SUMMARY OF THE PHD THESIS

THE ROLE OF NUCLEAR MEDICINE INVESTIGATIONS IN DIAGNOSIS, TREATMENT AND MONITORING THE PROSTATE CANCER

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INTRODUCTION

I have chosen the theme of the thesis because prostate cancer is one of the most important medical problems, being the most frequent neoplasia in male oncological pathology and the second death cancer cause following lung cancer. Molecular imaging techniques have focused on improving the sensitivity and the specificity in detecting the cancer by looking for the specific characteristics of the disease’s biology. The evolution of these techniques have determined a new role for imaging in the diagnosis and treatment of prostate cancer.

Current research on prostate cancer diagnosis faces the following clinical dilemmas: 1) identification of specific markers which could differentiate between aggressive and mild prostate tumors; 2) identification of specific tests which could allow an evaluation for the results of the biopsy in order to exclude unnecessary biopsies; 3) seeking for methods of imaging to accurately determine the areas of intraprostastic tumor in view of taking effectively biopsy samples; 4) the treatment of prostate cancer resistant at castration, which often leads to bone metastases, the only major cause of death in prostate adenocarcinoma.

What is the role of nuclear medicine in investigating and treating this cancer? This is the question I began with seven years ago. Nuclear Medicine is the specialty I have chosen 14 years ago following the exam of residency in February 1997. I had two reasons in choosing this specialty: it opened unexpected perspectives in imaging - the field which I was heading to - and the second reason, a personal one, it brought the memory of a pleasant atmosphere, as though enveloped in peace, that of the biophysics courses taken in first year of college, the courses taught by Professor Valeriu Rusu, the Head of the Nuclear Medicine lab, the courses which introduced me to the world of medicine and gave me the motivation to persevere.

Two months after starting the residency, I went to the United States to accompany my husband who was offered a scholarship to a theological seminary. I tried then to get familiar from books with physics and biophysics of Nuclear Medicine. Two years later, I returned to Romania and I resumed the residency. Two years I have spent to raise up Ioana, born less than a year after returning from the United States. In 2002, I came back to Nuclear Medicine Lab, where, under the guidance of the distinguished Professor Valeriu RUSU and of Mrs. Maria RUSU I have learned joyfully - in an atmosphere fitted to studying, having access to the extensive library of the laboratory - the interpretation of scintigraphic examinations.

In December 2004, being in the last year of residency, after passing an exam for admission to PhD, I became a PhD student at UMF "Gr T. Popa "Iasi. In 2005 I received the qualification as a physician and my desire was to work in the lab where I got trained, in the place I felt like being my second family. In order to remain hooked up with Nuclear Medicine, I decided to work as a volunteer one or two days a week in the Nuclear Medicine Lab. Meanwhile, I continued to prepare myself for the exams and do the papers for the PhD.

Mr. Professor Valeriu Rusu told me even from the beginning of my PhD that an internship in a Nuclear Medicine Lab in a country with a good tradition in this area would be very useful. The opportunity showed up in March 2009 when a Romanian colleague from France sent an e-mail to all nuclear medicine doctors across the country, announcing that a job will be available in the fall that year at the Nuclear Medicine Lab in Besançon, France. Therefore, I had the chance to work in a lab equipped with a SPECT gamma camera, a SPECT / CT gamma camera, a PET / CT and a semiconductor gamma camera for nuclear cardiology.

At Besançon and Montbéliard - where is the second laboratory of Nuclear Medicine where I worked due to contract work - I found a rich casuistry of patients who had bone scintigraphy and were treated with QUADRAME. In addition, beginning with June 2010, a number of patients- relatively small - had PET / CT 18F-NaF examination at Montbéliard, an additional examination for bone scintigraphy. At the moment, these are the nuclidic examinations mostly used in clinical practice; they are accompanied by PET / CT 18F-Colina, but this radiotracer is available especially in Centres for fighting cancer.
The year 2011 is recognized as the year of Marie Curie, a tribute to Nobel prize awarded in 1903 in physics for her studies on radioactivity – a prize awarded as well to her husband, Pierre Curie, and to Henry Becquerel who "accidentally" discovered natural radioactivity in 1896 - and Nobel prize awarded in 1911 in chemistry for the studies on radium. Marie Curie is actually the one who coined the term for "radioactivity" and the history of nuclear medicine is built on the discovery of radioactivity. Several decades later, the daughter of Marie Curie, Irene, along with her husband, Frederic Joliot Curie, will discover artificial radioactivity, a moment in time considered as a milestone in nuclear medicine. They will be awarded with the Nobel Prize in chemistry in 1935.

In the near future, Nuclear Medicine, the first speciality to ever use computers in medicine on a daily basis, will likely have a role in treating patients equal to surgery: it would not be merely "molecular diagnosis" cancer, but molecular treatment and monitoring at the molecular level of the treatment’s efficiency (Wagner, 2006, ref. 175).
I. THE PRESENT STAGE OF THE KNOWLEDGE ON THE MECHANISMS OF PROSTATE NEOPLASM CARCINOGENESIS

1. Molecular pathology of PC is complex. There are many genes involved in its pathogenesis and the environmental factors - diet and inflammation - play a role as well.
2. From an epidemiological point of view, PC has two forms: hereditary and sporadic, yet they cannot be differentiated at the molecular level and, unlike other cancers, there were not identified penetrating inherited genes which confer malignant phenotype.
3. Some polymorphisms have been associated with risk of PC as well as with increased risk of its progression.
4. There were identified several chromosomal and somatic abnormalities in CP, including the expression of oncogenes bcl-2 and the reduced expression of tumor suppressor genes, such as GSTP1, as well as changes in the expression of factors of growth and of their receptors. The highlight of TMPRSS2 fusion is considered one of the most important discoveries in molecular pathology of PC for the last 15 years, occurring in 49% of localised PC, and these have a worse prognosis than the PC not presenting this fusion (Cross, 2008 ref. 33).
5. The application of DNA microarray technology, of proteomics and metabolomics for the study of CP, has improved our knowledge regarding the initiation, development and progression for the disease (Table I).

Table I. Genetic aberrations at different stages of CP (by Porkka, 2007)

<table>
<thead>
<tr>
<th>Genetic Aberrations</th>
<th>Chromosomal Changes</th>
<th>Changes in Gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>PIN</td>
<td>loss 8p - 30% 13q - 30%</td>
<td>GSTP1</td>
</tr>
<tr>
<td>PC spotted</td>
<td>gain 6p - 20% 7q - 30% 10q - 10% 16q - 20% 18q - 20%</td>
<td>KLF6 - ? ATBF1 - ?</td>
</tr>
<tr>
<td>CP metastatic</td>
<td>8q - 5% 7p/q - 10%</td>
<td>PTEN - 60% TP53 - 30% EPHB2 - ?</td>
</tr>
<tr>
<td>CPHR</td>
<td>loss 7q - 30% Xq - 40%</td>
<td>AR - 10% (changelings)</td>
</tr>
<tr>
<td></td>
<td>gain 10q - 50% 16q - 55% 18q - 20%</td>
<td>AR - 30% (amplification)</td>
</tr>
</tbody>
</table>

6. Three current major challenges remain:
   • a better understanding of the molecular basis of cancer initiation which could help identify the markers that will differentiate between mild the aggressive disease;
   • elucidating the ways that lead to resistance to castration in order to identify new therapeutic strategies;
   • understanding the molecular mechanisms which represent the basis for bone tropism of PC, the bone metastases determining much of the PC morbidity and its mortality.
II. THE ROLE OF NUCLEAR MEDICINE INVESTIGATIONS IN DIAGNOSING AND STAGING OF THE PROSTATE CANCER

II.1. PROSTATE CANCER SCREENING
The results of the two large studies, in the U.S. and in Europe, published in 2009, evaluating the effect of screening on mortality in CP are contradictory. Currently screening in CP remains a source of uncertainty and controversy. Early detection of PC is not clearly recommended, nor contraindicated. In this case, the patient’s informed decision plays an important role in screening (Vedel, 2011, ref. 173; Evans, 2010, ref. 44 Perrin, 2008, ref. 118).

II.5. MOLECULAR STAGING OF PROSTATE CANCER
PC shows different biological behaviours. Preoperative serum PSA, Gleason score and the stage are the variables currently most used to assess the prognosis, the recurrence and the metastatic potential. As a result of early detection in PC, the patients show up with increasingly more intracapsular disease. However, a significant percentage of these patients have relapse after prostatectomy. The purpose of molecular staging for prostate cancer is to identify the genes involved in the relevant ways for the pathogenesis of prostate cancer and their use as prognostic markers.

II.6. IMAGING STRATEGY USEFUL IN DIAGNOSIS AND STAGING OF PROSTATE CANCER, OTHER THAN RADIOISOTOPES
II.6.1. Ultrasound
Cross-rectal biopsy eco guided is the standard diagnostic test in the localisation of the tumor. (Fig. 1)

![Ultrasound Images](image)

Fig. 1. 80 years old patient, diagnosed with prostate cancer, Gleason score 10; images crossing the middle region of the prostate. a) Classic ultrasound in gray scale reveals a hypo ecogene area in the left middle sided area (arrows). b) Real-time elastography reveals reduced elastic tissue at the level of hypo ecogene area of classic ultrasound (arrows). c) Colour Doppler shows increased vascularisation inside and around the tumor mass (arrows) (after Halpern, 2006, ref. 63).

II.6.2. Computed tomography has a role in evaluating the disease’s extension (Fig. 3).

