Detecting prostate cancer metastases - PET/CT and the sentinel node technique

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Detecting prostate cancer metastases

PET/CT and the sentinel node technique

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Abstract

Prostate cancer is one of the most common malignancies. Its treatment is highly dependent on the presence or absence of metastases. The available invasive and non-invasive modalities for detecting metastases are imperfect. Positron-emission tomography fused with computed tomography (PET/CT) is a non-invasive method for detecting metastases that is presently evaluated for prostate cancer. Fluoride and choline are PET/CT tracers with different properties; fluoride detects bone metastases only, while choline may detect metastases in bone, lymph nodes, and other organs. Sentinel node (SN) detection is an invasive method that allows selective dissection of the lymph nodes most likely to contain metastases. The SN technique may increase the detection rate by identifying metastases also outside the template of a standard lymphadenectomy. The clinical implications of the combination of choline and fluoride PET/CT were prospectively evaluated in Study I. The findings of choline PET/CT were compared with extended pelvic lymph node dissection (ePLND) in Study II. The clinical implications of early choline PET/CT in patients with biochemical recurrence (BCR) after radical prostatectomy (RP) was evaluated in Study III. SN detection was prospectively evaluated and compared with ePLND in Study IV.

The main results were:

1) A fifth of patients with high-risk prostate cancer and normal or inconclusive planar bone scan had extensive metastatic findings on the PET/CT exams, leading to change of management. The choline and fluoride scans did on their own indicate metastases in patients in which the other scan did not.

2) Choline PET/CT had a high specificity (0.98) but, depending on the cut-off value of tracer uptake, had a low sensitivity (0.21–0.46) for lymph node metastases.

3) Choline PET/CT indicated metastases in 28% of hormone-naïve patients with BCR after RP and prostate-specific antigen of less than 2 ng/mL.

4) SN detection performed at least equal to ePLND in determining lymph node stage, with sensitivity 0.96.

Conclusions: Choline and fluoride PET/CT and SN detection may be valuable diagnostic modalities for detecting metastases of prostate cancer.

Key words: Prostate cancer; Metastases; PET/CT; Choline; Fluoride; Sentinel lymph nodes

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Cover: Maximum intensity projection (MIP) rendering of the fusion images of a fluoride (left) and choline (right) PET/CT scan, both of the same patient.

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To my beloved wife and children

Contents

Abbreviations

ADT	Androgen deprivation therapy
ASTRO	American Society for Therapeutic Radiology and Oncology
BCR	Biochemical recurrence
CSM	Cancer-specific mortality
CT	Computed tomography
DRE	Digital rectal exam
EAU	European Association of Urology
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organisation for Research and Treatment of Cancer
EPC	Early Prostate Cancer trial
ePLND	Extended pelvic lymph node dissection
FDG	Fluorodeoxyglucose
HT	Hormonal therapy
lPLND	Limited pelvic lymph node dissection
MDP	Methylene diphosphonate
MRI	Magnetic resonance imaging
NPCR	National Prostate Cancer Registry
NPV	Negative predictive value
PET/CT	Positron emission tomography fused with computed tomography
PPV	Positive predictive value
RP	Radical prostatectomy
RT	Radiation therapy
SN	Sentinel node
SPCG	Scandinavian Prostate Cancer Group
SPECT	Single-photon emission computed tomography
SUV	Specific uptake value
TRUS	Trans-rectal ultrasound
UICC	Union for International Cancer Control

List of studies

I. Kjölhede H, Ahlgren G, Almquist H, Liedberg F, Lyttkens K, Ohlsson T, Bratt O. Combined ^{18}F-fluorocholine and ^{18}F-fluoride positron emission tomography/computed tomography imaging for staging of high-risk prostate cancer. *BJU International* 2012, 110(10), 1501-1506. Reprinted with permission from John Wiley and Sons.

II. Kjölhede H, Ahlgren G, Almquist H, Liedberg F, Lyttkens K, Ohlsson T, Bratt O. ^{18}F-fluorocholine PET/CT compared with extended pelvic lymph node dissection in high-risk prostate cancer. *World Journal of Urology* 2014, 32(4), 965-970. Reprinted with permission from Springer.

III. Kjölhede H, Ahlgren G, Almquist H, Liedberg F, Lyttkens K, Ohlsson T, Bratt O. ^{18}F-choline PET/CT for early detection of metastases in biochemical recurrence following radical prostatectomy. In manuscript.

IV. Kjölhede H, Bratt O, Gudjonsson S, Sundqvist P, Liedberg F. Simplified intraoperative sentinel node detection performed by the urologist accurately determines lymph node stage in prostate cancer. Accepted for publication. *Scandinavian Journal of Urology*.

Introduction

Prostate cancer overview

Demographics

Prostate cancer is one of the most common malignancies worldwide. For American men, the life-time risk of being diagnosed with prostate cancer is around 15%, which means that about one in every six to seven men will at one point be diagnosed with this malignancy [1]. In Sweden, the cumulative risk is 11.8% by the age of 75 years [2]. However, the life-time risk of dying from prostate cancer is only about 3–5%, which means that most men diagnosed with prostate cancer will die of other causes than their prostate cancer [3,4]. Five-year relative survival in Europe increased from 73.4% in 1999 to 81.7% in 2007 [5]. There are probably several explanations for this improvement in survival, such as better treatment and earlier diagnosis. The incidence of prostate cancer is strongly correlated with age: the highest incidence rates are noted in the age group 65–75 years, very few cases are diagnosed before the age of 45 [1,6].

Cancer biology

Ninety-five percent of prostate cancers are adenocarcinomas, and examples of more unusual types are neuroendocrine cancers and small cell carcinomas [7]. The most widely used histological classification of prostate adenocarcinomas was described by Donald F. Gleason in 1966 [8]. A slightly modified version of that system is used today (Figure 1) [9]. Gleason grading is based on the histological appearance of the cancer, with grade 1 being the most similar to normal prostate tissue and grade 5 being the most abnormal. In Gleason's original classification, the two grades that constitute the largest parts of the examined material were added to form a score, for example 3 + 3 = 6 or 4 + 5 = 9. In the latest modification, any occurrence of high-grade cancer in needle biopsy material, even if less common, was included to form the score. Also, the use of Gleason grade 1 was essentially discontinued, and grade 2 should be used only very sparingly, and not at all for biopsy material. This basically limited the applicable scores to 6 to 10, with 6 being interpreted as well differentiated (low-grade) and 8–10 as poorly differentiated (high-grade).

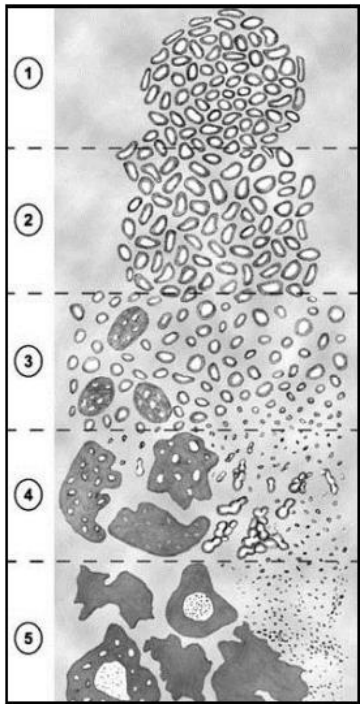

Figure 1.
Illustration of the patterns of the modified Gleason grades [9]. Reprinted with permission from Wolters Kluwer Health.

Our understanding of the natural progression of prostate cancer was greatly advanced in 1941 when Huggins and colleagues found that growth of this malignancy depended on testosterone and other androgens, and thus could be treated by castration [10]. Huggins was awarded the Nobel Prize in Physiology or Medicine in 1966 for this discovery, and later research has confirmed the role of the androgen receptor in progression of prostate cancer. When activated by circulating androgens, the androgen receptor acts as a factor that induces transcription of a variety of genes that promote cell growth and division. In prostate cancer, particularly in later stages of the disease, the function of the androgen receptor is frequently affected by mutations, either indirectly through up-regulation or directly resulting in activation even in the absence of androgens [11].

Cancer markers

Among other actions, the androgen receptor controls the expression of a protein that is excreted in the seminal fluid and is instrumental in dissolution of seminal coagulum. This protein was discovered by Wang et al in 1979, and it was determined to be specific to the prostate and was therefore given the name prostate-specific

antigen (PSA) [12]. Catalona et al later evaluated the usefulness of PSA in early detection of prostate cancer and found that prevalence of the disease increased with increasing PSA levels and that extra-prostatic spread was more likely with more elevated PSA levels [13]. Subsequent research demonstrated a statistically significant association between PSA level and the risk of detecting prostate cancer, especially high-risk prostate cancer [14]. Later it was shown that the PSA level in middle-aged men predicts the risk of metastatic and lethal prostate cancer later in life [15].

Staging

Staging of prostate cancer is usually done according to the TNM system, outlined by the Union for International Cancer Control (UICC), the latest (7^{th}) edition of which was published in 2009 [16]. The three letters TNM in the name of the system stand for tumour, nodes, and metastasis (Table 1).

Table 1.
Description of the TNM classification of prostate cancer [16]. A prefix "c" denotes clinical stage, and the prefix "p" indicates pathological stage (*e.g.*, cT2a or pT3b). Pathological stage is determined from histological specimens, either biopsies or prostatectomy specimens. The TNM stage represents a combination of the tumour, node, and metastasis stages (*e.g.*, T3bN1M0).

Tx	Primary tumour cannot be assessed
T0	No primary tumour detected
T1	Tumour not clinically apparent, neither by palpation nor imaging
T1a	Incidental finding in ≤ 5% of material from resection
T1b	Incidental finding in > 5% of material from resection
T1c	Identified by needle biopsy
T2	Tumour confined within prostate
T2a	Tumour involves ≤ half of one lobe
T2b	Tumour involves > half of one lobe but not both
T2c	Tumour involves both lobes
T3	Tumour extends through the prostatic capsule
T3a	Extracapsular extension, including microscopic bladder neck involvement
T3b	Seminal vesicle invasion
T4	Tumour is fixed or invades adjacent structures other than seminal vesicles
Nx	Regional lymph nodes have not been assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
M0	No distant metastases
M1	Distant metastases
M1a	Non-regional lymph nodes
M1b	Skeletal metastases
M1c	Other sites (such as visceral metastases)

The T stage indicates the local extent of the tumour, with the most important distinction being between T2 and T3, thus considering organ-confined versus non-organ-confined growth. The reference standard for local staging of prostate cancer is the combination of digital rectal exam (DRE) and trans-rectal ultrasound (TRUS). Varenhorst et al (1993) showed that DRE has a high inter-observer reliability, but only the posterior part of the prostate can be examined, and thus it is not possible to evaluate extraprostatic extensions in other directions [17]. TRUS is better at visualising all parts of the prostate although Enlund et al (1990) used that method to study 59 patients with prostate cancer and noted that it under-staged a large proportion of T3 tumours [18]. In a later investigation, May et al (2001) found that the overall accuracy of TRUS in staging prostate cancer was only 63% in comparison with the histopathological examination of the prostatectomy specimens [19].

The N stage is defined by the presence or absence of regional lymph node metastases. Regional refers to being located within the true pelvis, that is, approximately below the aortic bifurcation.

The M stage denotes distant metastases, *i.e.* spread of the disease to non-regional lymph nodes or to other organs. Distant metastases in prostate cancer are most commonly located in the skeleton, usually in the axial skeleton such as the vertebrae. Less commonly, metastases occur in visceral organs, such as the liver or the lungs. Visceral metastases are frequently manifestations of more aggressive cancers associated with poor prognosis [20].

Localised prostate cancer

Risk groups

Prostate cancer without evidence of extraprostatic growth or metastases (*i.e.*, cT1-2, N0, M0) is considered localised. D'Amico et al (1998) described a system using T stage, PSA level, and biopsy Gleason score to classify localised prostate cancer into low-, intermediate- and high-risk disease (Table 2) [21]. In the original publication, the risk of biochemical recurrence (BCR) after curative treatment was reported: 5-year BCR-free survival was more than 80% for patients with low-risk cancer, but less than 30% for those with high-risk disease. In a validation study performed by Boorjian et al (2008) at the Mayo Clinic (Rochester, MD, USA), 7,591 patients previously treated with radical prostatectomy were assessed, with a mean follow-up time of 7.7 years. The hazard ratio was 3.3 (95% CI 2.9–3.7) for BCR in the patients with high-risk cancer compared to those with low-risk disease [22]. The risk of death from prostate cancer was 12 times higher (95% CI 5.9–22) for men

with high-risk than men for low-risk cancer, although the cancer-specific mortality (CSM) among the men with high-risk disease was only 1.5% after 5 years and 5% after 10 years.

Table 2.
Summary of the D'Amico risk groups of localised prostate cancer, adapted from the original publication [21].

Risk group	Criteria
Low	PSA < 10 ng/mL and Gleason score ≤ 6 and Clinical T stage ≤ T2a
Intermediate	All patients not in the low-risk or high-risk groups
High	PSA > 20 ng/mL or Gleason score ≥ 8 or Clinical T stage T2c

Abbreviations: PSA, prostate-specific antigen.

In the 2013 annual report of the Swedish National Prostate Cancer Registry (NPCR), which includes virtually all patients who are diagnosed with prostate cancer in Sweden, the cumulative CSM at 15 years from diagnosis, regardless of treatment, was 9% for the low-risk group and 35% for the high-risk group [6]. The CSM for the entire group of patients with metastases was 69%, with a median cancer-specific survival of approximately 4.5 years. There was a marked difference between age groups, with patients older than 75 years having a much higher competing-causes mortality. Even so, more than 30% of men with high-risk, non-metastatic prostate cancer, who were older than 75 years at diagnosis, died from their cancer.

Treatments with curative intent

Several curative treatment options are available for patients with localised prostate cancer. Radical prostatectomy (RP), which is the surgical removal of the entire prostate, can be performed either with open surgery, traditional laparoscopy, or with robot-assisted laparoscopy. RP was assessed in the Scandinavian Prostate Cancer Group (SPCG)-4 trial, in which 695 patients with localised prostate cancer were randomised to RP or watchful waiting (*i.e.*, no treatment until the onset of symptoms, when non-curative treatment is initiated) [23,24]. After 12 years of follow-up, CSM was 13% in the surgery group and 18% in the watchful waiting group, which was a statistically significant difference ($p = 0.03$). RP was also significantly associated with a 19% (95% CI 12–27) absolute reduction in the use of hormonal therapy and a 5.2% (95% CI 0.1–10) absolute reduction in the use other palliative treatment. After 18 years of follow-up, RP conferred a 12.7% (95% CI

5.1–20.3) absolute risk reduction of death from any cause, but this was only statistically significant for patients who were younger than 65 years. Interestingly, for men with high-risk cancer the only benefit of RP found in this investigation was less use of hormonal therapy.

