الحمل في الحمول اللاحقة.

تقدم

يعرف التخلف العقلي على أن أقل من 2% من عامة الشعب. الشكل الأكثر شدة مع أقل من 50% حدة نسبة Nature 2009, 205 (3) Hamel (0.5%).

والفرصة

ونقلت deletions أو الفقدان أكثر من 100 كيلوب جين (أي 100 ألف جين) الأزواج الأساسية) وباستخدام هذه الطريقة يمكن الكشف عن الأورغان الوراثي حتى نسبة 15% من المرضى الذين لديهم تخلف علقي بالطريقة كاريوغرام التقليدية. مع ذلك يمكن أن الأغلبية العظمى من مرضى التخلف العقلي هي مورثية أحادية مع تبدلات في زوج
The hereditary causes in the majority of the cases are genetic. Recently, specific DNA sequences (adaptors) are merged to the DNA fragments allowing its widespread amplification and labelling. Labelled DNA fragments are then hybridized onto millions of short oligonucleotides covering known polymorphisms in the genome which will be scanned allowing detection of missing (deleted) or duplicated DNA fragments.

If these routine screening methods do not detect chromosomal aberrations and if the physical characteristics of one patient do not allow a specific differential diagnosis and thus directed genetic testing, one usually has to rule out inborn error of metabolism which will not be the scope of this review. Even then, the underlying cause of MR remains unknown in more than 65% (Rauch et al. 2006). Here we will concentrate on novel genetic screening technologies allowing the identification of the genetic causes in the fast majority of patients with syndromal and non-syndromal MR for which environmental or toxic causes have been ruled out. One recent technique which is already fundamental as a routine diagnostic tool, is the so-called chip or microarray technology, also known as molecular karyotyping, to identify deletions or duplications usually of an entire or several genes. This approach led to the definition of novel microdeletion / duplication syndromes.

However, even with this technology, the great majority of genetic causes of patients with MR is not being deciphered. Here we give first insights into the transition of the most recent new generation sequencing technology to track down single base pair changes causing MR even without knowing the respective candidate gene or region. In combination both technologies will allow the detection of nearly all genetic causes of MR changing the routine of clinical syndromology and allowing more accurate family planning in future pregnancies or for close relatives.

In future pregnancies or for the follow-up of children with syndromic MR for which genetic causes have been ruled out, one can use conventional karyotyping (karyotype) and subsequently of multiplex ligation-dependent probe amplification (MLPA) small deletions or duplications are detected particularly analysing telomeric regions (Flint and Knight 2003) in about 5-10% of unexplained MR.

The most recent new generation sequencing technology and in particular exon sequencing technology (exon-extraction) led to the definition of novel molecular karyotyping (karyo-MLPA) which allows the detection of deletions or duplications in several genes. Here will give first insights into the transition of the most recent new generation sequencing technology to track down single base pair changes causing MR even without knowing the respective candidate gene or region. In combination both technologies will allow the detection of nearly all genetic causes of MR changing the routine of clinical syndromology and allowing more accurate family planning in future pregnancies or for close relatives.

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SNP Microarrays to detect de novo duplications / deletions in patients with MR

Recent developments using array technology now allows scanning of the entire genome for microdeletions / duplications (Fig. 1). Any variation in the copy number is called copy number variant (CNV). Most of the CNVs are benign (Buysse et al. 2009), have no obvious causative influence on the disease and may be inherited by one of the parents. However, there is a scientific debate whether these benign CNVs contribute to common multifactorial diseases (Zhang et al. 2009) as the level of expression of genes within or adjacent to the genomic interval may be affected. Nevertheless, in a child with MR most of the de novo CNVs which are not present in the parents and do not overlap with known CNVs are causative for the disease.

Caution needs to be taken if the deleted / duplicated chromosomal region does not contain any known genes or if the gene involved is not expressed in the brain or totally unknown in MR. In our diagnostic experience we found several examples of deleted genes which were unknown to be a benign CNV at the time of analysis or, for genes on the X chromosome which was transmitted by the mother, also be present in the unaffected uncle of the child with MR. Despite caution is needed if interpreting undescribed CNVs, the sensitivity of the microarray analysis is thought to have a 100 times higher resolution than conventional karyotyping and thus superior in deciphering genetic causes of MR (Fig. 2).

