PROSPECTIVE ASPECTS IN THE ONCOLOGICAL TREATMENT OF PROSTATE CANCER

Ph.D. Thesis

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Szeged

2020

List of full papers that served as the basis of the Ph.D. thesis

I. **Varga L**, Kószó RL, Fodor E, Cserháti A, Varga Z, Darázs B, Kahán Zs, Hideghéty K, Borzási E, Szabó D, Müllner K, Maráz A. Daily Setup Accuracy, Side-effects and Quality of Life During and After Prone Positioned Prostate Radiotherapy. Anticancer Research 38:(6) pp. 3699-3705. (2018)

IF: 1.935

II. Kószó RL, **Varga L**, Fodor E, Kahán Zs, Cserháti A, Hideghéty K, Együd Zs, Szabó Cs, Borzási E, Szabó D, Müllner K, Varga Z, Maráz A. Prone Positioning on a Belly Board Decreases Rectal and Bowel Doses in Pelvic Intensity-Modulated Radiation Therapy (IMRT) for Prostate Cancer. Pathology and Oncology Research Pathol Oncol Res. 2019 Jul;25(3):995-1002. doi: 10.1007/s12253-018-0436-2. Epub 2018 Jun 7.

IF: 2.433

III. Küronya Z, Sükösd F, **Varga L**, Bíró K, Gyergyay F, Géczi L, Nagyiványi K, Jorgo K, Szarvas T, Kovács Á, Laczó I, Varga Z, Pósfai B, Pepó J, Maráz A. ERG expression can predict the outcome of docetaxel combinedwith androgen deprivation therapy in metastatic hormone-sensitiveprostate cancer. Urol Oncol. 2019 Apr;37(4):289.e1-289.e9. doi: 10.1016/j.urolonc.2018.12.007. Epub 2019 Jan 21. PMID: 3067908

IF: 2.863

1. Introduction

Prostate cancer (PC) is the second most common malignancy worldwide; the incidence is growing in every industrial country. Depending on the stage, surgical therapy, radiotherapy, and hormonal therapy are the potential therapeutic options. The elevation of radiation dose significantly improves biochemical control and disease-free survival independently of the type of radiotherapy (RT).

The short-term and long-term side-effects of therapy are very important as PC patients usually have long survival. Although RT is getting more targeted, tolerance of normal tissues limits dose escalation and increases acute and chronic gastrointestinal (GI) and urogenital (UG) morbidity, exacerbating the pre-existing urological, sexual, and psychological problems. Symptoms depend on the degree and extent of the tissue damage and have a significant adverse effect on the patient's quality of life (QOL).

In clinical practice, toxicity can be reduced by the use of modern radiotherapy techniques by decreasing the safety margins (e.g. intensity-modulated radiotherapy (IMRT), image-guided radiotherapy (IGRT)), by advantageous patient positioning and with almost constant fullness of the rectum and the urinary bladder.

During radiotherapy the supine position is the most frequently used laying method. Patients can be treated also in a prone position (with the use of belly board - BB). The use of BB is associated with lower dose burden of intestines in several clinical trials of pelvic cancers formerly in the 3DCRT and nowadays in the IMRT-IGRT era.

Despite advances in loco-regional medical treatment, advanced or metastatic PC is still very serious problem. Systematic treatment of metastatic prostate cancer can be divided into hormone-sensitive (HS) and castration-resistant (CR) pathophysiological phases. For metastatic hormone-sensitive prostate cancer (mHSPC) until recently, androgen deprivation therapy (ADT) alone by surgical or medical castration was the standard-of-care.

Although the histological classification of PC is well-known, the different molecular subtypes and variants may respond differently to certain therapies. In recent years, many retrospective studies have focused on identifying potential predictive factors for optimizing treatment decisions.

2. Aims

The primary aim of the dissertation is to investigate the potentially prospective aspects in the oncological treatment of PC, which provide better survival opportunities and to improve the QOL of patients.

2.1. Determine during pelvic RT of PC patients whether a supine or prone position (on a BB) results in the reduction of the radiation dose to organs at risk (OARs), particularly the rectum, colon, and small intestines.