Complications and side-effects of surgery are common. Most modern reports on surgical complications use the modified Clavien grading system, wherein the grades are based on the level of management required by the complications [25]. The most significant cut-off is between grade 2 complications, which can be managed by non-surgical means, and grade 3 complications, which require surgical, endoscopic or radiological interventions. In a large retrospective analysis, Rabbani et al (2010) observed a 10% risk of Clavien grade 3 or higher surgical complications during the first 90 days following prostatectomy [26]. The investigators identified the following risk factors for Clavien grade 3 or higher surgical complications: the poor performance status of the patient, open surgery, high estimated blood loss, hypercoagulable disease, and high body mass index. Novara et al (2012) conducted a systematic review of complications after robot-assisted RP and noted a mean rate of Clavien grade 3 or higher complications of 2.4%, although the study may have under-estimated the long term complication risk (the length of follow-up was not stated) [27]. The functional outcomes, relating to erectile function and urinary continence, are highly dependent on how extensive the surgery is, which is in turn determined by the pre-operative cancer stage and grade. The experience of the surgeon and non-cancer-related patient factors such as age and co-morbidity also affect the functional outcome of surgery [28].

Radiation therapy (RT) of prostate cancer can be given either as brachytherapy or as external beam RT. The SPCG-7 trial was conducted to explore the effects of using external beam RT in addition to hormonal therapy, and randomised 875 patients with localised high-grade or locally advanced, non-metastatic prostate cancer to either hormone therapy alone or combined with radiotherapy [29]. After 10 years of follow-up the addition of RT conferred a 12% (95% CI 4.9–19) absolute risk reduction in CSM, as well as a 10% (95% CI 0.8–19) absolute risk reduction in overall mortality. The risk of BCR was reduced from 75% to 26% ($p < 0.001$). Although 78% of the patients had clinical stage T3 cancers, the CSM risk reduction was similar and also statistical significant for T1b-T2 high-grade cancers. Similar results were also found in a joint Canadian and British study (the NCIC CTG PR3/MRC UK PR07 trial) for locally advanced prostate cancer [30].

RT is also associated with complications and side effects, such as urinary urgency and incontinence, radiation proctitis, and erectile dysfunction [29,31,32]. Furthermore, RT to the prostate increases the risk of later being diagnosed with bladder cancer [33].

There are no reports from prospective randomised studies comparing the two curative treatment options, RP and RT, only retrospective outcome studies in which

the results mainly favour of RP [34,35]. The planned SPCG-15 trial, a randomised trial between RP and RT, will hopefully shed some light on this issue. However, only patients with locally advanced prostate cancer will be included in SPCG-15.

Treatments with non-curative intent

Hormonal therapy (HT) is based on Huggin's discovery that the progression of prostate cancer is, at least initially, dependent on androgens, such as testosterone. Early treatments were based on surgical castration, *i.e.* excision of the testes to stop testosterone production. Later advances led to medical castration, achieved by using either analogues or antagonists of gonadotropin-releasing hormone (GnRH). Either surgical or medical castration are jointly called androgen-deprivation therapy (ADT). Another approach to HT for prostate cancer is using anti-androgens that inhibit the androgen receptor. HT is not considered a curative treatment for prostate cancer, but may delay the progression of the disease and prolong survival [36].

HT is usually not used alone in the treatment of localised prostate cancer, but it is often used as an adjunct to RT, especially in high-risk disease [37]. Bolla et al (2002) studied RT combined with three years of ADT compared with RT alone in high-risk prostate cancer and found that overall mortality was significantly lower in the group that received the combination therapy (22% versus 38% after 5 years of follow-up) [38]. The 5-year CSM was 6% versus 21% ($p = 0.0001$). These observations were confirmed by Pilepich et al (2005) in an investigation using a similar protocol. Their study showed a 10-year overall mortality of 51% for treatment with RT followed by continuous ADT versus 61% for RT alone ($p = 0.002$) [39]. The 10-year CSM was 24% and 39%, respectively ($p < 0.0001$).

Short-term side effects of ADT are usually mild and include hot flushes, fatigue, and reduced libido. However, in the longer term there is an increased risk of osteoporosis and related fractures and prolonged HT has also been associated with onset of diabetes and coronary heart disease [40,41].

In the Early Prostate Cancer (EPC) trial patients with non-metastatic prostate cancer were randomised to receive an anti-androgen in addition to standard of care or to standard of care alone [42]. After a median of 9.7 years of follow-up, the addition of anti-androgen was associated with improved progression-free survival in patients with T3 cancer, but provided no benefit in overall survival. In the subgroup of patients with T3 cancer undergoing RT anti-androgen was, however, associated with a reduction of overall mortality.

Recurrence after curative treatment

Following curative treatment of prostate cancer, clinical recurrence is almost invariably preceded by rising PSA levels. Most current guidelines advise follow-up with measurements of PSA for at least 10 years following curative treatment [43]. The definition of BCR (*i.e.*, recurrence detected by an elevated PSA) is different after RP and RT. Following RP PSA should drop to and remain < 0.1 ng/mL. The current consensus definition of BCR after RP is two consecutive increases in PSA ≥ 0.2 ng/mL [44,45]. The 10-year overall risk of BCR after RP is about 24%, but can be both higher and lower depending on clinicopathological risk factors [46,47]. The clinical significance of BCR after RP is perhaps best illustrated by the study by Freedland et al (2005) which found a 10-year CSM of 27% (95% CI 21–34%) after BCR [48]. An earlier study by Pound et al (1999) described the natural history of progression after BCR following RP. In that study the median time for development of distant metastases following BCR was 8 years [49].

Following RT, interpretation of the PSA level is more complicated. PSA levels decreases gradually over the course of several months and do not always reach < 0.1 ng/mL. Up to 20% of patients experience transiently increasing PSA values after the initial decrease without evidence of recurrence; a so-called PSA bounce [50]. Furthermore, many patients, especially those with high-risk cancer, receive neoadjuvant and/or adjuvant HT which affects PSA levels. The American Society for Therapeutic Radiology and Oncology (ASTRO) has recommended several different definitions of BCR after RT, with the most recent being the so-called Phoenix criteria from 2006, which defines the BCR as an increase in PSA of > 2 ng/mL above the lowest PSA value after treatment [51]. ASTRO recommends that this definition should be used primarily for the evaluation of RT on a group level and not for individual treatment decisions. In the SPCG-7 trial 26% of the men treated with RT in combination with HT for high-risk, non-metastatic prostate cancer had BCR according to the Phoenix criteria at 10 years [29]. In the SPCG-7 trial, the 10-year CSM was 46% among the patients who experienced BCR after RT [29].

In effect, virtually all patients who die from prostate cancer after curative treatment experience BCR. The rare exceptions are men with non-adenocarcinoma prostate malignancies that do not express PSA, such as neuroendocrine cancers. The best studied local therapy for patients with BCR following RP is salvage RT. Briganti et al (2012) found no difference in BCR-free survival between early salvage RT and immediate adjuvant RT in a retrospective study with matched controls. Three independent multi-centre randomised trials have established that immediate adjuvant RT for patients with pT3 pN0 prostate cancer or positive surgical margins significantly improves progression-free and metastasis-free survival, compared with watchful waiting [38,52,53]. King et al (2012) presented a systematic review on salvage RT, showing that lower PSA levels at the time of salvage treatment and

higher radiation doses increased recurrence-free survival to at best 64% [54]. They calculated that for each 0.1 ng/mL PSA increment, there was a 2.6% absolute loss of BCR-free survival. In a similar review, which also included previously unpublished data, Pfister et al (2014) showed a 5-year BCR-free survival of 71% after salvage RT when PSA was ≤ 0.5 ng/mL, and a linear association between PSA levels and BCR-free survival in most of the included studies [55]. The increasing likelihood of salvage RT failure with increasing PSA levels at the time of its initiation is probably related to an increasing risk of undetected metastases. Since postoperative RT is associated with an up to 20% risk of complications, salvage RT should preferably be used in patients with non-metastatic recurrence only [55].

For local recurrences after RT, currently there exists no generally accepted curative treatment. Several modalities, such as cryotherapy, high-intensity focused ultrasound, and salvage prostatectomy, have been tried but none have been evaluated in randomised trials [56–62]. The risks of serious complications, such as urinary incontinence and rectourethral fistulas, are higher for secondary treatments after RT than after RP.

HT may be used for BCR when local treatments are not suitable, *e.g.* for metastatic recurrence. The aims are to delay onset of symptoms and improve survival and HT can be given either immediately following BCR or deferred. In a retrospective study, Moul et al (2008) found that early HT improved metastasis-free survival after BCR following RP for patients with Gleason score ≥ 8, PSA doubling time < 12 months, or non-organ confined disease [63]. Similar results were reported by Tenenholz et al (2007) and Mydin et al (2013) in two independent studies of BCR following RT [64,65]. Whether chemotherapy can improve survival in this setting remains to be seen. In the SPCG-14 trial patients with BCR after curative treatment and who are at high risk of metastatic recurrences despite negative imaging are randomised to anti-androgen treatment with or without the addition of chemotherapy (docetaxel).

Metastatic prostate cancer

The presence of metastases has a large impact on survival. According to the Swedish NPCR the median overall survival after diagnosis is currently about 5 years for the entire group of patients with lymph node metastases, and about 7 years for those younger than 65 years of age at diagnosis. By comparison, the median overall survival is about 9 years for patients with localised disease and more than 15 years for patients younger than 65 years of age [66]. The prognosis is poorer for patients with distant metastases, with a median overall survival of about 3 years [6].

RP is generally not recommended for patients with metastatic prostate cancer [43]. However, it is possible that cytoreductive surgery could provide an improvement in survival, by removing the bulk of a cancer that would otherwise metastasise faster.

Two retrospective studies suggested that this could be the case, with significantly better survival in patients who underwent prostatectomy despite the presence of lymph node metastases, compared to those who did not [67,68]. While the authors of both studies adjusted their results for differences in patient and cancer characteristics, there was likely some remaining bias towards a worse prognosis among the patients who did undergo prostatectomy. In both studies the patients with lymph node metastases had significantly worse outcomes than those without. There are no prospective studies which demonstrate an effect of RP on patients who have distant metastases.

There are currently no randomised studies demonstrating improved survival using local RT for patients with metastatic prostate cancer. The MRC UK PR07 trial referred to earlier included patients with lymph node metastases, but the results for these patients have not been reported separately and the staging procedures were uncertain [30]. It is possible that RT both to the prostate and to lymph nodes could improve outcomes, but two randomised studies have reported conflicting results of including the pelvic lymph nodes in the radiation field [69,70].

HT only is the recommended treatment for patients with metastatic prostate cancer according to the EAU guidelines [43]. A Cochrane systematic review in which early ADT at diagnosis of locally advanced and metastatic prostate cancer was compared with deferred treatment until symptoms was published in 2001. The odds ratio was 0.7 (95% CI 0.4–1.0) for 5-year CSM and 0.6 (95% CI 0.4–0.7) for complications related to disease progression in favour of immediate treatment [36]. Comparable results were also later obtained for overall mortality in the European Organisation for Research and Treatment of Cancer (EORTC) Trial 30891, with an odds ratio of 0.8 (95% CI 0.7–1.0) at 10-year follow-up [71]. However, that investigation showed no statistically significant improvement in cancer-specific survival. In the EPC trial, early treatment with an anti-androgen was associated with a statistically significant improvement in progression-free survival in men with locally advanced disease, a large proportion of whom must have had lymph node metastases [72]. Recently, preliminary results from an Eastern Cooperative Oncology Group (ECOG) trial indicated that the addition of early chemotherapy (docetaxel) to ADT in patients with metastatic prostate cancer may improve overall survival [73]. The effect was most marked in the group of patients who had the largest metastatic burden, and less so in the group with low-volume disease. Whether these results hold up on more detailed analysis remains to be seen.

Modalities for detecting metastases

Nomograms and tables

Several nomograms and tables have been developed to help calculate the risk of extraprostatic extension and lymph node metastases. The first of these was described by Partin et al in 1993, who combined PSA levels, clinical local stage, and biopsy Gleason score to predict the risk of extra-capsular extension, seminal vesicle involvement (pT3b), and lymph node metastases [74]. Since then, the "Partin table" has been revised on several occasions, with the most recent update in 2013 based on 5,629 cases treated between 2006 and 2011 at Johns Hopkins Hospital in the United States [75]. However, it is important to note that only 1% of all the cases reported in that series had lymph node metastases, and only 3% had seminal vesicle involvement. Moreover, most of the lymphadenectomies were limited to the obturator fossa, rather than extended which is the current standard (discussed below). Therefore, it is uncertain whether the risk of metastases for patients with high-risk cancer is accurately estimated by the Partin table.

Briganti et al (2006) developed a similar nomogram based on the same parameters in patients with clinical stage T1–T3 disease who underwent an extended lymphadenectomy [76]. It was updated in 2012 to also incorporate the percentage of positive biopsy cores as a predictive factor, which increased the accuracy [77].

The Partin table and the Briganti nomogram have both been externally validated [78–80]. Nevertheless, nomograms merely provide risk estimates and cannot identify which patient has metastases and which has not. Accordingly, they can only complement, not replace, the diagnostic modalities.

Computed tomography

Computed tomography (CT) uses x-ray imaging from many angles around the body to computationally create a tomographic image, and is one of the most widely applied x-ray techniques in modern health care. One of the main advantages of CT is that it generates a fairly large amount of information in a relatively short time. A modern multi-slice CT system can scan the entire body in less than a minute and the cost per examination is very low.