![CT Image](image)

Fig. 3. Cross-section CT: suprarenal metastasis (arrow). PC hardly metastasize at the lungs, liver, or suprarenal pleura (after Kundra, 2007, ref. 90).

II.6.3. Magnetic resonance imaging has a role in tumor localization (Fig. 4).
II.6.3.1 *Spectroscopic magnetic resonance imaging* allows the assessment of prostatic metabolites coline and citrate. Compared with normal peripheral zone, there are significantly higher levels of coline and significantly lower levels of citrate in the areas with cancer (Fig. 5).

![Fig. 5. Prostate cancer detected in the left peripheral region. A. T2-weighted MRI cross section and three-dimensional MRSI spectrum. B. Corresponding three-dimensional MRSI spectrum indicating the presence of an apparently aggressive tumors (the pick of the coline is very high and that of the citrate very low) in the left peripheral zone. C. RM DWI (diffusion of MRI) reveals prostate tumor in the same place as T2 MRI and IRMS. D. Representative spectrum taken from the region of healthy prostate tissue and tumoral. PPM, parts per million (after Carroll, 2006, ref. 27)](image)

II.7. USEFUL RADIOISOTOPES INVESTIGATIONS IN DIAGNOSIS AND STANDING OF PROSTATIC MALIGNANCIES

II.7.1 *Bone scintigraphy*: it does remain the standard imaging method for identifying bone metastases (Fig. 7).
II.7.2. **Radioimmunoscintigraphy**
Unlike anatomical imaging, radioimmunoscintigraphy detects signals from radiomarked antibodies which recognize the prostatic tissue.

Fig. 8. **Merged SPECT-CT images.** A. Radioimmunoscintigraphy. B. Computed tomography. C. **Merged images.** Periaorti node (PAN). Bo: activity at the colon level. A: aorta, IVC: inferior vena cava. (After Keane, 2006, ref. 82).

II.7.3. **PET-CT**
In the last 15 years PET-CT has become one of the most innovative and important applications in oncology imaging (Rusu, 2006, ref. 129).
• **18 F-FDG** indicates a more important capture in tumors with high Gleason score; there is a good correlation between PSA level and FDG caption (Fig. 9) (Jadvar, 2011, ref. 75).

Fig. 9. **67 year old man with prostate cancer confirmed at biopsy (Gleason 8), with PSA of 14.6 ng/ml.** PET / CT 18F-FDG shows an intense hypermetabolism in the right prostate lobe (SUV 7.7) (after Jadvar H, 2011, ref. 75).
• **11 C-acetate.** The acetate participates in the synthesis of the cytoplasmic lipid, which is probably increased in tumors. In primary tumor detection it is more sensitive than 18F-FDG.

• **11 C-Colina.** 11 C-colina PET is a sensitive and accurate method in preoperative staging of pelvic lymph nodes in prostate cancer (fig. 11).

![Image](image.jpg)

**Fig. 11. PET-CT 18-F Colina.** Patient with prostate cancer treated by radical prostatectomy, in biochemical relapse. Abnormal accumulation of radiopharmaceutical in the right internal iliac lymph node (arrows) (After Jadvar, 2011, ref. 75).

• **18 F-Fluoride** seems to be more sensitive for detecting bone metastases if compared to 99mTc-MDP bone scintigraphy.

### II.7.4. Lymphoscintigraphy

Currently there is no non-invasive means to identify with certainty the patients with node invasion. The main means of identifying lymph node metastases remains surgical staging lymphadenectomy. Lymphoscintigraphy is used to identify the lymph node sentinel which will be subsequently submitted to biopsy.

### II.8. Conclusions

Ideally, imaging could accomplish in PC:
• diagnosis, localization and characterization (mild vs. lethal) of primary tumor
• determination of extra capsular extension
• guidance and evaluation of local therapy of the disease limited to prostate
• staging loco regional lymph nodes
• detecting the recurrent or metastatic disease
• guidance in radiotherapy
• prognosis of tumor response to therapy and systemic salvage
• monitoring of the active surveillance and defining a trigger for definitive therapy
• prognosis of the time until to hormone refractory tumor stage and of overall survival (Jadvar, 2011, ref. 75).

Recent development of imaging techniques, especially PET and MRI, could lead to significant improvements in detecting and staging located PC. Diffused MRI could improve the tumor detection - including by guiding the targeted biopsy, especially in the cases with patients who had previously negative biopsies - staging, determining the aggressiveness of the tumor and monitoring the post-treatment evolution (Kim, 2011, ref. 86).
III. THE TREATMENT OF PROSTATE METASTASIS. THE ROLE OF RADIONUCLIDE THERAPY

III.1. CURRENT TREATMENTS OTHER THAN RADIONUCLIDES

III.1.1. Newly diagnosed prostate cancer
There are several treatment options for newly diagnosed prostate cancer, treatments with curative intent or not, depending on the stage of the disease, in view of associated co morbidity and of patient preferences as well (fig. 12).

![Treatment options for newly diagnosed prostate neoplasm](after Wilkinson, 2008, ref. 179)

III.2. RADIONUCLIDE TREATMENT

In HRPC painful bone metastases represents one of the prevalent clinical problems. Pain relief can be achieved by local radiotherapy, chemotherapy and treatment with biphosphonates. Another effective way of treatment is radionuclidic treatment (Bagi, 2005, ref.13, Henk, 2007, ref. 68).

1. 50% of the patients receiving radionuclide therapy for painful bone metastases experience decrease of pain.
2. 32P and 89 Sr has a natural affinity for bone, while 186 Re, 188 Re and 153 Sm requires their binding to diphosphonates.
3. Several parameters are associated with a favourable response to pain: good OMS status during the treatment, higher values of serum Hb and a limited number of bone metastases.
4. Myelosuppression with thrombocytopenia and neutropenia occurs with a similar frequency, but the administration of radionuclides with shorter half-life appear to be accompanied by a faster return to the initial number.
5. Repeated administration of radionuclides is possible at intervals of at least 6 weeks.
6. Concomitant administration of CHT proved to be effective in improving the effect on the decrease of pain and on the occurrence of new painful bone metastases. (Bagi, 2005, ref. 13).

IV. THE ROLE OF NUCLEAR MEDICINE EXPLORATION IN MONITORING THE PROSTATE CARCINOMA

IV.1. MONITORING THE EVOLUTION AFTER THE CURATIVE TREATMENT

The patients diagnosed with PC treated curatively are usually monitored at least 10 years (fig. 13).
IV.2. MONITORING THE EVOLUTION AFTER HORMONOTHERAPY

Recurrence of cancer after castration

Its exact definition is controversial. Prostate cancer resistant to castration (CRPC) is different from hormone-resistant prostate cancer (HRPC). CRPC is still hormone-sensitive, responding to secondary hormonal manipulation (suppression of ant androgens, estrogens, corticosteroids). HRPC is resistant to all hormonal treatments (Fig. 14).
V. THE OBJECTIVES OF THE STUDY

For the study I formulated the following hypothesis:

A) Between the results of bone scintigraphy, the total PSA value and the Gleason histological score there may be a direct correlation.

B) Bone scintigraphy is an important element in the management of prostate cancer, in staging and monitoring the evolution.

C) Imaging PET / CT 18NaF can be an effective method for detection of bone metastases in prostate cancer.

D) Metabolic therapy with 153Sm can be an effective alternative for pain treatment in bone metastatic prostate cancer.

In order to support the hypotheses stated above, I had the following objectives:

1. Correlation of total PSA value, of Gleason histological score and of bone scan results for different age groups.

2. Comparison of sensitivity and specificity of two types of nuclear medicine exams - bone scan with diphosphonates and MET / CT 18F-NaF - in detecting the bone metastasis of prostate cancer.

3. Assessing the efficiency and the toxicity of the QUADRAMET treatment in patients with painful bone metastases from prostate cancer.

4. The role of bone scintigraphy in managing the prostate cancer in the context of other imaging and laboratory investigations.

I have analyzed 4 lots of patients, one prospective (lot 2), and three retrospective:

Oncology Clinic from the Polyclinic no. 1

- Lot 1: 180 patients with bone scintigraphy recommended for the evaluation of bone metastases in the initial assessment or in the development of prostate cancer. Bone scintigraphies were performed in the Laboratory of Nuclear Medicine of the University Hospital "St. Spiridon "Iasi, in 2004-2009. For PSA values and histological results I checked out the files of the patients from the archive of the Department of Oncology and Radiotherapy of "St. Spiridon " Hospital Iasi as well as the archive of the.

- Lot 2: 13 patients with bone scintigraphy and PET / CT 18F-NaF, for the evaluation of prostate cancer bone dissemination. Scintigraphic acquisitions were made in the Laboratory of Nuclear Medicine Hospital in Montbéliard, France, from June to December 2010.

- Lot 3: 57 patients treated palliatively with 153Sm EDTMP for bone metastatic prostate cancer, from 2001 to 2011, in the Nuclear Medicine Department of the University Hospital of Besançon, France.

- Lot 4: 178 patients diagnosed with prostate cancer who had bone scintigraphy for initial staging, restaging or for therapy evaluation. For this lot I monitored the patient’s age at diagnosis, the percentage of patients with metastases at diagnosis, the circumstances at diagnosis, the results for digital rectal
examination and the correlation of these results with Gleason score, the associated malignancies, the clinical or pathological stage at diagnosis, the PSA value at diagnosis, the concordance surgery Gleason score - biopsy Gleason score, the time from diagnosis to RCB depending on the initial local treatment, the number of patients with previous negative biopsies, the number of the deceased patients and the cause of death.