Most importantly, all previously known microdeletion syndromes are also detected using microarrays (McMullan et al. 2009). Furthermore, even low-level chromosomal mosaicism and uniparental disomy (UPDs) can be detected using this technology (McMullan et al. 2009, Al tug-Teber et al. 2005). We strongly encourage applying molecular karyotyping only after genetic counselling as some microdeletions may reveal risks cancer, and several inherited microduplications indicate a risk of epilepsy (Heinzen et al. 2010) or psychiatric disorders such as schizophrenia (Need et al. 2009, Stefansson et al. 2008).

Summarizing a large proportion of publications on the use of microarrays in about 22,000 patients with MR Miller and colleagues came to the conclusion that chromosomal microarrays should be the first-tier genetic diagnostic test (Miller et al. 2010). Even considering costs for the genetic analysis, microarray testing for chromosomal imbalances is superior to conventional strategies (karyotyping and subtelomere analysis) in MR (Regier et al. 2010). Currently, molecular karyotyping should be performed as basic test in patients with autism, developmental delay, mental retardation, and/or multiple congenital anomalies. However, despite its high resolution, deletions / duplications smaller than 100 kb or even at a single base pair level are not detectable even with the most superior in deciphering genetic causes of MR (Fig. 2).

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dense high resolution microarrays. Thus, for this diagnostic area a new technology which is called next generation sequencing has been developed basically allowing the sequence analysis of the entire genome or at least of nearly all coding genes of an individual which is now being transferred from research into the clinic.

Next Generation Sequencing

Using very sophisticated novel technology, known as next generation sequencing (NGS), we are now able to reliably sequence entire individual genomes at reasonable costs and time (Ng et al. 2009). Actually, the generation of sequencing data of individual genomes is not the greatest challenge anymore but rather the bioinformatical analysis and evaluation of the clinical relevance of the received data. Recent application of this technology onto the identification of genetically unknown syndromes revealed the genetic causes even in single families. Despite initial doubts whether one would be able to identify a single disease causing mutation due to the complexity of the data and the

large number of polymorphic DNA changes in one individual in general (two individuals differ each other at 2 to 3 Mio positions!) as well autosomal dominant (Hoischen et al. 2010) as autosomal recessive traits (Bilguvar et al. 2010) and de novo mutations (Vissers et al. 2010) were solved through NGS. Even individual risk predictions for cardiac diseases and early sudden death seem to become possible (Ashley et al. 2010). In the field of MR we clearly have now two options: sequencing of a large number of genes known to be mutated in patients with MR, and unbiased sequencing of entire genomes in individual patients.

Due to the complexity of the data sequencing whole genomes, one currently uses the strategy to sequence only regions of which are being transcribed into RNA, the called exons. The entire number of exons is also called “exome”, the strategy to sequence virtually all exons “all-exome-sequencing”. For this, the exones have to be enriched by hybridization capturing, a method, which has not yet to-

karyotyping and subtelomere

lund MR is called karyotyping (analysis of DNA, 2010). It can be seen that the technique (Regier et al. 2009) has been developed on the basis of different methods for the diagnosis of syndromes in newborns. The technique allows the detection of deletions and duplications of the entire genome in individual patients. The de novo occurrence of the deletions was clearly possible in patients with MR, and especially the number of genes known to be mutated in syndromes with MR (Ashley et al. 2010). Even small deletions in patients with MR are now being transferred from research into the clinic.

The figure 2 illustrates the 5.4 Mb deletion in 2q36.1-36.3 with the 500K Affymetrix SNP Array in a severely mentally retarded girl. a) Image of the parents-patient trio analysis, showing the de novo occurrence of the deletion (red arrow) and mapping of the deleted region according to Ensembl release 60 - Nov 2010. b) Selected GTG-banded chromosome 2 pair of the patient. The der(2) (red arrow) and the normal chromosome 2 can not be distinguished unequivocally at the 550 band level.
Fig. 3: Diagnostic work flow for clinical genetic testing implementing next-generation technologies to decipher the causes of MR.