The chief drawback of CT for detection of prostate cancer and metastases is that it provides little cancer-specific information. Hence, lymph node metastases are suggested by a CT scan solely by the presence of enlarged lymph nodes (diameter $\geq$ 10 mm). Bone metastases can be suggested by sclerotic or lytic lesions in the skeleton. At present, there is no contrast agent that can identify metastatic lesions

specifically. The iodine-based contrast agents that are available today visualise the blood-flow in the tissues, which can be affected by many factors. Tiguert et al (1999) explored the relation between lymph node sizes smaller than 10 mm on CT scans and the presence of lymph node metastases in a retrospective study, but found no association [81]. Briganti et al (2012) retrospectively investigated 1,541 patients with prostate cancer who underwent a CT scan and a lymphadenectomy, and noted that sensitivity and specificity were only 0.18 and 0.94, respectively, in the high-risk group, and 0.08 and 0.96, respectively, in the low-risk group [82]. Saokar et al (2010) reported that CT was significantly less efficient than magnetic resonance imaging at detecting lymph node metastases [83]. Therefore, CT is currently not recommended as a routine procedure for the detection of such metastases. Although CT is commonly used to detect visceral metastases in various forms of cancer, no studies have assessed its accuracy for detecting visceral and bone metastases from prostate cancer.

Magnetic resonance imaging

Magnetic resonance imaging (MRI) is based on that hydrogen atoms (in the body) in a strong magnetic field are raised to an excited state by a radio frequency pulse and that electromagnetic photons are emitted when the atoms relax again. This physical phenomenon is called nuclear magnetic resonance. The emitted photons can be detected by the MRI scanner, and a tomographic image is produced through computer analysis. Varying the parameters of the process can provide different types of images (*e.g.*, T1-weighted images, T2-weighted images, diffusion-weighted [DW] images, and apparent diffusion coefficient [ADC] images). Different types of tissue are better visualised using specific parameters. A general advantage of MRI is that it does not use ionising radiation. Disadvantages of this method are that it is time-consuming and that some patients cannot undergo MRI scans due to claustrophobia or the presence of magnetic implants or other foreign materials.

The use of MRI in lymph node staging has been investigated in several studies. Thoeny et al (2014) recently studied 120 patients who had either prostate or bladder cancer and were examined with DW-MRI. The sensitivity and specificity for lymph node metastases on a per-patient basis were approximately 0.75 and 0.80, respectively [84]. However, when considering per-lymph node site, the average sensitivity was only 0.37 (specificity not calculated). It is important to note that only patients without enlarged lymph nodes (cut-off 10 mm) were included in the study cohort. The results obtained were significantly better for MRI than for computed tomography (CT), however. Harisinghani et al (2003) described a protocol with an alternative approach, using the lymph-node specific contrast agent ferumoxtran-10 to produce an MRI lymphangiogram [85]. Ferumoxtran-10 is normally ingested by macrophages in non-metastatic lymph nodes but such uptake is inhibited in

metastatic lymph nodes, and hence the diagnosis of metastases is based on the absence of contrast agent in otherwise normal-looking lymph nodes. Compared with lymphadenectomy, the MRI lymphangiogram yielded 1.0 sensitivity and 0.96 specificity per-patient, and 0.91 sensitivity and 0.98 specificity per lymph node site. Heesakkers et al (2008) later repeated this assessment in a larger cohort comprising 375 patients, 61 (16%) of whom had lymph node metastases determined by lymphadenectomy. They reported lower per-patient sensitivity and specificity of 0.82 and 0.93, respectively. No results were given per lymph node site [86]. These observations are definitely interesting, but must be further validated before they can be considered for routine use.

As for detecting skeletal metastases, Lecouvet et al (2007) showed that MRI of the axial skeleton was more accurate than bone scintigraphy with superior sensitivity and specificity. [87]. However, bone scintigraphy is generally recommended in the various guidelines due to a higher availability and a lower cost than MRI.

Scintigraphy

Scintigraphy was the first nuclear medicine procedure to be applied and is still the most common investigation of this type. It is based on the gamma decay of certain isotopes, usually ^{99m}Tc, which produces a gamma ray that can be detected with a gamma camera. The radioactive isotope is chemically coupled to a targeting carrier molecule so that it will accumulate in the desired part of the body after intravenous administration. Initially, only planar scans were performed, analogous to the use of planar x-ray scans. Later single-photon emission computed tomography (SPECT) was developed, in much the same way as the CT scanner.

For prostate cancer, the carrier molecule most often used for scintigraphy is methylene diphosphonate (MDP), which accumulates in skeletal sites with a high bone matrix turnover, such as fractures or metastatic lesions. Planar bone scanning with ^{99m}Tc-MDP was long considered to have a sensitivity near 1.0 and therefore the reference standard for detecting skeletal metastases. However, most studies using this method were hampered by the lack of a control modality, and therefore did not take into account smaller sub-clinical metastases. By comparison, later studies showed that SPECT provides a sensitivity and specificity of 0.71 and 0.85, respectively, compared to only 0.39 and 0.79 for planar bone scans [88]. As was mentioned earlier, also MRI provides better diagnostic accuracy than planar bone scanning. For recurrent prostate cancer, planar bone scans rarely detect metastases until PSA levels are above 5–10 ng/mL, at which time salvage RT is unlikely to be successful [89–91].

^{111}In-labelled capromab pendetide (ProstaScint™) has been approved by the Food and Drug Administration of the United States for visualisation of prostate cancer metastases [92]. Capromab is a monoclonal murine antibody which targets Prostate-

Specific Membrane Antigen (PSMA). Early results were promising but in later studies specificity was low and other modalities were shown to have better diagnostic performance [93].

PET/CT

Positron emission tomography (PET) is based on the detection of emitted positrons, the positively charged antiparticles of electrons. Electrons and positrons, collectively called beta particles, can be emitted from an atomic nucleus through the process of beta decay, whereby an unstable isotope decays into a more stable one. In the case of positron emission, this is called beta-plus decay. An example is ^{18}F, which is an unstable isotope of fluorine with a half-life of about 110 minutes, that decays into ^{18}O, a stable isotope of oxygen, while emitting a positron (and for completeness sake, also an electron neutrino, which interacts very weakly, is hard to detect, and will therefore not be discussed further). Another example is ^{11}C, an unstable isotope of carbon with a half-life of about 20 minutes, which decays into ^{11}B, a stable isotope of boron, and a positron. The emitted positron then travels through the tissue, on the order of up to a few millimetres depending on the energy of the positron ($\approx$ 0.5 mm in the case of ^{18}F), before hitting an electron in another atom. This causes a particle-antiparticle annihilation that results in the emission of two photons in diametrically opposite directions. This process is illustrated in Figure 2. Two detectors, one on each side of the decaying atomic nucleus, can then detect the coincidental photons (*i.e.*, they arrive at approximately the same time at both detectors) signalling a beta decay event.

In the same manner as computed tomography, by rotating the detectors in a full circle around the body, a tomographic image can be computed. Further, by performing a computed tomography at the same time, the two types of image (positron emission tomography and computed tomography) can be fused together giving a combined functional (PET) image and morphologic (CT) image, thereby showing exactly what organ or tissue is accumulating the isotope used.

The most common isotopes used for PET are ^{18}F and ^{11}C, although use of ^{68}Ga and ^{121}I has also been described also. The choice of isotope is based mainly on the half-life being suitable for the handling needed before use. Also, the positron energy of the isotope should be suitably small, so that the photon emissions will be reasonably close to the positron emission source (Figure 2). To be useful however, the isotope needs to incorporated in a molecule that accumulates in the desired tissue; a tracer. There are a multitude of tracers that have been reported, but only a handful which have been more thoroughly tried.

Fluorodeoxyglucose (FDG) is a glucose analogue which accumulates in tissue with increased glucose metabolism. Since cancer cells predominantly metabolise glucose, FDG is the most commonly used tracer molecule for PET/CT imaging in

cancer. The isotope most often incorporated in FDG is ^{18}F. FDG is used with good accuracy in several forms of cancer, but early studies showed that there was virtually no accumulation in prostate cancer tissue, neither in primary untreated prostate cancer, nor in recurring cancer [94,95].

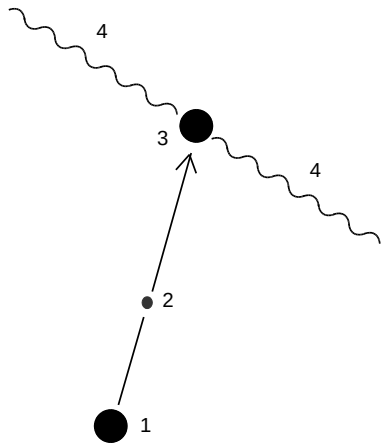

Figure 2.
Schematic illustration of positron emission, not to scale. An atom (1) of a radioactive isotope emits a positron (2), which hits an electron of another atom (3) in the vicinity. This causes a particle-antiparticle annihilation event, leading to the emission of two electromagnetic photons (4) travelling in almost diametrically opposite directions. The distance the positron travels before hitting an electron depends on the energy of the positron, with a higher energy leading to a longer distance, which in turn affects the resolution of the PET scan.

Acetate is a building block in the synthesis of the lipids in cell membranes, and is accumulated in tissue with higher rates of cell turnover. Since cancer cells generally have a high turnover, acetate can be used for detecting cancer manifestations. The isotope most often used is ^{11}C, although ^{18}F-fluoroacetate has also been reported [96–102]. At least one report suggests that these are not physiologically similar, however [103].

Choline is likewise a building block of cell membranes and can be used to detect cancer foci with PET/CT imaging. Use of either ^{11}C or ^{18}F has been reported. There have been no studies comparing the use of the different isotopes. Examples of PET/CT images are given in Figure 3.

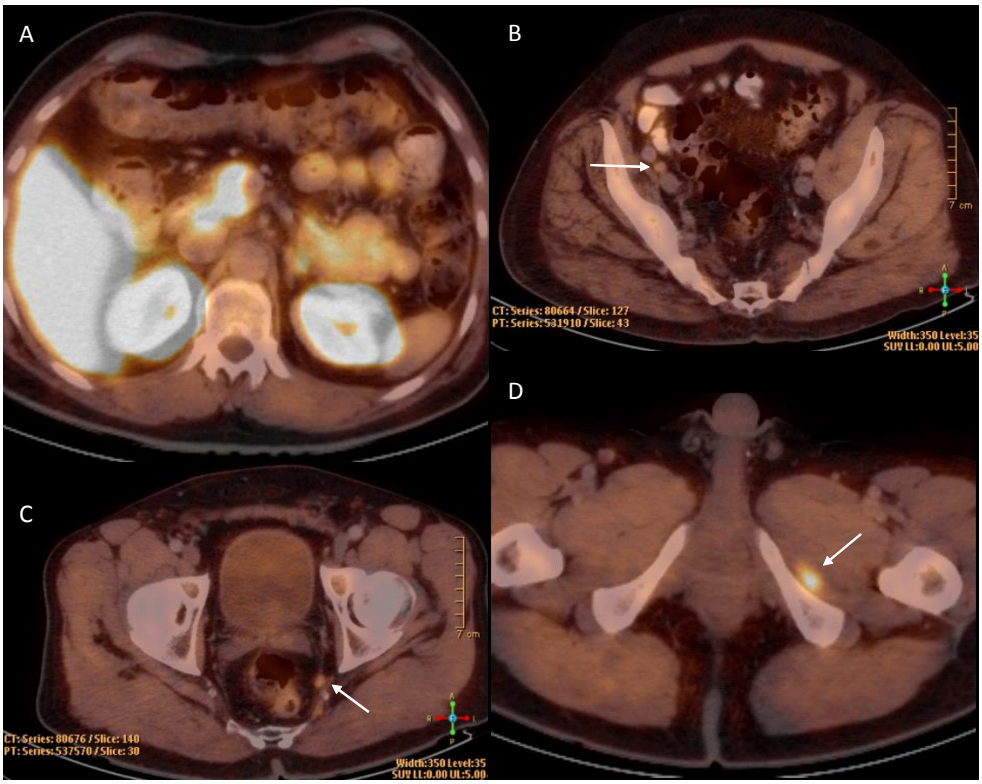

Figure 3.
Examples of ^{18}F-choline PET/CT images, not all from the same patient. (A) PET/CT fusion image with PET image in yellow overlaid CT image. This image shows physiologic uptake of 18F-choline in the kidneys, the liver, and the pancreas. There is also some uptake in the intestines, which is normal. (B) PET/CT fusion image showing a normal-sized lymph node (white arrow) between the right external iliac artery (ventral to the lymph node) and vein (dorsal to the lymph node), with pathological choline uptake indicating a possible metastasis. The site of the lymph node is consistent with a primary lymphatic landing site of prostate cancer, which is excised by an extended pelvic lymph node dissection. (C) PET/CT fusion image of the lower part of the pelvis, showing a normal sized lymph node in the left para-rectal area (white arrow) with pathologic choline uptake. The site is consistent with a primary landing site of prostate cancer, but which is not excised in either a limited or an extended pelvic lymph node dissection. (D) PET/CT fusion image showing pathologic choline uptake (white arrow) in the left inferior ramus of the pubic bone. The CT image shows a sclerotic area (not visible with this image window) corresponding to the uptake site. In this PET/CT fusion image there is actually a slight mismatch due to the patient moving slightly between the scans, causing the uptake to appear in the muscular tissue, but on the PET images it is apparent that this is a bone site.

Figure 4.
Example of ^{18}F-fluoride PET scan. Fluoride PET/CT fusion images are similar to choline PET/CT fusion images. In this image, a volume-based reconstruction of the entire torso is shown, which is analogous to a planar bone scan but with more details. Several uptakes are evident in the axial skeleton that on CT images (not shown) are clearly degenerative in nature. The uptake in the humerus (black arrow) does not correspond to any degenerative findings on CT and is highly suspicious for metastasis.

Fluoride is the fluorine ion and is often used as a salt, sodium fluoride (NaF), for PET/CT imaging. Fluoride has a high affinity for the skeleton, accumulating especially in skeletal sites with a high turnover of bone matrix, such as fractures or metastases (Figure 4). It was first suggested as a bone-imaging agent in 1962 in a paper by Blau et al, but was initially abandoned in favour of scintigraphy, which was technically simpler [104]. However, recent improvements in PET technology has renewed interest in this tracer. A very high sensitivity and specificity for the detection of bone metastases, superior to planar bone scan and SPECT, has been reported for several forms of cancer [88,105,106].

The level of uptake of each tracer is usually measured and compared to uptake in normal tissue, giving a ratio called the specific uptake value (SUV). Several different algorithms exist for calculating normal uptake, leading to difficulties in

comparing SUVs between different centres and different studies. However, in a given centre with a given algorithm SUVs are highly reproducible [107].