Of the 178 patients, 37 had bone metastases; they were considered a lot of study for which I examined the age at diagnosis, the PSA at diagnosis, the general time from diagnosis to metastases, the time from diagnosis to metastasis depending on the initial treatment, the correlation between the initial clinical or pathological stage and the occurrence of metastases, the correlation Gleason score – metastasis and the correlation between the results of the digital rectal examination and the metastasis.

A special group have been the patients with metastases at diagnosis. Another distinct group is represented by the patients likely having family PC.

VI. INTRODUCING THE FOUR LOTS OF PATIENTS

VI.1. A COMPARISON BETWEEN TOTAL PSA, GLEASON SCORE AND THE RESULTS OF BONESCAN FOR DIFFERENT AGE GROUPS

VI.1.1. Introduction

Currently, bone scan performed with 99mTc - methylene diphosphonate (99mTc-MDP) is the standard imaging method used to detect bone metastases. PSA is the biomarker used in screening, diagnosis and monitoring the evolution of prostate cancer. Researches have shown a positive relationship between the PSA value and the presence of bone metastases (Lai, 2009, ref. 91; Chow, 2005, ref. 30). The purpose of this study was to compare the value of PSA with the pathologic Gleason score and with the results of bone scintigraphy for different age groups (Albersten, 1998, ref. 5).

VI.1.2. Material and methods

Bone scintigraphy was performed by using a double-head gamma camera (Axis - Philips, or Siemens). Image acquisition was performed 2-3 hours after the intravenous injection of 15-20 mCi (740 MBq) of 99mTc-MDP depending on the body weight. Scintigraphic examination consisted of whole body planar images to which were added static images focused on areas of interest or tomoscintigraphic images in order to have a higher resolution.

VI.1.3. The study group

Between 1 January 2004 to March 31 2009, 180 patients diagnosed with prostate cancer performed bone scintigraphy in our Department of Nuclear Medicine. Bone scintigraphy has been recommended for initial pre-treatment staging or in the case of increase value of PSA during disease progression or for bone pain, regardless of the PSA.

For 86 patients the PSA was known, that representing the value of PSA at diagnosis (in the case of newly diagnosed patients) or the maximum value of PSA (in the case of patients evaluated during the treatment). Out of the 86 patients, the Gleason score is known for 55.

The patients were divided into three age groups: • ≤ 60 years; • 61-70 years; • > 70 years. The 86 patients were included, also, depending on the value of PSA in 5 groups: • 4 - 10 ng / ml, • 11 - 20 ng / ml, • 21-50 ng / ml, • 51-99 ng / ml, • ≥ 100 ng / ml.

In this study group there were not patients with PSA values ≤ 3 ng / ml.

The 55 patients with known Gleason score were divided into three groups: • <7, • = 7, • > 7. The scintigraphic results allowed for inclusion of the patients into 3 groups: • without bone metastases; • with a probability (low, intermediate or high) of bone metastases.
Depending on the number of metastases, the 33 patients with metastatic bone scintigraphy were classified in the four groups of Soloway: • I degree - less than 6 metastases (a lesion of an entire vertebral body is considered as two metastases); • II degree - between 6 and 20 metastases; • II degree: more than 20 metastases, but less than a super scan (fig. 16); • IV degree: super scan (diffuse, intense, symmetric radiotracer fixation, with the absence of the kidney shadows).

The results of our study can be summarized as following (Table II and III):

1. Among the patients with PSA t higher than 20 ng / ml, themselves considered at high risk for bone metastases according to CCAFU recommendations in 2007, 21 (32.81%) out of 74 patients do not show bone metastases.

2. For PSA t higher than 50 ng / ml: • All the 6 patients under the age of 60 years show metastases (5 patients) or high probability of metastasis (1 patient); • 10 (58%) of the 17 patients from the group of 61-70 years old show metastases, 1 (5.88%) show a low probability and 1 (5.88%) show intermediate probability. • 15 (62.5%) out of 24 patients aged over 70 years show metastases, and 1 (4%) low probability. • 13 (27.65%) out of 47 patients from this group do not have metastases (7 aged 61-70 and 6 aged over 70 years).

3. 6 (21.42%) out of 28 patients with PSA t> 100 ng / ml do not show metastases.

4. Out of the 8 patients with PSA t = 11-20 ng / ml, with intermediate risk of metastasis, 1 patient has bone metastases, 1 degree Soloway (fig.14).

5. Out of the 11 patients with PSA t = 4-10 ng / ml, 1 patient has intermediate probability.

6. 10 (43.4%) out of 23 patients with Gleason score <7, themselves considered with low risk for developing metastasis, show up secondary bone lesions (6 patients - 26%) or low probability of metastasis (4 patients - 17.4%) (Table II, Fig. 19).

7. 7 (50%) of 14 patients with Gleason score = 7 show scintigraphic bone metastases.

8. 10 (56%) out of the 18 patients with Gleason score> 7 show metastases (8 patients - 44%) or the probability of metastasis (2 patients - 12%).

9. There is no direct link between Gleason score and the presence of metastases for the groups with intermediate risk (14 patients) and high risk (18 patients). It is likely that this incongruity is due to the small number of patients.
TABEL II. Corelație rezultate scintigrafice - Scor Gleason

<table>
<thead>
<tr>
<th>Number of cases</th>
<th>Gleason score</th>
<th>Metastases present</th>
<th>Probability of metastasis</th>
<th>Metastases absent</th>
</tr>
</thead>
<tbody>
<tr>
<td>23</td>
<td>&lt;7</td>
<td>6</td>
<td>4</td>
<td>13</td>
</tr>
<tr>
<td>14</td>
<td>≥7</td>
<td>7</td>
<td>-</td>
<td>7</td>
</tr>
<tr>
<td>18</td>
<td>&gt;7</td>
<td>8</td>
<td>2</td>
<td>8</td>
</tr>
</tbody>
</table>

Fig. 19. Correlation scintigraphic results - Gleason score. Graphical representation of data in Table II.

3. The two patients with metastases in the group 21-50 shows metastasis PSA t = grade II Soloway.
4. Of the 30 patients with metastases and PSA t > 50 ng / ml, 8 represents the level II, 16 grade III (Fig. 15) and 4 grade IV Soloway (fig.16).

TABLE III. Correlation scan result - total PSA - age (M - metastases, P - probability)

<table>
<thead>
<tr>
<th>number cases</th>
<th>PSA (ng/ml)</th>
<th>age (years)</th>
<th>M. present</th>
<th>Grad Soloway</th>
<th>M. absent</th>
<th>P. low</th>
<th>P. intermediary</th>
<th>P. high</th>
<th>No. of cases (partly)</th>
</tr>
</thead>
<tbody>
<tr>
<td>14</td>
<td>4-10</td>
<td>50-60</td>
<td>-</td>
<td>-</td>
<td>4</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>61-70</td>
<td>-</td>
<td>-</td>
<td>6</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;70</td>
<td>-</td>
<td>-</td>
<td>3</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
VI.1.5. Conclusions
Our study confirms that the probability of bone metastases in an increased PSA is inversely proportional to the age, probably due to benign prostatic hyperplasia common in elderly patients. There is not a direct correlation between Gleason score and bone scan results at intermediate and high risk groups of bone metastases.

VI.2. COMPARISON OF SENSITIVITY AND SPECIFICITY OF BONE SCINTIGRAPHY DIPHOSPHONATES WITH PET-CT 18F-NaF

VI.2.1. Introduction
Evaluation of bone metastases from PC is now being made by bone scintigraphy with diphosphonates, as the first exploratory method. Rebirth of scintigraphic examination with 18F-NaF, mainly due to technological progress of hybrid PET-CT, allows also the evaluation of metastases in the entire skeleton.

VI.2.2. The purpose of the study
Our study compares the sensitivity and specificity of bone scintigraphy HMDP and PET-CT 18F-NaF in detecting bone metastases of PC.

VI.2.3. Materials and methods
Bone scintigraphy was performed using a dual-head gamma detection cameras (Axis - Philips), equipped with a large rectangular detector with a high resolution and low energy collimator, the peak energy of Tc - 140 keV + / - 20%, at 3 hours after the intravenous injection of 99mTc-HMDP 10 MBq per kilogram of body mass. There were made acquisitions for the whole body, as well as SPECT focused on different regions with anomalies on planar whole body images.

PET-CT examination was performed with a PET camera (Siemens) and the images were subsequently fusioned with the CT images. There were made whole body acquisitions. The images were recorded one hour after an injection of 2 MBq/kg per kg of body weight 18F-NaF. The two tests were conducted within an average time of 11.7 days, with the extremes from 5 days to 56 days, in a nuclear medicine department at Montbéliard Hospital, France.

VI.2.4. The study group
13 patients diagnosed with PC have been investigated with a double nuclear medicine exploration, bone scintigraphy with 99mTc-HMDP and PET-CT with 18F-NaF during June to December 2010. The average age of the patients was 72 years, with the extremes from 62 to 86 years. The indication of radioisotope exploration was represented by the evaluation of the extension of the newly diagnosed neoplasia or by the detection of the bone extension during the evolution of PC in the case of increasing PSA values.

VI.2.5. Results
Comparing the results obtained by PET / CT using 18F-NaF with those from the bone scintigraphy (OS) in detecting the bone metastases, I identified the following cases:

- Examination PET / CT negative and scintigraphy examination negative: PET / CT - / SO -;
- Examination PET / CT positive and scintigraphy examination positive: PET / CT + / SO +;
- Examination PET / CT positive and scintigraphy examination negative: PET / CT + / SO -;
- Examination PET / CT negative and scintigraphy examination positive: PET / CT -- / SO +;
- Probability of metastases, both in PET / CT study and bone scintigraphy.
- Probability of metastases at PET / CT examination and normal examination at bone scintigraphy.