2.2. Evaluate the daily setup accuracy, define the necessary safety margins.

2.3. Analyse the patients' QOL and side-effects of the therapy in case of PC patients treated with extended (with therapy of regional lymph nodes) radiotherapy in a prone position by IMRT-IGRT technique.

2.4. Investigate the possible predictive factors for tailored approach in mHSPC, that may help predict the response to docetaxel chemotherapy (ChT) as well as clinical outcomes.

3. Patients and methods

All the clinical studies had been approved by the Research Ethics Committee. In the two prospective analyses all the enrolled patients gave their written informed consent before being registered as participating in the study.

3.1. Prone positioning on a belly board decreases rectal and bowel doses in pelvic intensity-modulated radiation therapy (IMRT) for prostate cancer

3.1.1. *Patients*

Patients with histologically confirmed PC graded according to the Gleason score system (high risk, localized or locally advanced, stage T2–4 N0–1 M0 tumour), and receiving a definitive pelvic RT. The tumour stage assessment was based on thoracic, abdominal and pelvic computed tomography (CT), prostate magnetic resonance imaging (MRI), and whole-body bone scintigraphy. Clinical and pathological data were collected from the patient records.

3.1.2. *Methods*

Patient positioning and scanning

Patients were immobilized with a six-point thermoplastic mask fixation on supine (with bent knees), and prone (with BB and a polystyrene wedge between the buttocks) position. All

patients underwent 5 mm slice-thickness topometric CT scanning in both positions, with full bladder according to our internal protocol.

Target and OARs structure delineation

In both position target volumes and OARs were delineated by radiation oncologists and reviewed by an experienced radiologist.

GTVp – prostate
GTVvs – seminal vesicle (the proximal thirds, or in case of involvement, the full extension)
GTVn – pathological lymph node, if present
CTVN – parailiac, upper subaortic presacral and obturator lymph nodes
PTVp – included GTVp with a 10 mm margin along the supero–inferior, left–right axis, in anterior direction and 7 mm in posterior direction
PTVpvs – the combination of GTVp and GTVvs with a safety margin of 10 mm and 15 mm in posterior direction and any other directions
PTV – determined as PTVpvs, a 7 mm margin around CTVN and 10 mm around GTVn, if present
The OARs were: femoral heads, and bony structures, urinary bladder (from the apex to the dome), large and small intestines (contained all identifiable segments) and rectum (from the ischial tuberosities to the sigmoid flexure). Each rectal section, the whole rectum (R), the segment at the height of the prostate (R1), and R1 + 10 mm along the supero-inferior axis (R2) were individually delineated.

Rectal extension and rectum–prostate distance measurement

Two independent radiation oncologists performed rectal extension and rectum–prostate distance measurements, both of them twice. At the height of the largest antero-posterior (AP) prostate diameter, rectal diameters (AP and left–right axis) were defined, and lines were created from the center and lateral edges of the back wall of the prostate to the outer anterior rectal wall in both supine and prone positions.

Intensity-modulated radiotherapy planning and dosimetric analysis

IMRT planning was performed, the prescribed doses were 45 Gy to the center of the PTV (1.8 Gy/day, 5 days/week), 14 Gy of the PTVpvs and 18 Gy of PTVp, both delivered in daily 2 Gy fractions, 5 days per week. IMRT plans were created to obtain 95% coverage of the PTV with the 95% isodose curve. For the PTV sliding window IMRT plans were designed in both

positions with a seven-field beam arrangement using 6 MV photon beam quality. For the PTVpvs and PTVp volumetric modulated arc therapy plans were generated. The highest priority was PTV coverage, and the second one was the sparing of OARs.

OAR dose constraints were determined as the following:

V55Gy (bladder) ≤ 50%	V50Gy (colon) ≤ 50%
V70Gy (bladder) ≤ 30%	V70Gy (colon) ≤ 20%
V50Gy (rectum) ≤ 50%	V52Gy (small intestine) = 0%
V70Gy (rectum) ≤ 20%	V50Gy (femoral heads) < 5%

Radiation treatment and image-guidance

Irradiation was carried out in prone position. Image-guidance was based on daily kV-cone beam CT (CBCT) scanning of the pelvis prior to treatment, then an automatic match algorithm was used to match the bony structures displayed on the planning CT and the CBCT.