Lymphadenectomy

Lymphadenectomy is a surgical procedure in which a number of lymph nodes are excised to be examined microscopically by a pathologist. Depending on the primary cancer, different groups of lymph nodes are removed. Previously, the most common procedure for prostate cancer was a limited pelvic lymph node dissection (lPLND), encompassing only the lymph node tissue in the obturator fossae (Figure 5). However, the current standard for determining the lymph node stage (N stage) according to both European and American guidelines is an extended pelvic lymph node dissection (ePLND), removing all the lymph node tissue around the internal and external iliac arteries, in the obturator fossa, and around the common iliac artery up to the crossing of the ureter [108,109]. This procedure is performed bilaterally either at the same time as a prostatectomy or as a separate surgical procedure before RT, and can be performed either as open or laparoscopic surgery. More extensive schemes that can increase the yield of lymph nodes have been proposed, but there is no consensus regarding these approaches. Also, a multimodality mapping study performed by Mattei et al (2008) showed that a large proportion (up to 25%) of primary lymph node metastases can occur outside the ePLND template and will therefore be missed [110].

The main drawback of lymphadenectomy is the risk of complications. In an early study of lymphadenectomy for staging or prostate carcinoma, Paul et al (1983) found complications in 33% of cases, one third of which were considered serious [111]. Bratt et al (1994) evaluated a series of 156 prostate cancer patients who underwent open lPLND and found a 7% risk of serious complications, and also noted that 5% of the patients developed wound infections post-operatively [112]. It is likely that the risk of complications increases with more extensive lymphadenectomy. Briganti et al (2006) observed that the overall rate of complications was 20% for ePLND compared to 8% for lPLND ($p < 0.001$), with increasing risk the more lymph nodes that were removed, and this also applied when the procedures were performed by more experienced surgeons [113]. Similar results were also reported from Sweden by Lindberg et al (2009) [114].

In an early study of laparoscopic lymphadenectomy, Stone et al (1997) found that the risk of complications was 36% in patients such surgery compared to only 2% in those who underwent open surgery ($p < 0.0001$), although the former group also had a larger number of lymph nodes removed [115]. Later Liedberg et al (2012) reported that laparoscopic ePLND in a series of 133 patients led to 10% complications with Clavien grade 2 or higher, and only 2% with grade ≥ 3 [116]. Mattei et al (2013) performed a similar study of robot-assisted laparoscopy in 134 patients and found a

2% risk of complications of Clavien grade ≥ 2 for ePLND [117]. Liss et al (2013) described comparable results of 2% risk of Clavien grade ≥ 3 complications in a series of 54 robot-assisted prostatectomies with concomitant ePLND [118]. Thus, whereas there are no prospective comparative trials, it is possible that the ongoing shift from open to laparoscopic surgery will decrease the frequency of complications. Complications would be more acceptable if the lymphadenectomy had a therapeutic effect (*i.e.*, improved survival). There is at least one ongoing randomised trial investigating this question [119].

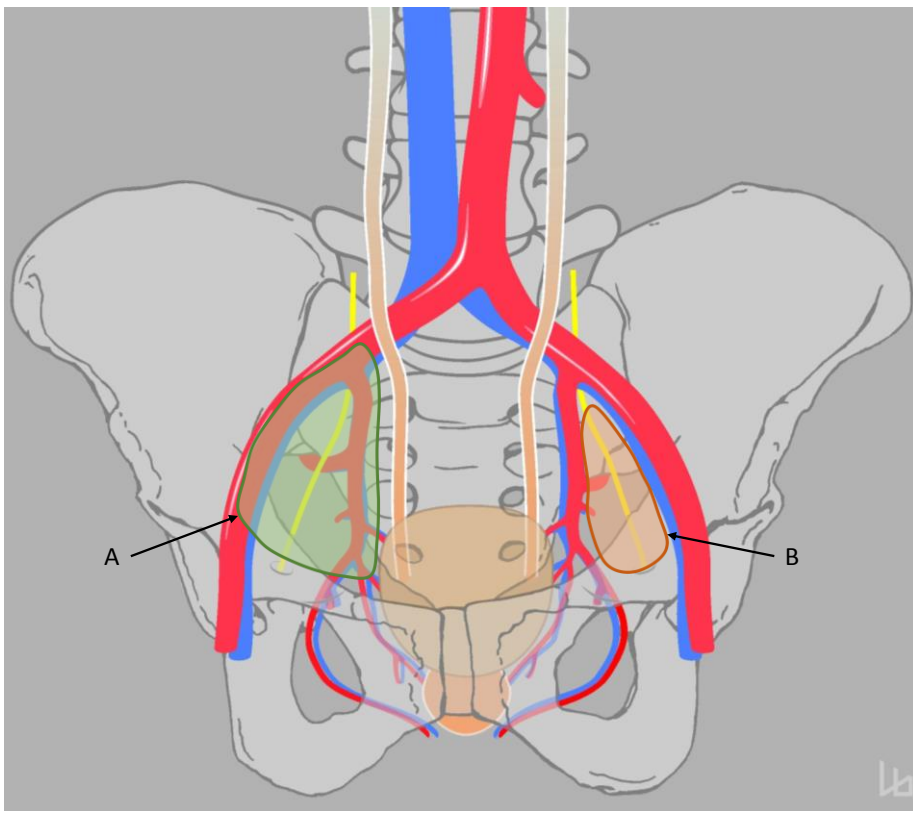

Figure 5.
Schematic overview of the anatomy of the pelvis relevant to lymphadenectomy. Adapted with permission from Dr Agostino Mattei and Prof. Urs Studer [110]. (A) The green area represents the template of an extended pelvic lymph node dissection (ePLND). All the lymphatic tissue around the internal iliac artery, around the obturator nerve (the obturator fossa) and to the lateral border of the external iliac artery. The proximal border is defined by the ureteric crossing of the common iliac artery. (B) The orange area represents the template of a limited pelvic lymph node dissection (lPLND), which only encompasses the obturator fossa.

Sentinel lymph node dissection

The sentinel node (SN) is defined as the first lymph node which receives lymphatic fluid from a given organ or specific part of an organ. The underlying assumption is that lymphatic fluid, and thereby lymphatically spreading cancer cells, travels in a stepwise fashion, first from the origin to the first echelon lymph nodes, and then further to later echelon lymph nodes. Sentinel lymph node dissection is a surgical procedure where the sentinel lymph node or nodes are identified and removed. These first echelon lymph nodes can then be examined histopathologically, determining the N stage of the patient if the underlying assumption is correct. Identification of the sentinel lymph nodes is done by a peri-tumoural injection of a marker, which then then follows the lymphatic pathways to the appropriate lymph nodes and accumulates there. This procedure was first described in malignant melanoma by Morton et al (1992) using a blue dye (patent blue) as marker, providing a visual identification of the SNs [120]. Van der Veen et al (1994) improved on the results by adding ^{99m}Tc-marked nanocolloid as marker, using a hand-held gamma-probe intraoperatively to easier identify the sentinel lymph nodes that were not easily visible [121]. It was found that the absence of metastases in the sentinel lymph nodes precluded other lymph node metastases with a very high accuracy. This meant that a large proportion of the patients could be spared complete lymphadenectomies and thereby possibly avoid common serious complications, such as lymphocele and deep vein thrombosis. At the same time, the patients who did have lymph node metastases could be treated with more aggressive strategies, in accordance with the higher risk of mortality. Additionally, since fewer lymph nodes needed to be examined primarily with histopathology, more thorough histopathological examinations could be done, increasing diagnostic sensitivity for micro-metastases (*i.e.*, metastases $\leq$ 2 mm in diameter), *e.g.* by examining more sections at smaller intervals from each lymph node [122]. A further potential advantage is that this method may detect lymph node metastases outside of the commonly dissected areas, thus increasing sensitivity compared with a standard ePLND. The SN technique is now standard-of-care for malignant melanoma and breast cancer patients, for whom a complete lymphadenectomy is now only performed if metastases are found in the sentinel lymph nodes.

Specific background to our studies

As has been discussed earlier, the treatment options for patients with metastases, especially distant metastases, is mainly limited to HT. Local therapy to the prostate have not been proven to improve survival or quality of life for men with metastases. Indeed, quality of life might even worsen due to complications and side-effects of RP or RT. At the time of initiation of the included studies, the regional guidelines on prostate cancer mandated imaging, in the form of a planar bone scan, for patients with high-risk disease. If there were no indications of bone metastases, a pelvic lymph node dissection at the time of prostatectomy, or before RT, was also recommended. Patients who had histologically proven lymph node metastases did then either not receive RT, or had by then already undergone a RP which was not considered beneficial because of the metastases. Patients with BCR after prostatectomy were generally offered salvage RT without lymph node dissection, if the PSA level was not too elevated (a vague concept). However, even in the group of patients with a PSA lower than 2 ng/mL a significant proportion did not respond to the RT, likely because of metastatic recurrence. If the patients with metastases had been identified, they could have been spared the potential complications of the ineffective RT.

A non-invasive method for identifying metastases with higher sensitivity than CT and MRI was therefore desirable. In 2007, PET/CT scans using either ^{18}F-choline or ^{18}F-fluoride became available at Skåne University Hospital, but evidence for their use for patients with prostate cancer was limited [123–134]. However, we believed that this non-invasive modality could identify at least some patients with metastatic disease, who would not benefit from curative treatment, and therefore would be better managed with HT alone.

For patients with newly diagnosed, untreated, prostate cancer there were in 2007 five independent previous studies, of which one concerned ^{18}F-choline and four concerned ^{11}C-choline [123–127]. Three of the ^{11}C-choline studies included less than 20 patients [124,125,127], while the fourth, which included 67 patients, showed a sensitivity of 0.80 and a specificity of 0.96 compared with pelvic lymph node dissection [123]. However, it was unclear how extensive the dissection was in the latter study, and patients with low-risk cancer did not undergo lymphadenectomy but were automatically classified as metastasis-free. Also, this study only assessed PET without CT, which might have affected the results. The

one study of ^{18}F-choline comprised 20 patients and only found pathological tracer uptake in a single patient [126]. This proved to be a false positive.

For patients with BCR after primary treatment, there were a few more studies; ten in total, there were six concerning ^{11}C-choline and four of ^{18}F-choline [125,127–134]. Almost all of these studies, however, included patients with a wide variety of primary treatments, wide ranges of PSA levels and in many cases the patients were already under HT at the time of the PET/CT scans. The clinical utility of choline PET/CT was therefore uncertain for patients for whom there was an evidence-based treatment available, *i.e.* were hormone-naïve and had a PSA below 1-2 ng/mL.

^{18}F-fluoride PET/CT had at the time of the initiation of our studies been reasonably well studied in prostate cancer, but there were no studies of performing both fluoride and choline PET/CT [88,106,135]. Since fluoride PET/CT can detect bone metastases only, its value compared with choline PET/CT, which may detect lymph node metastases, visceral metastases, and bone metastases, was uncertain. There was also uncertainty regarding the sensitivity of bone metastases for choline PET/CT. It could therefore be hypothesised that performing both choline and fluoride PET/CT scans would lead to treatment changes for more patients than if only one or the other was utilised, but with a significant increase in cost for the scans.

Another option for possibly minimising complications of ePLND, while increasing its diagnostic accuracy, was to employ SN dissection. Previously, two independent studies had proved the feasibility of SN dissection in prostate cancer [136,137]. Common to both protocols, however, was injection of tracer and subsequent scintigraphic imaging the day before surgery, creating logistic issues and increasing the discomfort for the patient. Additionally, it was possible that the long time between injection and operation could lead to difficulties in identifying the proper sentinel lymph nodes intraoperatively, due to increased spread of the tracer with time. It was therefore hypothesised that by injecting the tracer into the prostate immediately prior to surgery, forgoing scintigraphic imaging and only using a hand-held gamma-probe intraoperatively, the proper first echelon sentinel lymph nodes could still be identified. Furthermore, by performing the injections after anaesthesia, any additional discomfort to the patient could be avoided.

Aims

The aims of the included studies were as follows:

- To investigate how treatment decisions are affected by ^{18}F-choline and ^{18}F-fluoride PET/CT scans in patients that have high-risk prostate cancer and normal conventional imaging results (Study I).
- To evaluate the diagnostic accuracy of ^{18}F-choline PET/CT compared with ePLND for detection of lymph node metastases (Study II).
- To determine what proportion of hormone-naïve patients with BCR after RP show positive ^{18}F-choline PET/CT findings at PSA levels of < 2 ng/mL (Study III).
- To ascertain whether a simplified protocol for sentinel lymph node detection can accurately identify the SNs and diagnose the lymph node stage in patients with high-risk prostate cancer (Study IV).

Materials and methods

Patients

PET/CT

From March 2008 to November 2012, urologists in the Southern healthcare region of Sweden were invited to select patients, with either newly diagnosed high-risk prostate cancer or BCR after RP, for referral to PET/CT.

Inclusion criteria for patients with newly diagnosed prostate cancer were as follows: they were to have biopsy-confirmed prostate cancer, PSA ≥ 20 ng/mL or a Gleason score of 8–10, a normal or inconclusive planar bone scan, and be eligible for curative treatment. Patients with PSA ≥ 100 ng/mL and previous or ongoing HT were excluded.

For recurrent prostate cancer the inclusion criteria were: previous RP with complete available pathology report, a rising PSA ≥ 0.2 ng/mL but below 2 ng/mL, Gleason score ≥ 7 in the prostatectomy specimen or a PSA doubling time ≤ 6 months, and patient eligible for salvage RT. Patients with previous or ongoing HT were excluded.

All clinical management was determined by the referring urologist. However, treatment decisions were often made after discussion of positive PET/CT findings with a member of the study group.

Sentinel node detection

Subsequent to a pilot study of five patients at Lund University Hospital performed in 2004, our investigation of SN detection covered the period April 2007 to May 2012 and included consecutive patients at Växjö Hospital who met these criteria: had biopsy-confirmed prostate cancer with high risk according to the D'Amico criteria, clinical local tumour stage T2–3, no evidence of distant metastases on planar bone scan or PET/CT, and were eligible for curative treatment.

PET/CT

The ^{18}F-choline was synthesised on a TracerLab MX_{FDG} module (GE Healthcare, Stockholm, Sweden) using the method described by Kryza et al (2008), but with the slight modification of using tetrabutylammonium hydroxide instead of Kryptofix 2.2.2 [138]. Tracer purity was controlled by ion chromatography and thin-layer chromatography, with specific activity of > 74 GBq/µmol and > 99% radiochemical purity.