PET / CT - / SO-
Only one patient was part of this group without having images of metastases, neither on scintigraphic images nor on those of PET / CT (Fig. 20).

Fig. 20. TEP 18F-NaF - MIP incidence (maximum intensity projection) multiple. The examination reveals degenerative phenomena in the spine and in the large joints, especially in the left knees and
ankles, and in the bilateral rizartroza thumb, without any site suspecte of secondary bone dissemination. (Laboratory of Nuclear Medicine Archive - Hospital of Montbéliard, France)

**PET / CT + / SO +**

This group was made up of 6 patients. Note that in all cases the lesions visible on bone scan were found in the PET-CT study. Only in one case a single lesion was found in both studies (one lesion at the level of ischiopubic ramus). In the other 5 cases, the PET-CT study showed more lesions than the conventional bone scintigraphy. Thus, in the case of a 76 years old patient, having the Gleason score 6 and the PSA 10.10 ng / ml, having as the recommendatation the initial assessment of the tumoral extension, PET-CT showed a site on the left parietal bone site, besides the costal site noticed on the bone scintigraphy (fig. 21).

![Bone scintigraphy images](image)

**Fig. 21.** Bone scintigraphy (06/04/2010): a) the whole body - anterior and posterior incidence and pelvis centered images. b) Tomoscintigraphy centered on thorax; PET / CT (June 9, 2010): c) PET whole body, multiple incidences d) images PET fusionned with CT images, centered on the skull). Suspect of the posterior arch of the 8th right ribs highlighted on bone scan. PET examination finds this anomaly and, moreover, highlights a hote area on the left parietal. (Laboratory of Nuclear Medicine Archive - Montbéliard Hospital).

**• PET / CT + / SO -**

In the group with abnormal fixation for the radiotrasor only for the PET / CT study, therefore with normal scintigram, two patients were included. One of them, a man of 73 years old, having biochemical relapse with no significant change of de radiopharmaceutical fixation, either for bone scintigraphy or for PET-FDG examination, presents three sites of metastases at PET-CT examination with 18F-NaF.
• **PET / CT - / SO +**
  There were no patients in this group to have been shown suspicious abnormalities in bone scintigraphy, while their PET / CT examination was normal.

• **Probability of metastases in both studies**
  Two patients were diagnosed by scintigraphy with the probability of bone dissemination scintigraphy in both studies. One of them has shown at bone scintigraphy the probability of bone dissemination on the right sacroiliac bone, in its upper part; the same issue is found on the examination with PET / CT. In addition, the latter examination shows the probability of metastasis for the posterior arch of the second dorsal vertebrae.
  The second patient from this group shows a small left scapular site, an anomaly found in both radioisotope exploration, suggesting the probability of dissemination at this level.

• **The probability of metastases in the PET / CT study and normal examination in bone scintigraphy**
  2 patients have been part of this group. The first one, a man of 73 years, shows no abnormalities of fixing the radiotracer to the bone scintigraphy, but PET-CT highlights a hypermetabolic retro-orbital site, at the right temporal bone level, whose etiology remains to be determined.

**VI.2.6. Discussion:**

• 18F-Fluoride is a PET radiotracer with bone tropism emitting positrons which is assessing the osteoblast activity (Beheshi, 2009, ref. 16). It was first described 40 years ago, yet it has been extensively investigated with respect to bone metastases only in recent years due to the improving of PET / CT devices (Cook, 2010, ref. 32, Rusu, 2007, ref. 131).

• 18F-fluoride capture reflects the blood flow and bone remodeling. 18F-Fluoride is greedily and early accumulated in the cortical bone in the case of bone response to a metastasis. In 2008 it was authorized on the French market, including for the evaluation of bone metastases of PC (Huchet, 2009, ref. 72).

• The assessment of 18 F-fluoride kinetics using PET quantitative methods allows for the characterization of lesions and monitoring of the response to therapy. Although the mechanism of 18F-fluoride capture corresponds to osteoblastic activity, this tracer is also sensitive in detecting the lytic metastases and those of bone marrow by identifying osteoblastic changes accompanying them, even when they are minimal (Even-Sapir, 2007, ref. 46).

• Positron emission tomography is a noninvasive functional imaging technique that allows highlighting regional metabolic processes. PET is coupled with a imaging morphological method. Because of the fact that the functional changes from the tumoral processes precede the morphologic changes, PET imaging provides a new dimension to classical imaging (Boujelbene, 2011, ref. 23).

• The number of the evocative lesions of bone metastases highlighted by PET / CT examination is superior to that detected by bone scintigraphy, so PET / CT has an important role in monitoring the PC, especially in the detection of its recurrence and of bone metastases (Bouchelouche, 2009, ref. 22).

• In the case of our study, two patients had PET / CT positive and normal scintigraphy, and 5 out of the 6 patients having both tests positive had more lesions at the PET / CT exam in comparision with SO. In one of the two cases of bone dissemination probability, a probability assessed both by SO and PET / CT, the PET / CT exam revealed a new hypermetabolic site in comparision to SO. 2 patients in our study had negative SO and a probability of bone dissemination at PET / CT. It can thus be inferred that the sensitivity of PET / CT method is superior to bone scintigraphy.

• The specificity of PET / CT is much improved by the presence of CT, with its essential role in attenuating the correction, leading to greater accuracy by reducing artifacts (Even-Sapir, 2006, ref. 7).

  Moreover, CT helps to locate the lesions and allows for their morphological characterization and for a better differentiation of metastasis in benign lesions. In our study, CT has differentiated intramedullary location of costal sites without cortical disruption, that being characteristic to bone metastases, in contrast to fractures (Fig. 23). However, NaF is fixed like diphosphonates in the areas of hyperemia and of important osteogenesis, including at the level of inflammatory or infectious sites, osteoarthritis,
post-traumatic, as well as in various bone diseases (Paget, metabolic bone diseases, osteonecrosis).
• The criteria for interpretation are similar to those used in the interpretation of bone scintigraphy.
There are osteolytic processes that can not be detected. The degree of captation does not differentiate
the malignant lesions from the benign ones. PET / CT 18F-NaF could be negative in intense sclerotic
lesions , which is probably reflecting the effect of treatment (Beheshti, 2008, ref. 17).
• PET / CT examination is faster than bone scintigraphy with diphosphonates (Grant, 2008, ref. 61).
Dosimetry is similar for the two exams (Segal, 2010, ref. 140).
• 18F-fluoride could provide a more sensitive "conventional" bone scintigraphy. PET with 18F-fluoride
is superior to FDG in the evaluation of tumors which do not capture FDG, although "early disease"
FDG has clear advantages over 18F-fluoride (Langsteger, 2006, ref. 96).
• Unlike PET / CT Colina, which is recommended in non invasive restaging of PC, in the case of increase
of PSA after radical treatment, the use of NaF in clinical practice requires yet to be confirmed (Picchio,
2011, ref. 119).

VI.2.7. Conclusions

1. PET / CT 18F-NaF is more sensitive and more specific than bone scintigraphy in detecting bone
metastases, including bone tomoscintigraphy.
2. For similar dosimetry, 18F NaF PET provides a faster study then bone scintigraphy with
diphosphonates.

VI.3. ASSESSING THE EFFICIENCY AND THE TOXICITY OF QUADRAMET TREATMENT
BONE METASTATIC PROSTATE CANCER

VI.3.1. Introduction
Radionuclide therapy is a palliative treatment method used for patients with pain caused by bone
metastases, especially when bone dissemination is multiple.

VI.3.2. Material and methods
The purpose of this retrospective study is to evaluate the effectiveness and the toxicity of Quadramet
treatment in the case of the patients diagnosed with bone metastatic prostate cancer.
For each patient, before administering the metabolic treatment, it was performed bone scintigraphy in
about 3 hours after intravenous injection of 10 MBq of 99mTc-HMDP per kilogram of body mass. The
exam consisted of acquisitions of the whole body, and in each case, centered static images or
tomoscintigraphic, depending on the anomalies of fixation for the radiotracer on the images of the
whole body.
Radionuclide treatment consisted of an intravenous dose of 37 MBq of 153 Sm-EDTMP (Ethylene
diamine tetramethylene phosphate) per kilogram body weight. Quadramet administration was
preceded and followed by a perfusion of 500 ml of physiological serum. The patient was hospitalized in
our laboratory for 5-6 hours. At 48-96 hours after Quadramet administration, a whole body scan test
was performed to confirm the fixation of the radiopharmaceutical at the bone metastases level,
highlighted by bone scintigraphy with diphosphonates.
Clinical examination performed before administering Quadramet, as well as in 6 weeks post
therapy, was to assess the pain locations and their intensity, using visual analog scale method and to
evaluate the OMS life quality status. After therapy, it was monitored the presence of the phenomenon
of "flare". It was also noted the treatment for before and after antalgic therapy.
By biological evaluation prior to therapy it was monitored the renal function and the ionogram.
PSA - tumor marker in PC - was measured before the treatment and in 6 weeks after the treatment.
CBC was analyzed pre and postoperatively, to assess metabolic haematoxicity treatment.
The access to the Axigate database, where I found the history of patients’s disease, to the Sirilog
database, where are shown the examinations carried out by the patients, as well as to the patients
records within the Nuclear Medicine Laboratory at Besancon allowed me to evaluate the effectiveness
of the treatment by analyzing the OMS status of life quality, the evolution of pain using visual analog
scale and the change in antalgic treatment. I monitored, also, the presence of “flare” phenomena and its predictive effect on the outcome of the therapy, as well as the evolution of PSA. Haematological toxicity of Quadramet was demonstrated by the results of CBC.