Implementing the very recent technologies does already change our diagnostic work up these days (Fig. 3). First step chromosomal analysis is being displaced by molecular karyotyping with higher sensitivity to visualize aberrations as small as 100 kb. Clearly, if the clinical geneticist does have a syndromal suspected diagnosis such as Angelman syndrome, testing of specific genes is indicated before unselected screening approaches. Also, relatively frequent genetic causes of MR such as Fragile X syndrome or myotonic dystrophy need always to be considered, in particular as large repeat expansions underlying MR are not being detected by next generation sequencing. However, in particular for affected males we propose sequencing of the X-ome analysing the great majority of known MR genes and most importantly also of non-syndromal manifestation in one test. If the cases are medical, and repeats behind the X-ome are not possible, one approach is to use a next generation sequencing panel targeting a number of known MR genes, including the X-ome X-chromosome.

E11.3:01-02

The X-chromosome

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References


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Baden-Baden
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Beautifully located in the sun drenched southwest corner of Germany at the foothills of the Black Forest, Baden-Baden is an elegant, world-famous thermal spa and climatic health resort, wellness and event paradise and cultural metropolis.

Today Baden-Baden is the perfect mix of Belle Époque ambiance and innovative 21st century wellness. Its famous healing thermal water, flowing from 12 springs, is not only used for well-tried therapies but also for modern and innovative treatments. Today the up to 68° degrees hot and healthful water pampers guests from all over the world in the two thermal baths – the modern Caracalla Spa and the historic Roman-Irish "Friedrichsbad". Furthermore many spa-hotels are particularly conducive to relaxation, offering unique wellness opportunities as well as individual health and wellness treatments. Eight highly qualified clinics with different focuses and medical specialists with high reputation offer individual medical Check-ups, subject-specific consultation, comprehensive prevention and rehabilitation methods to the point of medical necessary operations. Individual and culture-related wishes of the guests will be considered at any time.

For more than 350 years the three kilometre splendiferous parks and gardens “Lichtentaler Allee” has been Baden-Baden’s green and blooming visiting card. The masterpiece made of trees, fountains and flowers invites not only for healthy walks in crystal Black Forest air but also fascinates the botanical, artistic and cultural connoisseurs.

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as a stylish mile for art and culture with the historic “Trinkhalle” (Pump Room), the world-famous “Kurhaus” – the social meeting place of the city – the Casino, the neo-baroque theatre as well as the Museum of Modern Art Frieder Burda designed by star architect Richard Meier. Europe’s second largest opera and concert hall, the “Festspielhaus”, guarantees cultural pleasure at the highest level and offers over 300 top class events yearly.

During the whole year Baden-Baden is setting for outstanding and sophisticated events: Three times a year the International Horse Races, the International Vintage Car Meeting mid of July, outstanding concerts at the parks and gardens “Lichtentaler Allee” and at the romantic courtyard of “Castle Neuweier” as well as international artists and performances at the “Festspielhaus”.

In the picturesque streets and the small lanes of the neo-baroque old town of Baden-Baden, numerous exclusive boutiques invite you to first class shopping. Everyone who searches for brand products, international labels and individual antiques, jewellery and presents will find himself in the right spot.

Besides well-known starred restaurants, cozy little taverns with local colour and fine Baden cuisine, bistros and countless street cafés in the centre, there is also Baden-Baden’s “Rebland”, one of the most popular Riesling growing districts in Germany and an insider tip for the gourmet and connoisseur of good wines.

Germany’s oldest and according to Marlene Dietrich “the most beautiful casino in the world” rounds off a perfect day in a playful manner and entices guests from all over the world to try their luck at the roulette table.

In addition to the charming nightgowns of the Flaxhalle in the old Kurhaus, and also in the “castle Neuweier” as well as in the picturesque streets and the small lanes of the neo-baroque old town of Baden-Baden, numerous exclusive boutiques invite you to first-class shopping. Everyone who searches for brand products, international labels and individual antiques, jewellery and presents will find himself in the right spot.

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