All PET/CT scans were performed at Skåne University Hospital in Lund or Malmö, using an integrated PET/CT system (Philips Gemini TF, Philips Medical Systems, Cleveland, OH, USA). The patients fasted for 4 hours before injection of ^{18}F-choline, but not before ^{18}F-fluoride. PET scanning was performed 1–1.5 hours after intravenous injection of tracer at a dose of 4 MBq/kg body-weight (maximum dose 400 MBq), with 2 minutes per bed position. For the patients with both ^{18}F-choline and ^{18}F-fluoride PET/CT scans, the scans were performed 1–24 days apart (median 4 days). The ^{18}F-choline PET scans were acquired from the proximal femur to the base of the skull, whereas the ^{18}F-fluoride scans also included the whole skull and the proximal half of the femur.

CT scans were performed immediately before PET using a multi-detector spiral CT scanner. For the ^{18}F-choline PET/CT scans, the CT were performed as diagnostic quality CT using 5-mm reconstructed slice thickness, pitch factor 0.938, rotation speed 0.75 s, 120 kV, and high beam-tube-current modulation (120–300 mAs, depending on the patient's total body mass). Sixty minutes before a CT scan the patient was given 1000 mL of oral contrast (50 mL of Omnipaque [GE Healthcare] 240 mg I/mL and 30 mL of sorbitol 70%, mixed with 920 mL of water). Intravenous contrast (Omnipaque 350 mg I/mL, 350 mg I/kg body-weight) was administered using an automatic injection pump (Medrad Stellant Dual Head Injector, Pittsburgh, PA, USA). Three CT series were obtained: the liver was scanned without intravenous contrast and then the thorax was scanned with contrast in arterial phase, both during breath-holding, and lastly a full-body scan was performed with contrast in portal phase during normal breathing. The last scan was used for attenuation correction and for PET/CT image fusion. For ^{18}F-fluoride PET scans, a low dose (50 mAs) CT scan without any contrast was performed for attenuation correction and image fusion.

All PET/CT scans were interpreted by a radiologist as well as a nuclear medicine physician. Focal ^{18}F-choline uptake above background, corresponding to an abdominal or pelvic lymph node, was reported as a positive lymph node. Focal ^{18}F-choline or ^{18}F-fluoride uptake that was above background in bone and did not correspond to other pathology (*e.g.*, a fracture) was reported as a positive bone site.

For the patients that later performed a pelvic lymph node dissection, the ^{18}F-choline PET/CT scans were re-evaluated by a dedicated team consisting of a nuclear medicine physician and a radiologist (HA & KL), both PET/CT experts. Both were blinded to the results of the lymph node dissections and further management, but had access to the initial PET/CT evaluations.

Lymphadenectomy and sentinel node detection

The ePLND was performed as described by Heidenreich et al (2007), with the proximal border being at the ureteric crossing of the iliac arteries [139]. Surgery was performed at one of five centres (in Halmstad, Helsingborg, Lund, Malmö, or Växjö), either during the same session as RP, or as a separate surgical procedure prior to RT. The choice of laparoscopic or open procedure was made by the operating surgeon, according to his or her expertise and considering possible patient-related factors. The lymph node specimens were sent for pathology and handled as stipulated by to the local policies at each centre.

For the patients undergoing SN detection, 100 MBq of ^{99m}Tc-marked nanocolloid (NanoColl, GE Healthcare) was injected into the prostate immediately prior to surgery, but after induction of anaesthesia. The injections were given in four 0.25 ml aliquots, two on each side, adjacent to, but not into, a tumour that was palpable or visible on transrectal ultrasound. In the case of unilateral tumours, the injections on the contralateral sides were given in the peripheral zone, one at the base and one at the apex. All injections were given by the operating urologist, who also selected the injection sites. Ciprofloxacin (750 mg) was administered orally preoperatively as prophylaxis. During surgery, an ePLND was first performed, as described previously. After dissection on each side, a hand-held gamma probe was used to detect residual radioactivity in the accessible portions of the pelvis. Any lymph tissue showing residual activity was excised and sent separately for pathology. At the end of surgery, the gamma probe was used to detect any lymph nodes in the primary specimens showing tracer uptake, which were then isolated and sent separately for pathology. Any lymph nodes with tracer uptake were designated SNs, and all other lymph nodes were designated non-SNs.

At pathology, non-SNs were handled according to standard procedures, while SNs were cut into 3-mm thick slices that were embedded separately in paraffin. Each slice was step-sectioned at three levels at 150-µm intervals. These sections were then stained with haematoxylin-eosin and anti-cytokeratin antibodies (AE1/AE3). Any metastases that were $\leq$ 2 mm in diameter, detected in any of the lymph nodes, were designated micro-metastases.

Statistics

Enrolment of patients was prospective according to the protocol, with acquisition of outcome data performed retrospectively at the end of each study. Descriptive statistics were used exclusively, except in Study III, in which both univariate and multivariate logistic regression analysis were applied to assess possible predictors of positive PET/CT findings after BCR.

Ethical approval

All four of the investigations were approved by the Research Ethics Review Board of Lund University: EPN LU552/2007 for the PET/CT studies (I-III), and LU350/2005 (open surgery) and LU547/2006 (addendum for laparoscopic surgery) for the SN study (IV). Written informed consent was obtained from the patients.

Additional analyses

During the preparation of this thesis, after publication of the included studies, the following additional scientific questions were raised:

- How did choline PET/CT perform compared with fluoride PET/CT, with regards to the detection of bone metastases?

- Where there any factors that could predict which patients had multiple positive uptake sites for the choline and fluoride PET/CT scans?

- What was the optimal SUV cut-off level for choline PET/CT in detecting lymph node metastases?

- Were there any factors that could predict which patients would have a true-positive choline PET/CT scans, as opposed to a true-negative scan?

Consequently, the results of the PET/CT scans of Study I were re-analysed with regards to bone metastases alone. Additionally, the SUVs of all lymph nodes with increased tracer uptake in Study II were calculated and recorded, with the maximal SUV for each patient, and the N stage based on the lymphadenectomy, used for ROC analysis. Univariate and multivariate logistic regression analysis were performed for the patients in Study I, to asses for possible predictive factors for multiple positive uptake sites, and for the patients in Study II, for true-positive PET/CT scans compared with true-negative scans. In both cases, the factors with the lowest p-values in univariate analysis were used in multivariate analysis. The

number of factors used in each of the multivariate analyses were decided based on the number of positive outcomes in each analysis, with at least five positive outcomes per factor.

Table 3.
Clinical characteristics of the patients in the three investigations on staging of newly diagnosed prostate cancer (Studies I, II, and IV).

	Study I n = 90	**Study II** n = 112	**Study IV** n = 83
Age, years			
Mean (SD)	66.5 (5.6)	65.6 (6.2)	65.2 (6.3)
Median (range)	66.8 (49.9–77.2)	66.1 (47.8–77.4)	65.9 (43.2–75.8)
PSA, ng/mL			
Mean (SD)	27.9 (20.2)	30.1 (20.6)	19.5 (15.1)
Median (range)	22.0 (2.4–95)	25.5 (2.4–95)	17.0 (3.4–91)
Biopsy Gleason score, n (%)			
5–6	4 (4)	7 (6)	12 (14)
3+4	17 (19)	22 (20)	30 (36)
4+3	11 (12)	19 (17)	14 (17)
8–10	58 (64)	64 (57)	27 (33)
Local clinical tumour stage, n (%)			
T1c	14 (16)	23 (21)	–
T2	30 (33)	35 (31)	22 (27)
T3	46 (51)	54 (48)	61 (73)
Bone scan, n (%)			
Negative	73 (81)	102 (91)	83 (100)
Inconclusive	17 (19)	10 (9)	0
No. of patients included in more than one study			
Also in Study I	–	61	9
Also in Study II	–	–	30

Abbreviations: SD, standard deviation; PSA, prostate-specific antigen.

Results and comments

Primary staging

A total of 185 prostate cancer patients were included in the three investigations concerning primary staging (I, II, and IV), and nine of the patients participated in all three of these studies. The clinical characteristics of all the patients at inclusion are detailed in Table 3. The patient cohorts in Studies I and II were at least partly similar, because more than half of the patients participated in both investigations. The patients in Study IV had slightly different characteristics due to different inclusion criteria.

Table 4.
Comparison of the results of choline PET/CT and fluoride PET/CT. Results are shown for (A) all 90 patients evaluated, (B) the 18 patients with treatment plans changed based on the PET/CT scans, and (C) all 90 patients but considering only skeletal sites.

A			**Fluoride**		
		–	**+**	**++**	**Total**
Choline	**–**	40	11	4	55 (61%)
	+	7	2	2	11 (12%)
	++	6	5	13	24 (27%)
	Total	53 (59%)	18 (20%)	19 (21%)	90 (100%)
B			**Fluoride**		
		–	**+**	**++**	**Total**
Choline	**–**	–	–	–	–
	+	–	1	1	2 (11%)
	++	3	3	10	16 (89%)
	Total	3 (17%)	4 (22%)	11 (61%)	18 (100%)
C			**Fluoride**		
		–	**+**	**++**	**Total**
Choline	**–**	52	17	7	76 (84%)
	+	1	1	5	7 (8%)
	++	–	–	7	7 (8%)
	Total	53 (59%)	18 (20%)	19 (21%)	90 (100%)

Symbols: -, negative results; +, positive finding at a single site; ++, positive findings at multiple sites.

Table 5.
Clinical characteristics of the patients in Study I, categorised according to the results of the PET/CT scans.

	Negative n = 40	Choline ++ n = 24	Fluoride ++ n = 19	Either ++ n = 30	Both ++ n = 13	Combined ++ n = 32
Age, years						
Mean (SD)	66.8 (6.1)	66.7 (5.6)	67.3 (5.2)	67.0 (5.2)	66.6 (6.0)	66.8 (5.2)
Median (range)	66.8 (49.9–77.3)	67.1 (55.3–76.1)	68.0 (55.3–76.1)	68.0 (55.3–76.1)	67.0 (55.3–76.1)	67.8 (55.3–76.1)
PSA, ng/mL						
Mean (SD)	26.7 (18.6)	29.6 (21.5)	23.9 (17.9)	27.3 (20.1)	26.5 (20.4)	28.0 (19.9)
Median (range)	22.0 (2.4–81)	22.5 (6.0–82)	17.0 (6.0–77)	21.5 (6.0–82)	22.0 (6.0–77)	22.5 (6.0–82)
Biopsy Gleason score, n (%)						
5–6	4 (10)	–	–	–	–	–
3+4	8 (20)	1 (4)	–	1 (3)	–	3 (9)
4+3	7 (18)	2 (8)	2 (11)	2 (7)	2 (15)	2 (6)
8–10	21 (53)	21 (88)	17 (89)	27 (90)	11 (85)	27 (84)
Local clinical tumour stage, n (%)						
T1c	9 (23)	1 (4)	2 (11)	2 (7)	1 (8)	3 (9)
T2	16 (40)	7 (29)	4 (21)	7 (23)	4 (31)	7 (22)
T3	15 (38)	16 (67)	13 (68)	21 (70)	8 (62)	22 (69)
Bone scan, n (%)						
Negative	39 (98)	13 (54)	7 (37)	18 (60)	2 (15)	20 (63)
Inconclusive	1 (3)	11 (46)	12 (63)	12 (40)	11 (85)	12 (38)

Abbreviations: PET/CT, positron emission tomography fused with computed tomography; SD, standard deviation; PSA, prostate-specific antigen; ++, multiple uptake sites.

Ninety patients had both choline and fluoride PET/CT scans (Study I), and treatment plans were changed for 18 of the patients (20%) due to the results of their scans. The PET/CT results for all 90 patients are presented in a cross-table (Table 4a). Fifty-five patients (61%) had no evidence of metastases on choline PET/CT, and 15 (27%) of those subjects had one or more positive sites on fluoride PET/CT. Conversely, of the 53 patients who were negative on fluoride PET/CT, 12 (23%) had positive findings on choline PET/CT. In total, there was at least one positive finding in either of the scans in 50 (56%) of the 90 patients, and at least two positive findings in either of the scans in 30 (33%). In additional, two patients (2%) had a single finding on each scan. A cross-table for the 18 patients whose management was changed are given in Table 4b. All of those patients had at least one, and most at least two, positive findings on choline PET/CT. It would seem that the urologists who were treating the patients gave the most weight to the choline PET/CT results, since none of the 15 patients who only had positive fluoride PET/CT findings had

their treatments altered, but the reasons for this are unclear. Which tracer is best at detecting metastases could not be determined from these results, nevertheless it is evident that performing both scans revealed more suspected metastases than performing either alone.

All but one of the 13 patients with inconclusive bone scans had multiple positive findings on either of the PET/CT scans, and all but two had multiple positive sites on both PET/CT scans (Table 5). Therefore, it could be argued that an inconclusive bone scan should in fact be interpreted as positive, and treatment should be directed accordingly, but either choline or fluoride PET/CT may be used to confirm the presence of the metastases.

Table 6.
Results of comparison between ^{18}F-choline PET/CT findings and histopathology after ePLND when considering any tracer uptake above background as a positive PET/CT finding, *i.e.* best-case sensitivity and worst-case specificity. Separate cross-tables are presented for A) findings only within the ePLND template, B) findings only in the whole pelvis, C) any lymph node findings, and D) any lymph node or skeletal findings. Sensitivity and specificity, both with 95% confidence intervals, for ^{18}F-choline PET/CT in detecting metastases compared with ePLND, are given in each sub-table.

PET/CT		**ePLND**		**Sensitivity**	**Specificity**
		N0	**N1**	(95% CI)	(95% CI)
A	**N0**	59	32	0.33	0.92
Only template	**N1**	5	16	(0.21–0.49)	(0.82–0.97)
B	**N0**	54	26	0.46	0.84
Whole pelvis	**N1**	10	22	(0.32–0.61)	(0.73–0.92)
C	**N0M0**	53	26	0.46	0.83
Pelvis+abdomen	**N1 or M1**	11	22	(0.32–0.61)	(0.71–0.91)
D	**N0M0**	52	25	0.48	0.81
Whole body	**N1 or M1**	12	23	(0.34–0.63)	(0.69–0.90)

Abbreviations: PET/CT, positron emission tomography fused with computed tomography; ePLND, extended pelvic lymph node dissection; N0, no lymph node metastases detected; N1, lymph node metastases detected; M0, no distant metastases detected; M1, distant metastases detected; CI, confidence interval.