VI.3.3. The study group
From May 1991 until May 2011, 57 patients diagnosed with prostate cancer with painful bone metastases have received radiopharmaceutical treatment in the Nuclear Medicine Department of Besançon. Out of these, 5 patients had repeated the treatment with Quadramet, and 3 had three cures of Quadramet. The metabolic treatment was not administered in cases of the patients who received chemotherapy or external radiotherapy in the last 6 weeks, neither in the case of those treated with diphosphonates in the last 3 months.

The time from PC diagnosis to the treatment with 153 Sm was known for 42 patients. The average of this time is 5.45 years, with extremes between a few months from diagnosis for patients who had metastases at diagnosis up to 28 years after diagnosis (only 4 patients with a period over 10 years) for patients who developed late metastases.

IV.3.4. Results and discussion
153 Sm-EDTMP is a therapeutic agent consisting of a radioisotope - 153 Sm - and a chelate tetraphosphonate - EDTMP. The β particle of the radiotrasor (average energy of 233 keV) has a path of 3.1 mm in soft tissues and 1.7 mm in the bone marrow which limits the irradiation of bone marrow and other adjacent tissues. Physical half-life time is 46.3 hours (Chow, 2005, ref. 30). The radioisotope emits a gamma radiation of 103 keV (29%), which allows the imaging (Lam, 2008, ref. 93). 153 Sm-EDTMP capture is similar to diphosphonate captation in bone scintigraphy (Fig. 30).

Fig. 30. a) Whole body bone scintigraphy (23/05/2006). Multiple secondary dissemination in the axial skeleton and appendicular
b) Whole body scan two days after Quadramet (22/06/2006). Hiperfixantes sites overlapped of those from the bone scintigraphy (Archive of Nuclear Medicine Laboratory - University Hospital, Besançon, France).

a. Antalgic effectiveness of Quadramet
In our study, the effect of radionuclide therapy was evaluated primarily clinical - assessing the decrease, the persistence or worsening the pain at 6 weeks after Quadramet. Secondly, the antalgic effect was assessed with the help of the visual analogue scale. The antalgic effectiveness of vectorial internal radiotherapy was also assessed for the lot of patients with repeated administration.

- Clinical assessment – the characterization of bone pain after six weeks from Quadramet administration
Out of the 51 treatments, 38 (74.51%) were followed by a positive response to Quadramet, 15 (29.41%) recording a total attenuation of pain, and 23 (45.09%) decrease of pain: significant decrease (8 patients - 15.68%), moderate (6 patients - 11.76%) or partial (9 patients - 17.64%).
The absence of pain decrease was recorded in the case of 10 treatments (19.61%) and worsening the pain was reported in 3 treatments (5.88%), with a total of 13 ineffective treatments out of 51 (25.49%) (Table IV).

**TABLE IV. The distribution of the number of treatments depending on the characterization of pain development after administrating 153 Sm.** The evaluation has taken place at 6 weeks after radionuclide treatment.

* In this category are includes also the patients who have experienced loss of pain up to 5 weeks after the treatment, followed by their recurrence.

<table>
<thead>
<tr>
<th>Characterization of pain post Quadramet</th>
<th>Number of treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loss of pain</td>
<td>15</td>
</tr>
<tr>
<td>Important improvement</td>
<td>8</td>
</tr>
<tr>
<td>Moderate improvement</td>
<td>6</td>
</tr>
<tr>
<td>Partial improvement*</td>
<td>9</td>
</tr>
<tr>
<td>Absence of pain improvement</td>
<td>10</td>
</tr>
<tr>
<td>Pain worsening</td>
<td>3</td>
</tr>
</tbody>
</table>

- Assessing the evolution of pain using visual analog scale
19 patients have self-assessed the pain before and after the treatment with Quadramet EVA analogue-visual scale. (The patient receives a ruler graduated from 0 to 10; 0 degree meaning no pain and 10 degree meaning unbearable pain; on this scale the patient indicates manually the intensity of the pain he is complaining.) 14 patients (73.68%) mentioned a decrease of pain by an average of 3.05 points (out of 10), 2 patients (10.52%) perceived the same degree of pain and 3 (15.78%) accused an increased pain with an average of 1.66 points out of 10 (fig. 35).

- Antalgic effectiveness of Quadramet at repeated administration
If the case of the three patients, each having three radionuclidic palliative treatments, the therapy was always effective. Among patients treated twice, 4 showed improvement at one of the treatments, but therapy was ineffective at its repetition (3 cases) or - in one case – the therapy was initially ineffective and subsequently effective. The therapy was effective at the administration of two doses in the case of a patient.
In conclusion, Quadramet was effective in 74.5% of the cases (51 treatments) in regard to decrease or loss of pain. 73.68% of 19 patients mentioned - using visual analogue scale – the decrease of pain with an average of 3.05 points (10 points). Quadramet allowed for the reduced dosage or interrupting the treatment for 40.90% of the patients (from a total of 22). The antalgic effectiveness of Quadramet in our study is comparable to that found in other studies, 70-80% (Klingelschmitt, 2002, ref. 87; Dolezaj, 2007, ref. 39; Liepe, 2005, ref. 102; Liepe, 2007 , ref. 103, Lam, 2007, ref. 92).

b) Change in pain relief medication
9 patients (40.90%) have reduced or interrupted the posology of the antilalgic treatment, thus demonstrating the efficacy of Quadramet treatment. The treatment has remained unchanged in the case of 9 patients (40.90%) and the posology was increased in the case of 4 patients (18.2%) (Table VI).

TABLE VI. The distribution of the number of patients depending on Quadramet effect over the antalgic medication.

<table>
<thead>
<tr>
<th>The effect of Quadramet on antalgic therapy</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interruption of therapy</td>
<td>2</td>
</tr>
<tr>
<td>Reduction of dosage</td>
<td>7</td>
</tr>
<tr>
<td>Treatment unchanged</td>
<td>9</td>
</tr>
<tr>
<td>Increase of dosage</td>
<td>4</td>
</tr>
</tbody>
</table>

In the study of Liepe, 13% of the patients abandoned the antalgic therapy and have shown no pain (Liepe, 2007, ref. 103).

c) The evaluation of OMS quality of life score
Out of the 23 patients with known OMS score, assessed before and after the treatment with Quadramet, 3 (13.04%) are showing the improvement of the score by 1 level, 17 (73.91%) do not change the score, and 3 patients (13.04 %) are showing a degradation of OMS score by an average of 1.33 (Table VII and Fig. 36).

TABLE VII. The distribution of the number of patients depending on the evolution of OMS quality of life score.

<table>
<thead>
<tr>
<th>The evolution of OMS quality of life score</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>improvement</td>
<td>3</td>
</tr>
<tr>
<td>same score</td>
<td>17</td>
</tr>
<tr>
<td>worsening</td>
<td>3</td>
</tr>
</tbody>
</table>

Most patients - 17 out of 23 (73.91%) have the same OMS quality of life score, while 3 patients have improvement and 3 have degradation of OMS score. The result can be explained by the fact that this scale which is presenting values from 0 to 5 is less sensitive (Klingelschmitt, 2002, ref. 87), so then it is required a significant improvement of life quality to move from one level to another. In addition, our assessment was performed only 6 weeks after the treatment, therefore not allowing the assessment for the treatment’s effect on a long range.
Fig. 36. Graphical representation of the distribution of the number of patients depending on the evolution of OMS life quality score (data in Table VII).

d) "flare" phenomenon
Out of the 22 patients for whom it was noted the presence or the absence of "flare" phenomenon - a temporary increase of pain after metabolic therapy - 12 patients (54.54%) manifested this phenomenon, and 9 (40.90%) did not. 1 patient (4.54%) presented the "flare" phenomenon during an effective treatment but did not during the subsequent ineffective treatment.

In our study, there is no direct correlation between the presence of "flare" phenomenon and the response to Quadramet.

f) Haematological toxicity of Quadramet therapy
Out of the 29 patients, 11 (37.93%) do not show up haematological toxicity, 11 (37.93%) show a reduced toxicity, and 5 patients show moderate toxicity (grade II). 1 patient has tricitopeny (unknown grade), and 1 patient passes from grade II to grade III anemia. None of the patients had grade IV toxicity (Table IX). In total, 62% of patients experienced grade II haematotoxicity or lower grade.

TABLE IX. The distribution of the patients depending on the evaluation of hematologic toxicity.

<table>
<thead>
<tr>
<th>Assessing the hematologic toxicity</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absent</td>
<td>11</td>
</tr>
<tr>
<td>Reduced (degree 0 sau I)</td>
<td>11</td>
</tr>
<tr>
<td>Moderate (degree II)</td>
<td>5</td>
</tr>
</tbody>
</table>

Sartor (ref. 135) observed a toxicity of grade two or lower for the leukocyte and for the trombocytes in the case of 92%, respectively of 97% of patients who received 1 mCi of 153 Sm lexidronam per kg of body weight. Grade 3 of leukopenia was observed for less than 7% of patients, regardless of the number of administration of 153Sm (Sartor, ref. 136).