Statistical analysis

Data were reported as mean ± SD, mean ± SE or median values. The difference between the volumes and doses in supine and prone position was analysed with the paired samples t-test. Intra- and interobserver variabilities were calculated from the mean of distances by using correlation analysis, given a correlation coefficient. SPSS 20.0 for was used to perform the analysis. A p value <0.05 was considered significant.

3.2. Daily setup accuracy, side-effects and quality of life during and after prone positioned prostate radiotherapy

3.2.1. *Patients*

Patients with histologically-confirmed, localized or locally advanced high risk PC was enrolled between February 2016 and June 2017. Patients with permanent urinary catheter, or who could not lie in prone position due to any comorbidity (e.g. hip prosthesis, dyspnoea) were excluded. All patients received ADT. Stage was determined with standard methods (prostate specific antigen (PSA) level, thoracic, abdominal and pelvic CT, prostate MRI, and bone scintigraphy).

3.2.2. *Methods*

Patient positioning, target volumes and planning

Topometric CT was performed in prone position with BB, individual immobilization system and six-point thermoplastic mask fixation. Polystyrene wedge was placed between the buttocks. The patient's skin was marked in accordance with the laser marks. Standard bladder filling and antiflatulence diet were recommended.

Target volumes (pelvic lymph nodes, seminal vesicle and prostate) and organs at risk (OARs – bladder, rectum, bones, femur heads, penile bulb, small and large intestine) were delineated after MRI fusion with review of an experienced radiologist in all cases. For treatment isocentric 7 fields IMRT technique was administered with inverse planning.

Image-guided radiotherapy (IGRT) and determination of safety margins

Therapy was administered five times a week with 6 MV photon beams to 77 Gy total doses. During therapy, online and offline monitoring and data recording were performed by CBCT. After determining the systematic and random errors the CTV-PTV margin was calculated based on van Herk formula ($A=2.5 \bullet \Sigma pop + 0.7 \bullet \sigma pop$). In this calculated safety zone 90% of patients received 95% of prescribed dose

Daily evaluation of the rectal fullness

The anteroposterior (AP, 0–180˚), the lateral (LAT, 90–270˚) and the oblique (OBL, 135–315˚) diameters were determined in the upper and lower area of the symphysis on the topometric CT, then during the radiotherapy on the CBCT in the same regions. The daily alterations of treatment time were analysed.

Evaluation of side-effects and quality of life

Side-effects were graded based on the Common Terminology Criteria for Adverse Events (CTCAE, version 4.03). QOL and side-effects were evaluated based on the Hungarian version of European Organization for Research and Treatment of Cancer Quality of Life (EORTC) and the International Prostate Symptom Score (IPSS) before the start of the therapy, during the 3rd or 4th week, after completion of therapy, and 3 and 6 months after it.

Statistical methods

Data were reported as mean±SD or median values. Daily changes of rectal fullness were evaluated by the paired samples t-test. Statistical analysis (double T-test) of the questionnaires was made with IBM SPSS 20.0. A $p<0.05$ was considered significant.

3.3. Possible predictive factors for tailored approach in metastatic hormone-sensitive prostate cancer

Retrospective analysis of prospectively collected data at two Hungarian departments: the National Institute of Oncology, Budapest, and the Department of Oncotherapy, University of Szeged. All patients signed a written informed consent prior to the initiation of ChT.

3.2.1. *Patients*

Patients were eligible with mHSPC receiving docetaxel ChT between August 1, 2014 and October 31, 2017. Patients were included in the study if they had paraffin tissue blocks from diagnostic samples or metastatic sites. Staging procedures as well as ADT were carried out according to the conventional protocol. For each patient, treatment plan was designed by a multidisciplinary tumour board.

3.2.2. *Methods*

Systemic treatment

All patients received intravenous docetaxel ChT (every 3 weeks at a dose of 75 mg/m2 in 6 cycles depending on toxicity, without prednisone), starting within 120 days after the initiation of ADT. The use of prophylactic granulocyte colony stimulating factor, dose reduction or delay was allowed at the oncologist's decision. Physical examination and laboratory tests were carried out every 3 weeks. The severity of adverse events was evaluated based on CTCAE. Patients' general condition was assessed using the Eastern Cooperative Oncology Group (ECOG) scale. Data were collected prospectively starting in August 2014.