One hundred twelve patients had a choline PET/CT scan and later also underwent an ePLND (Study II). A further 62 patients had undergone PET/CT scans but were excluded from the study due to evidence of extensive metastatic spread and intercurrent illness (Figure 6). The PET/CT scans detected suspected lymph node metastases in 33 (29%) of those subjects. Two additional patients (2%) had suspected bone metastases only. The ePLND revealed lymph node metastases in 48 (43%) of the patients. The median number of lymph nodes dissected were 12 (range 3–47). When all suspicious lymph nodes on PET/CT were taken into consideration, the sensitivity was 0.46 and the specificity 0.83; when the analysis was limited to the nodes within the template area of an ePLND, the corresponding values were

0.33 and 0.92 (Table 6). These results were similar to those reported by other investigators, although the sensitivity we found was somewhat lower (Table 7) [123,124,126,140–146].

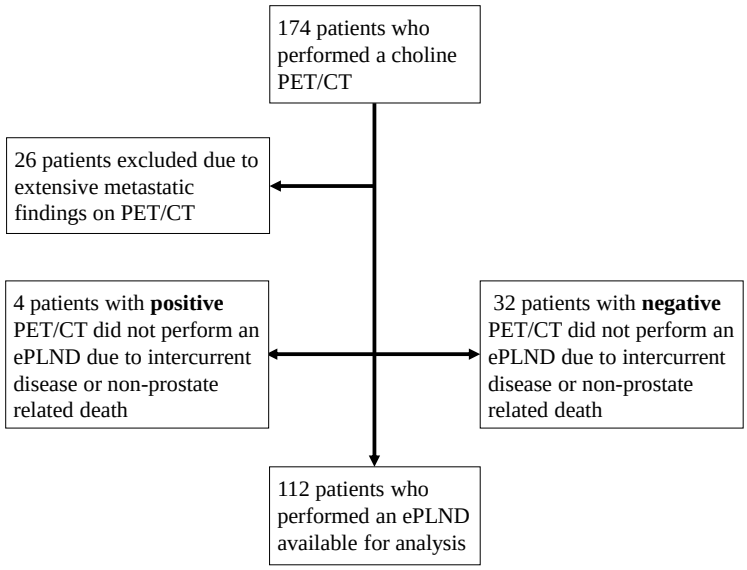

Figure 6.
Exclusion diagram of Study II. A total of 62 patients were excluded from the study due either to extensive metastatic findings on the choline PET/CT scans or to intercurrent disease or death.

Table 7.

Summary of published studies comparing choline PET or PET/CT with lymphadenectomy. The weighted means were calculated by the formula $\frac{\sum W_i S_i}{\sum W_i}$, where W_i is the number of patients in each study and S_i is the sensitivity or specificity noted in the respective investigations. Weighted means are given in two ways: only for the studies reported by other authors and for those investigations together with the present analysis showing any positive finding on ^{18}F-choline PET/CT.

Study	Isotope	Scan	No. of patients	Risk groups	Proportion N1	Proportion positive scans	Mean no. of lymph nodes	Sensitivity	Specificity
Kotzerke2000 [124]	^{11}C	PET	12	?	17%	17%	?	0.50	0.90
DeJong2003 [123]	^{11}C	PET	67	I+H	22%	21%	?	0.80	0.96
Häcker2006* [126]	^{18}F	PET/CT	20	I+H	50%	5%	14	0.10	1.0
Schiavina2008 [140]	^{11}C	PET/CT	57	I+H	26%	18%	16	0.60	0.98
Husarik2008 [141]	^{18}F	PET/CT	25	I+H	4%	14%	?	0.33	1.0
Steuber2010 [147]	^{18}F	PET/CT	20	H	45%	0%	15	0.00	1.0
Beheshti2010* [142]	^{18}F	PET/CT	130	I+H	17%	14%	8	0.45	0.96
Contractor2011 [144]	^{11}C	PET/CT	26	H	35%	54%	16	0.78	0.82
Budiharto2011 [145]	^{11}C	PET/CT	36	H	47%	11%	20	0.19	0.95
Poulsen2012 [146]	^{18}F	PET/CT	210	I+H	20%	24%	5	0.73	0.88
Weighted mean								0.58	0.93
Weighted mean including the present study								**0.57**	**0.91**

* These two studies were published by the same authors, and the study period used in the first investigation was included in the second. Accordingly, only data from the second study was used to calculate the weighted means.

Abbreviations: N1, lymph node metastases confirmed by histopathology; PET, positron emission tomography; PET/CT, positron emission tomography fused with computed tomography; ?, unknown; I, intermediary risk; H, high risk.

Eighty-three patients underwent SN detection (Study IV), and at least one SN was detected in 72 (87%) of those subjects, whereas there were no detectable SNs in 11 (13%, 95% CI 8–22%) (Table 8). This proportion of non-detection of SNs was higher than in all except two previous studies (Table 9). In one of the two previous studies reporting no detectable SNs in more than 10% of the patients, all of the 13% reported cases of non-detection were in the first 72 patients in which a lower dose of tracer was used [148]. After increasing the dose from 60 to 200 MBq, they had no cases of non-detection in the last 28 patients. It is therefore possible that the tracer dose used in our study (100MBq) is not optimal. Additionally, the other three studies with the highest level of non-detection where all performed with laparoscopic surgery, as opposed to open surgery. It is possible that laparoscopic SN dissection is more technically challenging than open SN surgery, leading to a longer learning curve and therefore a higher proportion of non-detection. Finally, in a study comparing the value of pre-operative imaging in SN dissection, Warncke et al (2007) found that the non-detection rate was similar (1–2%) when performing pre-operative scintigraphy compared with not performing any preoperative imaging, as was the number of dissected sentinel lymph nodes (median 8 per patient) [149]. It should be noted, however, that the number of patients was small, 36 in total, and that the 15 patients who were operated without imaging were the first in the series, such that the learning curve was a potential bias.

Of the 72 patients with detectable SNs, 99% were accurately staged based on the SNs, whereas at most 97% were accurately staged by the ePLND (Table 10). The SNs that were found in the ePLND specimens post-operatively were considered part of the ePLND results for this analysis, however it is not possible to determine whether the metastases would have been identified by the pathologists if only standard handling of the specimens had been performed. Thirteen patients (18%) had SNs outside the ePLND template. In six of these patients, the SNs outside the template contained metastases. Two patients had metastases only outside the ePLND template, and one patient had a metastasis within the template area but it showed no tracer uptake. Specificity was 1.0 for both methods, whereas the sensitivity for detecting metastases using SN detection was 0.96, with the combined results of both SN detection and ePLND as the reference test. The sensitivity of the method in our study is comparable to that of those previously published. The early results of Wawroscheck et al (2001) only showed a sensitivity of 0.84, but later in their series it was 0.94–0.99. It is possible that there was a significant learning curve affecting their results, but also that there are technical non-surgical factors that might need to be optimised, such as time from injection of tracer to detection, or where in the prostate the tracer is injected.

Table 8.
Clinical characteristics of the patients in Study IV, categorised according to the results of histopathology of the sentinel nodes.

	SN0 n = 50	**SN1** n = 22	**SNx** n = 11
Age, years			
Mean (SD)	65.0 (6.4)	64.7 (6.4)	67.7 (5.2)
Median (range)	65.5 (43.2–75.8)	65.4 (6.4)	68.6 (56.9–74.9)
PSA, ng/mL			
Mean (SD)	18.2 (12.4)	23.1 (19.4)	30.6 (24.3)
Median (range)	15.5 (5.0–62)	19.0 (3.0–91)	21.0 (7.0–91)
Biopsy Gleason score, n (%)			
5–6	9 (18)	2 (9)	1 (9)
3+4	21 (42)	6 (27)	3 (27)
4+3	8 (16)	2 (9)	4 (36)
8–10	12 (24)	12 (55)	3 (27)
Clinical local tumour stage, n			
2	16 (32)	3 (14)	3 (27)
3	34 (68)	19 (86)	8 (73)
Mode of surgery, n			
Open	18* (36)	6 (27)	2 (18)
Laparoscopic	32 (64)	16(73)	9 (82)
No. of lymph nodes dissected, median (range)			
Open	19.0 (6–38)	19.5 (14–23)	17.0 (14–20)
Laparoscopic	13.0 (6–39)	12.0 (4–27)	9.0 (7–12)
Total	14.0 (6–39)	14.5 (4–27)	10.0 (7–20)
No. of sentinel nodes dissected, median (range)			
Open	2.0 (1–8)	4.0 (2–7)	–
Laparoscopic	2.0 (1–7)	2.0 (1–6)	–
Total	2.0 (1–8)	2.5 (1–7)	–
Pathological local tumour stage, n (%)			
2c	13 (76)	2 (33)	1 (50)
3a	4 (24)	2 (33)	1 (50)
3b	–	2 (33)	–

Abbreviations: SN0, sentinel lymph nodes not showing metastases; SN1, sentinel lymph nodes showing metastases; SNx, sentinel lymph nodes not detected; SD, standard deviation; *, including one patient who did not undergo radical prostatectomy.

Table 9.
Summary of previously published studies on SN detection.

Study	No. patients	Risk groups	Preoperative imaging	Percentage no detection of SN	Percentage N1	Sensitivity	Reference
Wawroscheck2001* [136]	117	I+H	Scint	3%	26%	0.84	Lim
Corvin2006 [137]	28	I+H	SPECT/CT	7%	25%	?	Lim
Fukuda2007 [150]	42	I+H	SPECT/CT	2%	31%	0.92	Ext
Weckermann2007* [151]	228	H	Scint	0%	42%	0.98	Ext
Weckermann2007* [152]	1055	L+I+H	Scint	0%	20%	0.99	Ext
Jeschke2008 [153]	140	L+I+H	Scint	5%	14%	–	FS ± Ext
Meinhardt2008 [154]	35	I+H	SPECT/CT	17%	40%	1.0	Ext
Bastide2009 [148]	100	L+I+H	Scint	13%	12%	1.0	Ext
Holl2009* [155]	2020	L+I+H	Scint	2%	17%	0.94	Ext
Rousseau2014 [156]	203	I+H	SPECT/CT	6%	17%	0.97	Ext

* These studies are from the same group and centre and likely contain many of the same patients.

Abbreviations: SN, sentinel node; N1, lymph node stage positive; L, low risk; I, intermediary risk; H, high risk; Lim, limited pelvic lymph node dissection; Ext, extended pelvic lymph node dissection; FS, frozen section analysis of sentinel nodes with extended lymphadenectomy only in case of positive findings.

Table 10.
Cross-table of SN detection and ePLND compared with the combined results of both methods. N0 is defined as neither of the methods finding metastases, while N1 is defined as either of the methods detecting metastases. (A) Results for the 72 patients with one or more detected sentinel nodes. (B) Results for all 83 patients classifying undetectable sentinel nodes as a negative result. Sensitivity is calculated for each method with 95% confidence intervals in parenthesis.

		SN analysis		ePLND	
		Negative	**Positive**	**Negative**	**Positive**
A	**N0**	49	0	49	0
	N1	1	22	2	21
	Sensitivity	0.96 (0.76–1.0)		0.91 (0.70–0.98)	
B	**N0**	57	0	57	0
	N1	4	22	2	24
	Sensitivity	0.85 (0.64–0.95)		0.92 (0.73–0.99)	

Abbreviations: SN, sentinel node; ePLND, extended pelvic lymph node dissection; N0, N stage negative; N1, N stage positive.

Additional analyses

From the additional analyses of Study I it was found that in 13 patients (14%), choline PET/CT detected skeletal metastases that were confirmed by fluoride PET/CT (Table 4c). However, in six of those patients there was only a single skeletal uptake site, which would likely have required further confirmation before affecting the treatment decision. On the other hand, 24 patients with positive fluoride PET/CT findings had no skeletal uptake according to choline PET/CT, which could be regarded either as false-negative choline scans or false-positive fluoride scans. Using fluoride PET/CT findings as reference, sensitivity and specificity of choline PET/CT in detecting bone metastases were 0.35 (95% CI 0.21–0.53) and 0.98 (95% CI 0.89–1.0), respectively. However, it is likely that at least some of the fluoride PET/CT scans were false positive, and these figures do therefore arguably not represent the true diagnostic accuracy of choline PET/CT for bone metastases. The only other study specifically comparing choline and fluoride PET/CT available in the literature was conducted by Langsteger et al (2011) and showed sensitivity of 0.91 and specificity of 0.89 for choline PET/CT in detecting bone metastases, values that were similar to the values of 0.91 and 0.81 noted for fluoride PET/CT [143]. Additionally, Beheshti et al (2009) reported sensitivity 0.79 and specificity 0.97 for choline PET/CT in detecting bone metastases, but with a mixture of different imaging modalities used as reference tests. The fact that our investigation demonstrated lower sensitivity for choline PET/CT than did both of these cited studies could be explained by the pre-screening using planar bone scans that was part of our protocol (also discussed below). Notwithstanding, the difficulties in obtaining a reliable reference represented a limitation of all of these studies. These

results would seem to suggest that choline PET/CT could be performed first, with fluoride PET/CT only performed if choline was inconclusive. They also imply that planar bone scans would not need to be used, because such bone metastases that would have been detected by a bone scan, would also have been detected by choline PET/CT. However, this hypothesis was not tested in any of the included studies, and there was no attempt at a cost-benefit analysis or any logistical considerations.

Table 11.
Results of logistic regression analysis of factors predictive of a combined result of multiple positive findings on choline and fluoride PET/CT. None of the factors except scintigraphy results were significant predictors in multivariate analysis. Age (years) and PSA (ng/mL) were analysed as continuous variables, all the other were analysed as categorical variables. The three variables with the lowest p-values were selected for multivariate analysis.

	Univariate		Multivariate	
	OR	**95% CI**	**OR**	**95% CI**
Age	1.00	0.92–1.09		
PSA	1.00	0.98–1.03		
Biopsy Gleason score				
≤ 3+4	1 (reference)		1 (reference)	
4+3	1.24	0.17–9.25	0.57	0.03–9.75
8–10	**5.57**	**1.40–22.1**	4.20	0.83–21.3
Local tumour stage				
T1c	1 (reference)		1 (reference)	
T2	1.46	0.31–6.98	0.51	0.06–4.10
T3	**4.89**	**1.15–20.8**	2.43	0.40–15.0
Bone scan				
Negative	1 (reference)		1 (reference)	
Inconclusive	**24.0**	**2.91–198**	**49.1**	**3.77–640**

Abbreviations: PSA, prostate-specific antigen; OR, odds ratio; CI, confidence interval.