VI.3.5. Conclusions:
1. Systematic radionuclide radiotherapy has obvious advantages:
   - an important antalgeic effect; in our study 74.5% of the patients experienced disappearance or relief of pain;
   - 9 of 22 patients (40.90%) have reduced or interrupted the antalgic therapy.
   - simultaneous treatment of all secondary bone sites, while the selective absorption in bone metastases limits the irradiation of normal tissues;
   - a single intravenous injection to a patient who requires only a few hours of hospitalization;
   - the use of early radionuclides in managing the disease could be a complementary therapy or may delay the use of other palliative methods, such as external radiotherapy, chemotherapy, hormone therapy, bisphosphonates and analgesics
   - metabolic therapy may have not just only a palliative effect, but also a tumoricidal or tomorostatic effect. Early use of radionuclides in pain therapy may limit cancer progression by inhibiting the development of oligometastasis (Hillegonds, 2007, ref. 70).
   - in addition to the important effect of painkiller, radionuclide therapy allows for improving the mobilization for many patients, reducing the dependence on painkillers and offering a better quality of life (Lam, 2008, ref. 93).
   - there are several parameters associated with a favorable response to pain: good OMS status during the treatment, higher values of serum Hb and a limited number of bone metastases.
   - simultaneous administration of CHT was proved to be effective in improving the effect on pain relief and on the appearance of new metastatic bone pain (stick, 2005, ref. 13).
   - Repeated treatments and combining radionuclidic treatment with other therapies, such as bisphosphonates, chemotherapy and / or external radiotherapy are possible. In addition, combined therapy could provide a more effective pain relief caused by bone metastases (Anderson, 2007, ref. 6).
   - Particularly, the association of docetaxel - the only therapy proven to have an effect on prolonging life in the case of patients with metastatic HRCP, the standard therapy in the case of these patients - with 153 Sm-EDTMP can be performed at normal, repeated doses (Morris, 2009, ref. 109).

2. Haematological toxicity of Quadramet is reduced or moderate.
   - In our study, 62% of patients experienced grade II of haematotoxicity or lower.
   - Repeated administration of 153 Sm, as well as previous radiotherapy or chemotherapy, does not result in an increased myelotoxicity. Haematological toxicity is reversible in about 8 weeks.
   - Repeated administration of radionuclides is possible, at intervals of at least 6 weeks.
   - Patients with metastatic bone disease can survive for a long time and can be safely treated with multiple combined therapies (Heron, 2008, ref. 69).
   - Bianki (2009, ref. 20) proposes a method of quantification for Quadramet fixing depending on the radotrasor captation on the bonescan, therefore improving the dosimetry and optimizing the Quadramet administration.

VI.4. THE ROLE OF BONE SCINTIGRAPHY IN MANAGING THE PATIENTS WITH PROSTATE CANCER

VI.4.1. Introduction
Bone scintigraphy with diphosphonic labeled 99mTc is the method of choice for evaluating bone dissemination at diagnosis, during disease progression (the case of biochemical relapse), as well as to evaluate the therapeutic effect.

VI.4.2. The purpose of the study
Assessing the role of bone scintigraphy in managing the patients with prostate cancer and its correlation with different other parameters used in diagnosing and monitoring the development of PC.

VI.4.3. Material and method
Bone scintigraphy was performed using a dual head gamma camera for detection (GE and Philips) and consisted of early acquisitions - early phase - in the case of symptomatic patients, 3-minute planar acquisition centered on painful areas, and of late acquisitions - bone phase – the whole body and in
most cases, SPECT focused on the areas with abnormalities of the radiotracer caption seen on the whole body images. Axigate database access allowed me to know the history of the patients, and the access to Sirilog, which groups the explorations performed by the patients, allowed me to compare the bonescan results with results of other image explorations.

Therefore, I monitored the age of the patient age at diagnosis, the percentage of patients with metastases at diagnosis, the diagnosis circumstances, the results for the rectal touch examination and the correlation of these results with Gleason score, associated malignancies, clinical or pathological stage at diagnosis, PSA value at diagnosis, the concordance of operational Gleason score – the biopsy Gleason score, the time from diagnosis to RCB depending on the initial local treatment, the number of patients with previous negative biopsies, the number of patients deceased and the cause of death.

**VI.4.4. The study group**
Between November 2009 and October 2010, there were 178 patients who performed bone scan in the Nuclear Medicine Laboratory of Besançon College Hospital (some had repeated bonescan), most of them being recomended by the Radiotherapy and Oncology services. I mention the fact that the lot of 178 patients are only the patients whose history I found in the Axigate database.
Out of the 178 patients, 37 showed bone metastases; they have formed a study group for which I have analyzed the age at diagnosis, the PSA at diagnosis, the general time from diagnosis to metastases, the time from diagnosis to metastasis depending on the initial treatment, the correlation between the initial clinical or pathological stage and the occurrence of metastases, the Gleason score correlation – the metastasis and the correlation between the results for rectal touch examination and the metastasis.
A special group have been the patients with metastases at diagnosis.
Another distinct group is represented by the patients with a probability of PC in family.

**VI.4.5. Results and discussion**
Currently, most used radiotracers for bone scan are diphosphonates labeled with 99mTc (Rusu, 2003, ref. 132).

**VI.4.5.1. Age of patients at diagnosis**
The average age of the 178 patients sent to the Nuclear Medicine Laboratory of Besançon within a year (November 2009-October 2010) is 67.64, with extremes between 41 and 92 years (Figure 47).
Fig. 47. Graphical representation of the distribution of the patients according to their age at prostate cancer diagnosis (data contained in Table XI).

It is observed that the distribution of the number of patients follows the Gaussian curve demonstrating the homogeneity of the lot. Greene (2005, ref. 60) finds an age at diagnosis of 65 years.

VI.4.5.2. The proportion of patients with metastases at diagnosis

9 out of 178 patients showed bone metastases at diagnosis (5%) and 4 patients (2.24%) showed a probability of metastases at diagnosis.

In the post era of PSA, 5% of patients show metastases at diagnosis, according to Jadvar (2009, ref. 76).

VI.4.5.3. Circumstances of diagnosis

To evaluate the effect of screening on mortality in PC, two major studies were conducted in the United States (PLCO) and in Europe (ERSPC); in 2009 there were published their results. The results of these two studies are contradictory. Currently screening in PC remains a source of uncertainty and controversy. Early detection in PC is not clearly recommended nor contraindicated. In this case, the consident decision of the patient plays an important role in screening (Vedel, 2011, ref. 173; Evans, 2010, ref. 44 Perrin, 2008, ref. 118).

♦ Screening Algorithm

In the situation of patients who decide to benefit from screening, according to the American Cancer Society (Wolf, 2010, ref. 180):

• the screening is recommended with PSA or with PSA and TR.
• the screening will be canceled for men with PSA ≥ 2.5 ng / ml.
• for PSA <2.5 ng / ml, the screening will be performed in two years.
• in the case of patients with common risk, the biopsy is recommended for a PSA of 4 ng / ml.
• for PSA values from 2.5 to 4 ng / ml, it is calculate the individual risk especially for high level of PC, in view for the biopsy recommendation. The factors which increase risk of PC include the African-American population, the family history of PC, advanced age and an abnormal TR. A previous negative biopsy decreases the risk for prostate neoplasia (fig. 49).

European Association of Urology recommends an assessment of PSA at the age of 40 (baseline PSA), depending on which it will be decided the frequency of the following tests. For values of PSA <1ng/ml, 8 years would be enoght (Heidenreich, 2011, ref. 67).

Fig. 49. Screening algorithm, according to the recommendations of the American Cancer Society (Wolf, 2010, ref. 180).
In our study, the circumstances of diagnosis for the 92 patients (whose circumstance diagnosis were known) were:

- early detection / individual detection: 55 patients. In France, there is no PC screening performed for the population yet early detection is encouraged through PSA dosing and rectal digital examination.
- clinical manifestations: 29 patients. The most frequent clinical manifestations were: abnormal micturition, dysuria, prostatitis, acute urinary retention. A patient showed up for a leg edema and the CT scanning showed a large prostate tumor accompanied by retroperitoneal and groin lymph nodes (the latter causing the clinical edema).
- detection during the assessment of other diseases: 3 patients.
- the patients do not know the circumstances of diagnosis: 5 patients (Fig. 50).

**Fig. 50. The percentages of patients depending on the circumstances of diagnosis.**

VI.4.5.4. The results of rectal digital examination (known for 77 patients)

In our study, 26 out of 77 patients (33.76%) showed a normal rectal digital examination and 51 patients (66.24%) showed a pathological rectal digital examination (Fig. 51).

**Fig. 51. Graphical representation of the distribution on the number of patients depending on the rectal digital results.**

Paradoxically, in a study done by Ankerst et al (2009, ref. 9), it was noticed that 70% of the patients with abnormal TR, within a period of 1 year, have presented a normal TR, even the patients with PC. On the other hand, other studies argue that the probability of diagnosing PC at biopsy is higher for patients with positive TR and associating PSA ≥ 3ng/ml with abnormal TR leads to detecting a significantly higher number of PC with Gleason score> 7 (Gooslar, 2008, ref. 58).
VI.4.5.5. The correlation between rectal digital examination and Gleason score

The question where I have started is: Is there a correlation between clinical data (TR) and histological data (Gleason score)?

I analyzed separately the lot of patients with normal TR and the lot with pathological TR, correlated with biopsy or operator Gleason score (the latter known only for patients who have had prostatectomy). The data was grouped in Figure 56.