Response analysis

The assessment of outcomes was carried out before and 8 to 12 weeks after the completion of ChT and involved clinical examinations, PSA measurements, bone scan, and diagnostic chest-abdomino-pelvic CT examinations. Response to therapy and follow-up were assessed according to the Prostate Cancer Working Group criteria system. Good response was defined

as a ≥50% decrease in baseline PSA levels. Relapse-free survival (RFS) and overall survival (OS) were defined as the period from the initiation of ChT to the detection of CRPC or death.

Statistical analysis

The association between patient characteristics and RFS or OS was analysed by Kaplan-Meier analysis for categorical variables and by Cox regression for continuous variables. To detect the joint effect of the decrease in PSA level on RFS, multivariate Cox regression analysis (forward likelihood ratio method) was applied. All statistical analyses were performed using the IBM SPSS v22.0 software.

4. Results

4.1. Prone positioning on a belly board decreases rectal and bowel doses in pelvic intensity-modulated radiation therapy (IMRT) for prostate cancer

4.2. Daily setup accuracy, side-effects and quality of life during and after prone positioned prostate radiotherapy

Patient characteristics

Between 10/2016 and 10/2017 55 patients with high risk localized or locally advanced prostate cancer were administered definitive pelvic lymph node RT. Mean age of the patients was 65.60 (range=53.33–83.49 years) years. Most of the patients were overweight, mean BMI was 26.96 (range=19.37–41.62kg/m2) kg/m2. More than three-quarters of them had a cardiovascular co-morbidity, and one-third of them were smokers.

The number of patients with T2 stage was 41 (74.55%), T3 stage 12 (21.82%) and T4 stage 2 (3.64%). Gleason score was 7 in 27 (48.21%), while 8, 9 and 10 in 5 (9.09%), 19 (33.93%) and 4 (7.14%) cases, respectively. Initial PSA level was lower than 10 ng/ml and was between 10 and 20 ng/ml in 13 (23.21%) and in 9 (16.36%) cases, respectively. In case of 33 (58.93%) patients the initial PSA level was ≥20 ng/ml.

Most of the patients received ADT therapy. A total of 52 (94.55%) patients received the whole prescribed dose (77 Gy). RT had to be completed earlier in 3(5.45%) cases (74 Gy) due to necessity of a urinary catheter during treatment.

Determination of safety margins

CTV-PTV safety margins were the following: lateral: 4.44 mm, longitudinal: 9.69 mm,

vertical: 4.98 mm.

Rectal extension, rectum–prostate distance, daily evaluation of the rectal fullness

All rectal volumes were significantly higher in prone position. The rectum–prostate distance measured from the center of the rear prostate wall to the outer anterior rectal wall was significantly higher in prone position. Both intra- and interobserver variabilities showed close correlation. The exposure of all rectal segments was more favourable in prone position in dose ranges of 40 to 75 Gy. The relative volume receiving 30 Gy dose was lower in respect of R1 segment.

Side-effects and quality of life

The most common acute side-effects were cysto-urethritis and radiation induced entero-proctitis. Almost half and a quarter of the patients complained of GU and GI side-effects, respectively. Temporary urinary catheter was needed in 3 patients. Almost all patients had hot flashes and erectile dysfunction of different grade, but only 40% of them experienced significant complaints. Median period of follow-up was 6 months (range=3–12 months).

Based on the EORTC QOL, urination and defecation were significantly worse during the therapy than before. These complaints improved significantly after 3 and 6 months. Erectile dysfunction was detected in more than one third of patients initially and this rate decreased during the radiotherapy. Evaluation of the patients' sexual life was quite difficult because psychological factors may influence the patients' answers and erectile function can be also worsened by ADT. Based on total evaluation of the EORTC QOL, the patients' quality of life did not change significantly during therapy, although significant improvements could be detected in 3 and 6 months after therapy.