There was a higher proportion of high-grade cancer (Gleason score 8–10) and locally advanced disease (T3) in the patients with multiple positive findings. However, in multivariate logistic regression analysis, an inconclusive bone scan was the only factor found to significantly predict multiple positive findings on either type of PET/CT scans (Table 11). It is highly likely that the lack of significant predictors can be explained by the small sample size (*i.e.*, a type II error), because according to validated nomograms the risk of actually having metastases is significantly increased by higher PSA, higher Gleason score, and locally more advanced tumour stage [75,77].

When we performed analysis covering any of the lymph node findings, a per-patient ROC analysis showed that 4.1 was the lowest SUV with specificity of 1.0, but

sensitivity was only 0.19 (Figure 7). Using 2.4 as SUV cut-off provided sensitivity 0.25 and specificity 0.97. Because no other studies in the literature have analysed SUVs, and because SUVs are not always comparable between centres, these exact values should be viewed with caution. Nonetheless, they do indicate that the diagnostic accuracy is affected by the level of uptake in suspected lesions and provide evidence that the patients in Study I, whose treatment was changed from curative to non-curative because of extensive findings, did indeed have metastases.

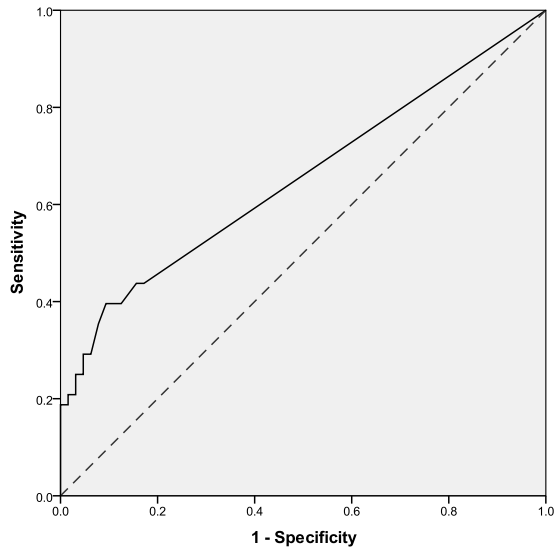

Figure 7.
Receiver operating characteristic curve of ^{18}F-choline PET/CT with varying specific uptake values (SUVs). Analysis was performed on a per-patient basis with the highest SUV of any lymph node compared with the results of lymphadenectomy. With 2.1 as SUV cut-off, sensitivity is 0.46 and specificity is 0.83; with 3.2 as SUV cut-off, sensitivity is 0.21 and specificity is 0.98. Area under the curve is 0.65 with a 95% confidence interval of 0.55–0.76.

Logistic regression analysis comparing the patients with true-positive PET/CT scans (using 2.4 as SUV cut-off) and those with true-negative scans did not reveal any significant predictive factors (Table 12). Likewise, among the patients with any abnormal tracer uptake in a lymph node, there were no predictive factors for true positivity. Schiavina et al (2008) are the only investigators who have published an analysis of factors that potentially affect the detection rate of choline PET/CT in detecting lymph node metastases, and these authors found that a greater number and larger size of the metastases increased the chance of positive findings on PET/CT [140]. In other words, these results imply that the higher metastatic burden a patient has, the greater the chance of choline PET/CT being positive, which is perhaps not

a great surprise. As was mentioned earlier, this provides a possible explanation for the low sensitivity noted in Study II, compared with the other cited studies. Because only patients with a normal or inconclusive bone scan were included, the patients with the largest metastatic burden were excluded.

Table 12.
Results of logistic regression analysis to identify factors predictive of a true-positive ^{18}F-choline PET/CT result with the SUV cut-off at 2.4. None of the factors were statistically significant. Age (years) and PSA (ng/mL) were analysed as continuous variables, biopsy Gleason score and local tumour stage were analysed as categorical variables.

	Univariate		Multivariate	
	OR	**95% CI**	**OR**	**95% CI**
Age	1.08	0.96–1.21	1.07	0.93–1.22
PSA	1.02	0.99–1.05	1.04	0.99–1.08
Biopsy Gleason score				
≤ 3+4	1 (reference)		1 (reference)	
4+3	3.75	0.52–26.8	3.35	0.32–34.6
8–10	2.80	0.52–15.0	6.53	0.75–56.6
Local tumour stage				
T1c	1 (reference)		1 (reference)	
T2	0.62	0.08–4.95	0.49	0.05–4.61
T3	2.40	0.43–13.4	1.13	0.17–7.56

Abbreviations: PSA, prostate-specific antigen; OR, odds ratio; CI, confidence interval.

Restaging after recurrence

Fifty-eight patients underwent choline PET/CT following BCR after RP (Study III), and 16 of those subjects (28%) had metastatic findings (Table 13). The PET/CT scans were positive for 12 of the 48 patients (25%) with PSA < 1.0, and for 8 of the 33 patients (24%) with PSA < 0.5. A summary of previously published investigations by other authors is presented in Table 15 [125,127–133,141,157–176]. In these studies, there was a large variation in the detection of both metastases and local recurrences, but also large differences in the inclusion criteria. Importantly, most of the cited studies included large proportions of patients who were receiving HT at the time of the PET/CT scans. Dost et al (2013) performed a review of the literature regarding HT and choline PET/CT, the results of which indicate that HT negatively affects the sensitivity of choline PET/CT in detecting prostate cancer metastases [177].

Table 13. Clinical characteristics of the patients in Study III categorised according to the results of ^{18}F-choline PET/CT.

	All patients	**No evidence of metastases**	**Any metastases**
	n = 58	n = 42	n = 16
Age at surgery, years			
Mean (SD)	63.2 (±5.4)	61.9 (±5.3)	66.4 (±4.2)
Median (IQR)	63.9 (59.2–66.9)	61.9 (57.3–66.6)	65.4 (63.6–69.7)
pT, n (%)			
2	32 (55)	24 (57)	8 (50)
3a	13 (22)	8 (19)	5 (31)
3b	13 (22)	10 (24)	3 (19)
Surgical margin status, n (%)			
Negative	32 (55)	21 (50)	11 (69)
Positive	26 (45)	21 (50)	5 (31)
pN, n (%)			
X	31 (53)	21 (50)	10 (63)
0	18 (31)	15 (36)	3 (19)
1	9 (16)	6 (14)	3 (19)
Prostatectomy Gleason score, n (%)			
5–6	3 (5)	3 (7)	–
3+4	26 (45)	18 (43)	8 (50)
4+3	19 (33)	14 (33)	5 (31)
8–10	10 (17)	7 (17)	3 (19)
Presence of Gleason grade 5, n (%)			
Yes	11 (19)	9 (21)	2 (13)
No	47 (81)	33 (79)	14 (88)
PSA nadir (ng/mL)**,** n (%)			
< 0.1	35 (60)	26 (62)	9 (56)
0.1 – 0.19	8 (14)	6 (14)	2 (13)
0.2 – 0.76	15 (26)	10 (24)	5 (31)
Time to relapse (months), n (%)			
< 12	12 (28)	9 (28)	3 (27)
12–24	13 (30)	10 (31)	3 (27)
> 24	18 (42)	13 (41)	5 (46)
PSA at PET/CT (ng/mL), n (%)			
< 0.5	33 (57)	25 (60)	8 (50)
0.5–0.99	15 (26)	11 (26)	4 (25)
1.0–1.49	6 (10)	4 (10)	2 (13)
1.5–1.99	4 (7)	2 (5)	2 (13)
PSA doubling time (months), n (%)			
< 3	11 (19)	7 (17)	4 (25)
3–6	20 (35)	15 (36)	5 (31)
6–12	15 (26)	10 (24)	5 (31)
> 12	12 (21)	10 (24)	2 (13)

Abbreviations: pT, pathological T stage; pN, pathological N stage; SD, standard deviation; IQR, inter-quartile range; PSA, prostate-specific antigen; PET/CT, positron emission tomography fused with computed tomography.

A possible exception was for patients with castration-resistant prostate cancer, but these patients are generally not candidates for curative treatment in any case, and the clinical value of choline PET/CT in that setting can therefore be questioned. Additionally, most of the studies included patients who had previously received curative RT, and for whom there are no evidence-based curative treatment options, regardless of whether they have metastatic disease or not. Lastly, the PSA levels of the patients included in the studies were generally well above the levels at which salvage RT is recommended. The only other investigation which did not suffer from these limitations was performed by Giovacchini et al (2013), who found metastatic lesions in 15% of the patients [174].

Our study was not designed to determine the diagnostic accuracy of choline PET/CT for detecting prostate cancer metastases at BCR. There are no studies that prospectively provide follow-up for all patients who have undergone a PET/CT scan, but there are investigators that have performed a lymphadenectomy on those patients that had only a few suspected lymph node metastases on PET/CT. In one such study, Tilki et al (2013) noted a positive predictive value (PPV) of 0.86 [178]. However, the patients in that investigations had PSA levels ranging from 1.7 to 9.4, and would therefore have a high expected rate of metastases. Suardi et al (2014) performed a similar study in which they noted a PPV of 0.80 [179]. Interestingly, in this latter study, the salvage lymph node dissections resulted in complete biochemical response (*i.e.*, PSA less than 0.1) for 59% of the patients. Whereas this does not necessarily translate into improved survival for these patients, it does indicate that if metastases are properly detected, patients could potentially benefit from tailored treatment.

Both univariate and multivariate logistic regression analysis showed that older age was the only significantly predictive factor of a positive PET/CT scan (Table 14). However, our study was too small for anything more than a cursory analysis, and it is unclear if this result has any clinical implications. Castelluci et al (2014) recently performed the hitherto largest study of this group of patients, and found that PSA value and PSA doubling-time were independent significantly predictive factors for positive results on choline PET/CT, whereas age was not [176]. In other words, the patients who have a higher risk of metastatic disease are more likely to get a positive result on PET/CT [180].

Table 14.
Logistic regression analysis of the factors that may predict positive ^{18}F-choline PET/CT results for patients with biochemical recurrence following radical prostatectomy. For multivariate analysis, the factors with the lowest p-values were selected. Only age was a significant predictor, both in univariate and multivariate analysis. Age at surgery (years) was analysed as a continuous variable, all other variables were analysed as categorical.

	Univariate		Multivariate	
	OR	**95% CI**	**OR**	**95% CI**
Age at surgery	**1.20**	**1.05–1.38**	**1.25**	**1.07–1.46**
pT				
2	1 (reference)			
3	1.33	0.42–4.23		
Surgical margin status				
Negative	1 (reference)		1 (reference)	
Positive	0.46	0.13–1.54	0.40	0.08–1.97
pN				
0	1 (reference)		1 (reference)	
X	2.38	0.56–10.2	3.60	0.65–20.0
1	2.50	0.39–16.0	7.75	0.78–77.0
Prostatectomy Gleason score				
≤ 3+4	1 (reference)			
4+3	0.94	0.25–3.46		
8–10	1.13	0.23–5.46		
Presence of Gleason grade 5				
No	1 (reference)		1 (reference)	
Yes	0.52	0.10–2.74	0.86	0.13–5.83
PSA nadir (ng/mL)				
< 0.1	1 (reference)			
0.1–0.19	0.96	0.16–5.66		
0.2–0.76	1.44	0.39–5.38		
Time to relapse (months)				
< 12	1 (reference)			
12–24	0.90	0.14–5.65		
> 24	1.15	0.22–6.10		
PSA at PET/CT (ng/mL)				
< 0.5	1 (reference)			
0.5–0.99	1.14	0.28–4.58		
1.0–1.49	1.56	0.24–10.2		
1.5–1.99	3.13	0.38–25.9		
PSA doubling time (months)				
< 3	2.86	0.41–20.1		
3–6	1.67	0.27–10.3		
6–12	2.50	0.39–16.0		
> 12	1 (reference)			

Abbreviations: pT, pathological T stage; pN, pathological N stage; PSA, prostate-specific antigen; PET/CT, positron emission tomography fused with computed tomography.

Table 15.
Summary of studies on choline PET/CT following biochemical recurrence after primary treatment, published after the current study was started. Several studies are from the same centres and the same study groups, but have different inclusion criteria and are therefore presented separately. Some of the studies did not report separate results for metastatic findings and findings in the prostatic fossa, and they are therefore presented combined.