I obtained the following results:

- **normal TR: 25 patients with known Gleason score** - biopsy (13 cases) or surgical (12 cases); for a patient Gleason score not known.
- **pathological TR: 50 patients with known Gleason Score** - biopsy or surgical; for a patient Gleason score not known.

![Graphical representation for comparing the results of TR and of biopsy or surgical Gleason score.](image)

I found the following results:

1. In the case of the patients with normal TR, 52% had a Gleason score <7; only 24% of the patients with pathological TR have the same score.
2. 40% of the patients with normal TR and 50% of those with pathological TR have 7 Gleason score.
3. 26% of the patients with pathological TR have a Gleason score >7, while only 8% of those with normal TR have the same score.

**In conclusion, there is a direct correlation between the value of Gleason score (histological result) and TR results (clinical evaluation).**

VI.4.5.6. Patients with prostate cancer associated with other malignancies.

In our group I found (Table XXIV):

<table>
<thead>
<tr>
<th>Associated neoplasia type</th>
<th>number of patients</th>
<th>percentage</th>
</tr>
</thead>
</table>

33
- 27 patients have shown two or more malignancies: 23 patients with two cancers, 2 patients with three cancers and two with four cancers.
- bladder cancer: 8 out of 33 (24.24%); renal cancer 5 out of 33 (15.15%); thyroid, colon and lung cancer: 3 of each out of 33 (9.09%, respectively).
- two patients with rectal cancer and two with melanoma; one patient each with hepatocellular carcinoma, colangiocarcinom, vocal cords, neurinom, myeloma, gastric and CML.

I observed:
- PC is most frequently associated - in our study - with urinary tract cancers. Bladder and renal neoplasms represent 39.39% of cancers associated with PC.
- Thyroid, colon and lung cancers show a significant association (i.e. 9.09% of the cases).

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bladder cancer</td>
<td>8</td>
<td>24.24 %</td>
</tr>
<tr>
<td>Kidney cancer</td>
<td>5</td>
<td>15.15 %</td>
</tr>
<tr>
<td>Thyroid cancer</td>
<td>3</td>
<td>9.09 %</td>
</tr>
<tr>
<td>Colon cancer</td>
<td>3</td>
<td>9.09 %</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>3</td>
<td>9.09 %</td>
</tr>
<tr>
<td>Rectal cancer</td>
<td>2</td>
<td>6.06 %</td>
</tr>
<tr>
<td>Melanoma</td>
<td>2</td>
<td>6.06 %</td>
</tr>
<tr>
<td>Hepatocellular carcinoma</td>
<td>1</td>
<td>3.03 %</td>
</tr>
<tr>
<td>Colangiocarcinoma</td>
<td>1</td>
<td>3.03 %</td>
</tr>
<tr>
<td>Vocal cord cancer</td>
<td>1</td>
<td>3.03 %</td>
</tr>
<tr>
<td>LMC</td>
<td>1</td>
<td>3.03 %</td>
</tr>
<tr>
<td>Neurinom</td>
<td>1</td>
<td>3.03 %</td>
</tr>
<tr>
<td>Myeloma</td>
<td>1</td>
<td>3.03 %</td>
</tr>
<tr>
<td>Gastric cancer</td>
<td>1</td>
<td>3.03 %</td>
</tr>
<tr>
<td>Total</td>
<td>33</td>
<td>100 %</td>
</tr>
</tbody>
</table>
VI.4.5.7. The stage at diagnosis (for patients recommended for scintigraphy)

In the lot of the 178 patients I have found persons who presented the following clinical or pathological stages at diagnosis:
T1 - 17 patients; T2 - 29 patients; T3 - 13 patients; T4 - 0.
PT2 - 23 patients; PT3 - 37 patients; PT4 - 1 patient.

I observed:
• 49.15% out of the 59 patients with known T-score were diagnosed with clinical T2 score, while only 22.03% were diagnosed with clinical T3. A large percentage of patients - 28.81% showed T1 stage at diagnosis.
• Out of the 62 patients with known pT score (i.e. patients who have been treated with radical prostatectomy), 98% were classified in classes PT2 (39%) and PT3 (59%). Only 1 patient has presented PT4 stage.

VI.4.5.8. PSA at diagnosis

Out of the 155 patients with known PSA at diagnosis, 5 patients had a PSA < 4 ng / ml (3.22%), 66 had a PSA of 4-10 ng / ml (42.58%), 54 a PSA of 10-30 (34.83%) and 30 patients had a PSA > 30 ng / ml (19.35%) (fig. 59).

![Pie chart showing PSA values](image)

**Fig. 59. The percentage of the patients depending on the PSA value (ng / ml) at diagnosis**

Patients considered formerly as belonging to "gray zone" (4-10 ng / ml) represent the largest percentage (42.58%) in our study, followed by the PSA group with values of 10-30 ng / ml (34.83%). These two groups represent 77.41% of diagnosed cases. 3.22% are patients with PSA < 4. Only 19.35% are patients with PSA > 30 ng / ml.

VI.4.5.9. Biopptic Gleason / surgical Gleason concordance (both values are known for the cases of 16 patients who received PR)

Out of the 16 patients with biopptic and surgical Gleason score known, the values in 8 cases were consistent and in 8 cases inconsistent.

VI.4.5.10. Biochemical recurrence

I have monitored the time from diagnosis to the biochemical relapse, according to the initial local treatment (PR, RT, brachytherapie, HT)
• PR (Figure 60)
  - 16 out of the 44 patients who have been treated with radical prostatectomy showed after surgery a detectable PSA. Of these patients, 3 had positive surgical margins, 6 extracapsular invasion, 2 invasion of seminal vesicles, and 2 patients showed positive surgical margins as well as extracapsular invasion.
  - 5 patients had a postoperative PSA ≥ 0.2 and one had 0.19.
  - RCB was observed on an average of 3.43 years after PR.
Fig. 60. Graphical representation of the distribution for the number of the patients depending on the time from diagnosis to biochemical relapse after radical prostatectomy.

- RT (figure 61)
  - the average time until biochemical relapse in the case of 17 patients who received external radiotherapy is 3.2 years.

Fig. 61. Graphical representation of the distribution of the patients depending on the time from diagnosis to biochemical relapse after external radiotherapy.

VI.4.5.11. Patients with previous negative biopsies

15 patients from the lot (8.42%) are known to have had historically at least one negative puncture biopsy. Of these, 3 had two series of negative biopsies and one patient had three negative biopsies.

V.4.5.12. PC in family (probably)

In the lot of the 178 patients I found 7 patients with the probability of PC in family. I observed:

- The average age for diagnosis of neoplasia is 63.85 years, compared to 67.64 years for the total lot.
- 6 of the 7 patients had siblings diagnosed with PC (3 patients one brother, 2 patients two brothers and one patient three brothers having the same neoplasia). Only in the case of a patient, his father was diagnosed with PC.
- A young patient (56 years) with metastases at diagnosis has a sister with breast cancer (probably he has also PC in family), and one patient introduced in this sublot has a daughter diagnosed with breast cancer. It has been confirmed the incidence of both cancers in some families.

VI.4.5.14. The group of the patients with metastases

- The age at diagnosis
The average age at diagnosis was 69.97 years, compared to 67.94 years for general lot

♦ **PSA at diagnosis** (known for 31 patients) (fig. 66)

![Graphical representation of the distribution for the patients with metastases depending on initial PSA value.](image)

I noticed that among the 31 patients with metastases having a known PSA at diagnosis, 8 (25.8%) had PSA values of 4-10 ng / ml. All 6 patients with PSA> 100 ng / ml (from the lot of 178 patients) showed metastases at diagnosis.

♦ **The time from diagnosis to metastasis**

9 of the patients showed bone metastases at diagnosis (4 of the 178 patients showed a probability of metastases at diagnosis), 4 in the first year, 10 in 2nd to 5th year, 8 in 6th to 10th year, 2 after 10 years and in the case of 4 patients the time from diagnosis to metastasis is unknown.

♦ **Correlation Gleason score - metastases (for 33 patients)**

77.77% of the patients with metastases had a biopsy score ≥ 7; of the 7 patients with known operatory Gleason score, none had a score <7. It is thus noticed that, in the case of the patients with metastases, high Gleason score correlates with bad prognosis.

♦ **Correlation of rectal digital examination - metastases**

For 12 patients with metastasis it is known the TR result: 11 pathological (91.67%), 1 normal (8.33%). An initial negative TR could be a less aggressive cancer. However, the number for the lot is very small.

♦ **The time from biochemical relapse to metastases** (known for 9 patients treated with RT and 7 patients treated with PR)

The patients who have been treated with PR present an average of 2.85 years from biochemical relapse to the appearance of metastases, 3 patients showing metastases in less than 2 years from RCB, 3 patients within 2 to 5 years and 1 patient after 5 years (the last one after 11 years from RCB). The patients who have been treated with RT have an average of 3.11 years from RCB to metastases, two men show metastases in less than 2 years from RCB and 7 patients – between 2 to 5 years after RCB.