Scores of IPSS questionnaire regarding quality of life were similar to these data, such as prostate specific symptoms: no significant worsening could be detected during the therapy; however significant improvements were registered during the follow-up visits.

4.3. Possible predictive factors for tailored approach in metastatic hormone-sensitive prostate cancer

Patient characteristics

55 patients were included in the study; most patients (94.5%) had high-volume disease (presence of visceral metastases and/or ≥4 bone metastases with at least 1 outside the vertebral column and pelvis – CHAARTED study definition). Most of them also had Gleason score ≥8 (mean value 8.67±0.14). At the time of diagnosis, the mean PSA level of patients was 629.6±161.7 ng/ml. The mean age 65.6±1.1 years (range: 43−79), performance status was generally good (ECOG 0: 67.3%; ECOG 1: 27.3%, ECOG 2 5.5%).

Response and survival

Between the initiation of ADT and docetaxel ChT the mean time was 73.9±3.9 days. The mean number of given docetaxel cycles was 5.69±0.17. RFS and OS were 10.5±3.2 months and 40.4±8.9 months, respectively.

PSA response was detected in 51 cases (92.7%), the mean rate of decrease was 84.7±4.1 ng/ml, 80% of the patients (44) had more than 50% PSA decrease, the nadir PSA level was 34.0±19.8 ng/ml.

Castration-resistant PC developed in 32 patients (58.2%), out of which 23 cases (41.8% of all patients) were detected within 12 months from the initiation of docetaxel ChT. The mean OS after the development of castration-resistant status was 17.2±5.4 months.

By the time of study completion, 17 patients had died (30.9%), due to prostate cancer 14, 1 due to the development of pneumonia after ChT, 1 due to ileus after ChT, and 1 due to subsequently detected advanced colorectal cancer.

Disease progression was mostly detected with increasing PSA levels in 31 patients (56.4%), out of which 19 (34.5%) were bone, 8 (14.5%) were visceral, and 4 (7.3%) were distant lymph node metastases.

Clinical factors and outcome

Performance status, PSA response, ERG, only biochemical or oligo-progression were associated with better clinical outcomes. Compare to progression after 12 month, the progression within 12 months from the initiation of docetaxel ChT was associated with poorer OS (40.4 ± 8.9 months vs. 17.97 ± 7.6 months, $p < 0.001$).

5. Discussion

5.1. Prone positioning on a belly board decreases rectal and bowel doses in pelvic intensity-modulated radiation therapy (IMRT) for prostate cancer

During the last 20 years many prospective randomized clinical studies have proven that local dose escalation significantly improves biochemical control. Clinically localized high-risk prostate cancer frequently shows micrometastatic spreading to the pelvic lymph nodes; therefore, RT and two/three years of androgen suppressing endocrine treatment are the standard of care. However there is no consensus recommendation for patient selection for pelvic RT in this population, considering the increased exposure of OARs and toxicity.

Based on the literature and our work despite the elevated dose in the target volume, the dose of OARs can be reduced without increased toxicity, using modern RT, positioning and immobilization techniques.

Radiation exposure of intestines is better in prone position with the use of BB, than in supine position, in case of 3DCRT and IMRT technique, which may decrease the GI morbidity in itself. Gonzalez et al. found that a significantly smaller volume of the small intestine receives more than 20 Gy dose in prone position with the use of BB, while the interfraction dose variation to the small bowel was similar to the supine position.

Regarding patient positioning, Zelefsky et al. and McLaughlin et al. have described, and also been confirmed in the phase II trial of O'Neil et al. significantly lower rectal doses in prone position, using 3DCRT technique. They could not confirm it in the case of urinary bladder, but the planning was made with empty urinary bladder. Bajon et al. have shown decreased dose exposure of the urinary bladder in prone position besides sparing the rectum and the small intestine.

In prone position, the decreased rectal exposure is a result of the posterior retraction of the rectum and anterior displacement of the prostate; however, the accurate mechanism of it is unknown.

Our study was limited by the lack of delineating the penile bulb, and the relatively small number of patients involved, which however double the number of patients, was previously reported.