Investigation	Centre	Isotope	No. patients				% hormone naïve	PSA (ng/mL) median (range)	% local findings	% metastatic findings
			RP	RT	Other	Total				
Picchio2003 [128]	Milano, I	^{11}C	77	23	–	100	?	6.6 (0.1–171)	10%	37%
DeJong2003 [129]	Groningen, NL	^{11}C	13	9	–	22	**100%**	5.0 (0.5–120)	36%	36%
Yoshida2006 [125]	Hamakita, JP	^{11}C	5	3	–	8	38%	5.7 (0.2–11)	25%	50%
Heinisch2006 [130]	Linz, A	^{18}F	31	3	–	34	53%	?	?	?
Cimitan2006 [131]	Aviano, I	^{18}F	58	21	21	100	36%	48 (0.2–512)	24%	44%
Rinnab2007 [132]	Ulm, D	^{11}C	**41**	–	–	41	90%	2.1 (0.4–12)	56%	32%
Vees2007 [133]	Geneve, CH	^{18}F	**11**	–	–	11	**100%**	**0.4 (0.1–0.7)**	45%	0%
Eschmann2007 [127]	Tübingen, D	^{11}C	?	?	?	25	?	?	?	?
Husarik2008 [141]	Zürich, CH	^{18}F	26	8	34	68	81%	11 (0.4–100)	53%	56%
Krause2008 [157]	Munich, D	^{11}C	42	21	–	63	73%	2.2 (0.2–39)	38%	24%
Reske2008 [158]	Ulm, D	^{11}C	**36**	–	–	36	81%	2.0 (0.3–12)	67%	–
Pelosi2008 [159]	Turin, I	^{18}F	**56**	–	–	56	**100%**	4.6 (0.1–39)	10%	36%
Rinnab2009 [160]	Ulm, D	^{11}C	32	–	9	41	90%	2.1 (0.4–12)	56%	32%
Castellucci2009 [161]	Bologna, I	^{11}C	**190**	–	–	190	89%	2.1 (0.2–25)	4%	35%
Zuazu2009 [162]	Pamplona, E	^{11}C	63	29	–	92	?	3.9	?	?
Giovacchini2010 [163]	Milano, I	^{11}C	**358**	–	–	358	57%	1.3 (0.2–45)	15%	36%
Bertagna2011 [164]	Brescia, I	^{11}C	140	70	–	210	65%	5.9	55%	
Castellucci2011 [165]	Bologna, I	^{11}C	**102**	–	–	102	84%	**0.9 (0.2–1.5)**	7%	22%
Graute2012 [166]	Munich, D	^{18}F	**82**	–	–	82	90%	4.4 (0.03–36)	24%	39%
Fuccio2012 [167]	Bologna, I	^{11}C	**123**	–	–	123	82%	3.3 (0.2–26)	2%	32%
Schillaci2012 [168]	Rome, I	^{18}F	**49**	–	–	49	**100%**	4.1 (0.09–16)	12%	59%
Panebianco2012 [169]	Rome, I	^{18}F	**84**	–	–	84	**100%**	?	?	36%
Rybalov2013 [170]	Groningen, NL	^{11}C	61	124	–	185	**100%**	5 (0.2–20)	43%	24%

Table 15.
(Continued)

Investigation	Centre	No. patients					% hormone naïve	PSA (ng/mL) median (range)	% local findings	% metastatic findings
		Isotope	RP	RT	Other	Total				
Detti2013 [171]	Florence, I	^{18}F	126	40	4	170	81%	3.5 (0.09–98)	35%	61%
Nanni2013 [172]	Bologna, I	^{11}C	**28**	–	–	28	**100%**	1.5 (0.2–15)	4%	14%
Mitchell2013 [173]	Rochester, US	^{11}C	127	41	8	176	?	7.2 (2.2–1000)		75%
Giovacchini2013 [174]	Milano, I	^{11}C	**75**	–	–	75	**100%**	**0.6 (0.2–1.5)**	9%	15%
Afshar-Oromieh2014 [175]	Heidelberg, D	^{18}F	?	?	?	37	?	? (0.01–116)		70%
Castellucci2014 [176]	Bologna, I	^{11}C	**605**	–	–	605	75%	**1.1 (0.2–2.0)**	6%	23%

Abbreviations: RP, radical prostatectomy; RT, radiation therapy; PSA prostate-specific antigen; ?, unknown.

General discussion

Determining the reliability of a new diagnostic modality requires a good reference test to determine "the truth", otherwise the results may be misleading. In the case of Study II, ePLND was used as reference, despite that Study IV and other SN investigations have established that not all primary metastatic landing sites are located within the ePLND template. This could have led to erroneous classifications of false-negatives and false-positives both. To compensate, we classified the choline uptake sites as within or outside the ePLND template, but anatomical variations and differences in technique between surgeons make direct comparisons between imaging and ePLND difficult, which leads to uncertainty regarding the sensitivity and specificity values both in this and other studies.

Table 16.
Negative and positive predictive values at various prevalence rates for tests with different diagnostic accuracies. The first column represents the pooled averages of the published investigations, while the other two columns represent the results of Study II with SUV cut-off values of 3.2 and 2.1, respectively.

Sensitivity	0.57		0.21		0.46	
Specificity	0.91		0.98		0.83	
Prevalence	**NPV**	**PPV**	**NPV**	**PPV**	**NPV**	**PPV**
5%	0.98	0.25	0.96	0.36	0.97	0.12
10%	0.95	0.41	0.92	0.54	0.93	0.23
15%	0.92	0.53	0.88	0.65	0.90	0.32
20%	0.89	0.61	0.83	0.72	0.86	0.40
25%	0.86	0.68	0.79	0.78	0.82	0.47
30%	0.83	0.73	0.74	0.82	0.78	0.54
35%	0.80	0.77	0.70	0.85	0.74	0.59
40%	0.76	0.81	0.65	0.88	0.70	0.64
45%	0.72	0.84	0.60	0.90	0.65	0.69
50%	0.68	0.86	0.55	0.91	0.61	0.73

Abbreviations: NPV, negative predictive value; PPV, positive predictive value.

How will our results from Study II affect the clinical management of future prostate cancer patients with results from choline PET/CT scans? The negative (NPV) and positive predictive values represent the post-test probabilities of a true result in

patients with either a negative or a positive scan, and are both highly dependent on the pre-test risk (*i.e.*, the prevalence of the condition). Table 16 summarises NPVs and PPVs of choline PET/CT at various rates of metastatic disease, using the results of the pooled average of the available investigations, and also with the results of the current study at two SUV cut-offs. For a given sensitivity and specificity PPV increases with an increasing prevalence, whereas NPV decreases. The prevalence of metastatic disease can, in the setting of primary staging, be estimated using for example the Briganti nomogram or the Partin table. However, the reported sensitivity and specificity for PET/CT represent the averages of all the studied patients' test results. Patients with a single low-grade uptake will have a lower PPV than patients with multiple high-grade uptakes, and this should affect the interpretation of the PET/CT findings for clinical decision-making.

A limitation of Study I and III was that the protocols did not include any verification of the positive PET/CT findings. Therefore, it was not certain that the patients whose management were changed did in fact have metastases. This was to some extent mitigated by Study II, which showed a high specificity, leading to a high PPV, for choline PET/CT in detecting prostate cancer metastases. The results of Study II also demonstrated that using higher tracer uptake cut-off for defining metastases of suspected nodes resulted in higher specificity. The patients whose management was changed in Study I all had multiple sites with highly pathological uptake, and most had positive findings on both PET/CT scans. Therefore, the conclusion must be that, despite the lack of histopathological verification, there was a very high probability that they had significant metastatic disease. One of the main limitations of Study II was that the patients with extensive uptake had been excluded, and hence it was not possible to determine to what extent a high number of pathological tracer uptake sites would increase specificity for defining metastatic disease. There was also a large proportion of patients who did not undergo ePLND due to intercurrent disease or death. In Study III, we did not assess whether the choline PET/CT scan led to any change in management, only what proportion of patients with BCR and low PSA levels had positive findings. Given the results that more than a quarter of the patients included in the study did indeed have suspected metastases, it is reasonable to conclude that further studies of the reliability of choline PET/CT in that setting are warranted. A general limitation of the PET/CT studies was that, although the enrolment was prospective according to the protocols, outcome data was collected retrospectively. Also, for Study II the reviews of the PET/CT scans were done in a blinded fashion, but the urologists performing the ePLNDs were not blinded to the results of the PET/CT, and the surgical technique might therefore have been changed for individual patients. Furthermore, the CT results in Study I were not evaluated separately. It is possible that CT scans would have detected a large proportion of the patients with extensive metastatic disease.

A limitation of Study IV was that the SNs within the ePLND template were not dissected separately in-vivo but were detected ex-vivo after ePLND had been

performed. Whether the large proportion of non-detection of SNs is a limitation of the simplified SN technique or a part of the learning-curve in our study is uncertain. Almost all other SN studies also had some patients where the SNs were not detectable, and this begs the question how this outcome should be handled in clinical practice. One difficulty in answering that question is that there is currently very little evidence regarding the benefits of lymphadenectomy. There are retrospective analyses that imply that CSM is similar in patients with one or two lymph node metastases and patients with no metastases, while patients with more than two metastases have significantly worse prognosis [181–183]. Whether these results represent selection bias, a benefit from removing the metastases, or simply differences in total cancer volume is unclear. If removing the metastases is indeed beneficial, it would imply that at least patients with high risk of metastases should undergo an ePLND if no SNs are detected. Furthermore, an implication would also be that patients with metastases in the SNs should have an ePLND. A further limitation was that the additional operating time for performing the SN detection was not quantified.

Conclusions

- A large proportion of patients with high-risk prostate cancer and a negative or inconclusive bone scan have metastases detectable by choline or fluoride PET/CT. For some of these patients the extent of metastatic disease led to withholding of a local treatment that may have been unnecessary. Both PET/CT tracers may detect metastases that the other tracer does not.
- Choline PET/CT may be a valuable diagnostic tool for detecting lymph node metastases of prostate cancer. Its main limitations are a low sensitivity and a low PPV.
- Choline PET/CT indicates metastases in a large proportion of patients with BCR following RP, even at PSA levels below 1–2 ng/mL.
- Sentinel node detection with a simplified protocol is feasible and defines the N stage at least as well as ePLND.

Future perspectives

Our studies of PET/CT mainly assessed the use of choline as tracer for metastases of prostate cancer. The results seem to imply an improvement over earlier modalities, although there are still limitations primarily stemming from low sensitivity. Also, a recent report from the Swedish Council on Health Technology Assessment (SBU) indicated that there is still a relative lack of high-quality data on choline PET/CT for prostate cancer [184]. This lack of data should be remedied in a larger multi-centre investigation of consecutive patients with high-risk prostate cancer who would all undergo ePLND regardless of PET/CT findings. From an ethical perspective that might not possible for patients with evidence of extensive metastases however, given the knowledge that already exists today. Ideally, such a study would randomise patients between performing and not performing choline PET/CT and observe outcome, such as CSM, after tailored treatments. Such a study design would be applicable both for patients with a primary diagnosis of prostate cancer and for patients with BCR following RP. For fluoride PET/CT histopathological validation of suspected bone metastases remains a difficulty, but a randomised outcome trial could be feasible as well.

An exciting development is that of target therapies, such as radiotherapy or surgical excision, for oligo-metastatic disease detected by choline PET/CT [179,185,186]. Such treatments should be evaluated in prospective randomised controlled trials. Furthermore, there are other tracers than choline and fluoride which show promise in increasing both sensitivity and specificity. In particular, the synthetic L-leucine analogue anti-3-^{18}F-FACBC has been assessed in a few preliminary investigations with promising results, and further research will hopefully clarify this [187]. There is also a potential for entirely new tracers.

For SN dissection, further prospective studies are needed. Our study only evaluated the diagnostic utility of identifying the SNs, not whether all SNs could be dissected in-vivo. There are reports of SN dissection based on large, single-centre series, but these should be confirmed in larger multi-centre trials [155]. A randomised, multi-centre trial comparing SN dissection and ePLND, with the proportion of patients with detected lymph node metastases as the primary endpoint, would be feasible. Ideally, such a trial could also include an arm with no lymphadenectomy, to assess the effect of removing lymph node metastases and improving N-staging on BCR rates, time to distant metastases and CSM.

A combination of radio-guided and fluorescence-guided surgery has been used with the aim to decrease the non-detection of SNs, with promising preliminary results [188,189]. This approach should be explored further, perhaps also with an optimised tracer dose, which may further decrease non-detection of SNs. Recently, there has also been a report of SN dissection using ferro-magnetic nano-particles, detectable with a hand-held magnetometer, as the tracer [190]. Furthermore, rates and grades of complications related to SN dissection need to be assessed, preferably using the Clavien system.

In conclusion, the field of research on the detection of prostate cancer metastases has advanced in the last few years, not least through our studies. Choline and fluoride PET/CT can be used in selected patients with prostate cancer, but the respective limitations need consideration. SN dissection still needs further research before it can become a routine procedure for men with prostate cancer.

Summary in Swedish

Populärvetenskaplig sammanfattning

Prostatacancer är idag den vanligast diagnostiserade cancerformen i Sverige. De flesta nya fallen som upptäcks är lokaliserade till prostatan och kan i hög utsträckning botas med antingen operation eller strålbehandling. För en del män har dock prostatacancern hunnit sprida sig redan vid diagnos och då är chansen till bot mycket liten. Vid utbredd spridning, så kallad metastasering, är risken för bieffekter och komplikationer av operation eller strålbehandling större än nyttan. Det är därför av stor vikt att utbredningen av cancern fastställs innan behandlingen påbörjas.

Utredning av metastaser sker i första hand med skelettscintigrafi för att upptäcka skelettmetastaser och lymfkörtelutrymning, ett kirurgiskt ingrepp för att upptäcka lymfkörtelmetastaser. Båda metoderna har dock klara begränsningar och för lymfkörtelutrymning finns dessutom risk för komplikationer.

Positron-emissions-tomografi kombinerat med datortomografi (PET/DT) är en icke-invasiv metod för metastasdiagnostik. Fluorid och kolin är två PET/DT-markörer med olika egenskaper. Fluorid kan enbart upptäcka skelettmetastaser medan kolin kan upptäcka metastaser i hela kroppen.

Portvaktskörtelkirurgi är ett sätt att selektivt operera ut de lymfkörtlar som har störst risk att innehålla metastaser. Därigenom kan man möjligen slippa en del av biverkningarna av en hel lymfkörtelutrymning och möjligen också upptäcka metastaser som ligger utanför området för lymfkörtelutrymning.

I våra studier har vi jämfört kolin-PET/DT och fluorid-PET/DT och studerat den kliniska nyttan av dessa två undersökningar när skelettscintigrafi har varit normal eller osäker. Vi har också undersökt tillförlitligheten hos både kolin-PET/DT och portvaktskörtelkirurgi för att upptäcka lymfkörtelmetastaser, genom att jämföra med vanlig lymfkörtelutrymning. Slutligen har vi undersökt den kliniska nyttan av kolin-PET/DT hos patienter med återfall i prostatacancer efter tidigare operation i botande syfte.

Våra resultat visade att både kolin-PET/DT och fluorid-PET/DT var för sig kan indikera metastaser som den andra undersökningen missar. Tjugo procent av patienterna hade så stor metastasutbredning synlig på PET/DT att den planerade botande behandlingen avstyrdes. Kolin-PET/DT hade en hög tillförlitlighet om

undersökningen visade ett kraftigt upptag av kolin i en lymfkörtel, men högst hälften av patienterna med metastaser upptäcktes. Portvaktskörtelkirurgi var åtminstone lika tillförlitligt som lymfkörtelutrymning, men hos 13 % av patienterna kunde man inte återfinna någon portvaktskörtel. Vid återfall efter operation talade kolin-PET/DT för metastaser hos 28 % av patienterna med prostata-specifikt antigen (PSA) < 2 ng/mL och 24 % av patienterna med PSA < 1 ng/mL.

Slutsatsen är att PET/DT, med kolin eller fluorid som markörer, och portvaktskörtelkirurgi kan vara värdefulla diagnostiska metoder, men deras begränsningar måste beaktas.

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