**VI.4.6. Conclusions**

- 5% of the patients show up with bone metastases at diagnosis.
- 59.78% of the patients were diagnosed by screening (early detection), and 31.52% showed clinical manifestations.
- 43% of the patients have a PSA between 4-10 ng / ml at diagnosis, the formerly "gray" zone.
- Rectal digital examination was negative for 33.76% of the patients with prostatic neoplasia.
- There is a direct correlation between clinical data (rectal digital examination) and histological data (Gleason score).
- 8.42% of the patients showed previous negative biopsies.
- 49.15% of the patients were diagnosed with clinical T2 score, while only 22.03% were diagnosed with clinical T3. 28.81% showed T1 stage at diagnosis.
- Most of the patients who received radical prostatectomy - 98% - were classified in stage pT2 (39%) and pT3 (59%).
- In our study, prostate cancer was most often associated with cancers of the urinary tract (39.39%), 8 of the 33 malignancies associated with PC being represented by bladder cancer (24.24%) and 5 (15.15%) of kidney cancer.
- 24.32% of the patients (37 patients) with metastases in our lot already showed metastases at diagnosis. 40.54% developed metastases during the first five years post diagnostic and 27.02% after 5 years. In the case of 4 patients (10.81%) it is unknown the time from diagnosis to metastasis.
- In the case of patients with metastases, high Gleason score correlates with bad prognosis.
- Bone scan with diphosphonates remains the standard examination in detecting bone metastases, commonly found it in prostate cancer.
- Bone scan is useful in staging, restaging and monitoring the evolution of prostate cancer as well as in assessing the response to therapy.

VII. CONCLUSIONS

1. The field of Nuclear Oncology has now - due to the advances in Nuclear Medicine - an important role in diagnosis and treatment of malignant tumors.

2. Prostate cancer is the most frequently diagnosed malignancy in male oncological pathology and is ranking second in cancer deaths. Therefore, I have chosen the theme of my thesis, The role of nuclear medicine investigations in diagnosis, treatment and monitoring the evolution in prostate cancer.

3. In the general part of the thesis, I have presented an overview of current data on the subject of the thesis, structured in four chapters, as it follows: ♦ I. Current status of understanding the mechanisms of carcinogenesis in prostate neoplasm ♦ II. The role of the radioisotope investigations in diagnosing and staging prostate cancer ♦ III. The role of the treatment of prostate neoplasia. The role of radionuclidic therapy ♦ IV. The role of radioisotopes exploration in monitoring the the evolution of prostate carcinoma, containing 14 figures and 1 table.

4. The personal contribution for the thesis includes ♦ Hyphotesis for work ♦ A comparison between total PSA, Gleason score and the results of bone scintigraphy for different age groups ♦ Comparative study of bone scintigraphy - PET / CT in detecting bone metastases in prostate cancer ♦ A study of effectivenes and toxicity for QUADRAMET treatment in metastatic prostate cancer at bone level ♦ The role of bone scintigraphy in managing the patients with prostate cancer, containing 53 figures and 37 tables.

5. Subsequently to these studies, I will mention the following:

- The probability of bone metastases for a high PSAt is inversely proportional to the age, probably due to benign prostatic hyperplasia commonly to elderly patients.

- I did not find a plain direct correlation between Gleason score and scintigraphic results, especially for the groups with intermediate and increased risk of metastasis.

- PET / CT 18F-NaF is more sensitive and more specific in detecting bone metastases than bone scintigraphy, including tomoscintigraphy.

- 153 Sm-EDTMP has a major antalgic effect. 74.5% of the patients treated with this
radiopharmaceutical for bone pain caused by metastatic prostate cancer experienced loss or relief of pain.

- Transient hematotoxicity associated with radionuclide therapy is reduced or moderate.
- 5% of the patients diagnosed with prostate cancer show bone metastases at diagnosis.
- Most patients with prostate cancer are diagnosed by early detection, but 31.52% are diagnosed due to clinical manifestations.
- 43% of patients show at diagnosis a PSA between 4-10 ng / ml, and 3% a PSA <4 ng / ml.
- Rectal digital examination was negative for 33.76% of the patients with prostatic neoplasia.
- In our study there is a direct correlation between clinical data (rectal digital examination) and histological data (Gleason score).
- 8.42% of the patients have previously showed negative biopsies.
- 78% of patients were diagnosed in clinical stage T1-T2.
- Prostate cancer was most often associated with urinary tract cancer (39.39% of the cases of multiple malignancies).
- Currently, bone scintigraphy represents an extremely valuable tool in staging, restaging and assessing the response to the therapy for the patients diagnosed with prostate cancer.
ANNEX 1
ABBREVIATIONS

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
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<tbody>
<tr>
<td>ADT</td>
<td>androgen deprivation therapy</td>
</tr>
<tr>
<td>AR</td>
<td>androgen receptor</td>
</tr>
<tr>
<td>BAC</td>
<td>complete androgen blockade</td>
</tr>
<tr>
<td>BPH</td>
<td>benign prostatic hyperplasia</td>
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<tr>
<td>BMD</td>
<td>bone mineral density</td>
</tr>
<tr>
<td>CGH</td>
<td>comparative genomic hybridization</td>
</tr>
<tr>
<td>CHT</td>
<td>chemotherapy</td>
</tr>
<tr>
<td>PS</td>
<td>prostate cancer</td>
</tr>
<tr>
<td>CT</td>
<td>computed tomography</td>
</tr>
<tr>
<td>CPRC</td>
<td>castration resistant prostate cancer</td>
</tr>
<tr>
<td>CPHR</td>
<td>hormone-refractory prostate cancer</td>
</tr>
<tr>
<td>DAI</td>
<td>intermittent androgen deprivation</td>
</tr>
<tr>
<td>DES</td>
<td>Diethylstilbestrol</td>
</tr>
<tr>
<td>DHT</td>
<td>Dihydrotestosterone</td>
</tr>
<tr>
<td>DNA</td>
<td>deoxyribonucleic acid</td>
</tr>
<tr>
<td>ER</td>
<td>estrogen receptor</td>
</tr>
<tr>
<td>ERSPC</td>
<td>The European Randomised Study of Screening The Prostate Cancer</td>
</tr>
<tr>
<td>FISH</td>
<td>Fluorescence in situ hybridization</td>
</tr>
<tr>
<td>FSH</td>
<td>follicle stimulating hormone</td>
</tr>
<tr>
<td>HIFU</td>
<td>high intensity focused ultrasound</td>
</tr>
<tr>
<td>HGPIN</td>
<td>high grade prostate intraepithelial neoplasia</td>
</tr>
<tr>
<td>HMDDP</td>
<td>hydroxymethyl diphosphonate</td>
</tr>
<tr>
<td>HT</td>
<td>hormone therapy</td>
</tr>
<tr>
<td>IRM</td>
<td>magnetic resonance imaging</td>
</tr>
<tr>
<td>IRMS</td>
<td>magnetic resonance spectroscopic imaging</td>
</tr>
<tr>
<td>In</td>
<td>Indium</td>
</tr>
<tr>
<td>LD</td>
<td>lineage disequilibrium</td>
</tr>
<tr>
<td>LH</td>
<td>luteinizing hormone</td>
</tr>
<tr>
<td>LMC</td>
<td>chronic myeloid leukemia</td>
</tr>
<tr>
<td>LOD</td>
<td>logarithm of the relative probability</td>
</tr>
<tr>
<td>LOH</td>
<td>loss of heterozigosity</td>
</tr>
<tr>
<td>LHRH</td>
<td>luteinizing hormone-releasing-hormone</td>
</tr>
<tr>
<td>LUTS</td>
<td>lower urinary tract symptoms</td>
</tr>
<tr>
<td>Mbq</td>
<td>megabequerels</td>
</tr>
<tr>
<td>MRI</td>
<td>magnetic resonance imaging</td>
</tr>
<tr>
<td>NaF</td>
<td>sodium fluoride</td>
</tr>
<tr>
<td>OS</td>
<td>overall survival</td>
</tr>
<tr>
<td>PET</td>
<td>Positron Emission Tomography</td>
</tr>
<tr>
<td>PIA</td>
<td>proliferative inflammatory atrophy</td>
</tr>
<tr>
<td>PIN</td>
<td>prostatic intraepithelial neoplasia</td>
</tr>
<tr>
<td>PLCO</td>
<td>Prostate, Lung, Colorectal and Ovarian Cancer Screening</td>
</tr>
<tr>
<td>PSA</td>
<td>prostate specific antigen</td>
</tr>
<tr>
<td>PSAD</td>
<td>PSA density</td>
</tr>
<tr>
<td>PSADT</td>
<td>time of PSD doubling</td>
</tr>
<tr>
<td>PSMA</td>
<td>prostate specific membrane antigen</td>
</tr>
<tr>
<td>PSAV</td>
<td>PSA velocity</td>
</tr>
<tr>
<td>RCB</td>
<td>biochemical relapse</td>
</tr>
<tr>
<td>Re</td>
<td>Radium</td>
</tr>
<tr>
<td>RT</td>
<td>radiotherapy</td>
</tr>
<tr>
<td>RT-PCR</td>
<td>reverse transcription polymerase chain reaction</td>
</tr>
<tr>
<td>SPECT/CT</td>
<td>Single Photon Emission Tomography/Computed Tomography</td>
</tr>
<tr>
<td>Sr</td>
<td>Strontium</td>
</tr>
<tr>
<td>SO</td>
<td>bone scintigraphy</td>
</tr>
<tr>
<td>Te</td>
<td>Technetium</td>
</tr>
<tr>
<td>TR</td>
<td>rectal digital examination</td>
</tr>
<tr>
<td>TSGs</td>
<td>tumor suppressor genes</td>
</tr>
<tr>
<td>TRUS</td>
<td>transrectal ultrasound</td>
</tr>
</tbody>
</table>
ANNEX 2. PAPERS PUBLISHED OR SUBMITTED TO RELATED TO PhD THESIS


175. Wagner HN. A Personal History of Nuclear Medicine. Editura Springer-Verlag, Londra, 2006, 244-252.