5.2. Daily setup accuracy, side-effects and quality of life during and after prone positioned prostate radiotherapy

With the use of IG-IMRT patient setting errors can be eliminated, so accuracy of spatial dose delivering can be increased, that may lead to improved clinical results. In case of prostate cancer patients, the extent of radiotherapy safety zone (CTV-PTV margin) is being studied (recommendations are available from 1 mm to 10 mm), it can be decreased by marking and mask fixation. Determination of the proper safety zone has to be estimated by the different institutions taking local conditions into consideration.

According to our results, abdominal positioning can be properly performed in IMRT irradiation of high risk PC patients. Using belly board and mask fixation, vertical and lateral setting accuracy detected with CBCT is similar to the literature. For further decrease of the safety zone, besides the precise patient positioning and daily IGRT, the transperineal gold marker implantation was introduced in our Institute, according to Jorgo et al.

As the technique of radiotherapy has improved and patient's overall survival has increased, the incidence of side effects and the way they influence the patients' QOL became important. Acute side-effects (mainly cysto-urethritis and radiation induced enteritis-proctitis) develop during radiotherapy (usually from the 6th week) and cease on the first follow-up visit after therapy (2-3 months). Late toxicities usually develop 90 days after completion of radiotherapy and include: chronic cystitis, incontinence, urethral stricture, chronic proctitis and rectal bleeding.

In 2011, Beckendorf et al. published the 5-year follow-up study of 70 Gy contra 80 Gy dose escalations: better 5-year biochemical relapse-free survival was detected in case of high-dose RT. Side-effects were similar in the two arms, however higher proportion of rectal (proctitis, rectal bleeding) and urinary (cystitis, haematuria, urinary obstruction) toxicities were detected in the 80 Gy group. In 2017, Sasaki et al. published their long-term outcomes of the effect of fraction dose reduction (2.2 Gy to 2 Gy/fraction) to late GI toxicity by using helical tomotherapy and IM-IGRT. They found that the reduced dose fraction schedule decreased the incidence of late GI toxicity without compromising prostate-specific antigen control.

Unlike Sasaki, Jorgo at al. prospectively investigated the acute and late toxicity after moderate hypofractionation RT with simultaneous integrated boost for patients with intermediate and high risk localized, locally advanced and node positive PC. According them results it was feasible, safe and seems to be associated with a tolerable frequency and severity of acute GU

and GI toxicities. The rate of severe late GI and UG toxicities are low and comparable to rates with conventionally fractionated treatments.

The change in patients' QOL during RT is tolerable, urination and defecation function deteriorated as previously described. Improvements 3-6 months after RT may demonstrate rapid recovery of acute adverse events and treatment efficacy.

The limitation of this study is its relatively small number of patients. The late toxicities and the QOL after pelvic IMRT for prostate cancer are under further examination.

5.3. Possible predictive factors for tailored approach in metastatic hormone-sensitive prostate cancer

We investigated the potential relationship between clinical and immune-histochemical factors, and response to docetaxel ChT in mHSPC patients treated with early docetaxel and ADT. The combined docetaxel + ADT regimen was well-tolerated; no new adverse events were recorded. The possible correlation between ERG expression and outcome of docetaxel chemotherapy in combination with ADT in patients with mHSPC was has already been presented by Küronya in her PhD thesis.

The introduction of early docetaxel to ADT in the hormone-sensitive phase opened up new perspectives in the management of mHSPC. However, certain aspects need to be considered in the indication of therapy, and also biomarkers can help predicting the response to Cht.

In the phase III GETUG-12 and GETUG-15 studies docetaxel-based ChT was associated with improved RFS in ERG positive patients, but not in ERG negative patients, suggesting a potential role for ERG as an important biomarker of the effectiveness of docetaxel chemotherapy. In our present study, ERG positivity was also significantly associated with better RFS and a lower frequency of early progression, than ERG negative status among mHSPC patients treated with early docetaxel and ADT.

Moreover, the finding that good PSA response was associated with better RFS is in line with previous observations suggesting a predictive value for PSA progression in terms of survival in metastatic prostate cancer.

Our work supplements the existing knowledge base with new data from mHSPC patients receiving the early docetaxel + ADT regimen, although we have to know our limitations: the small sample size and the retrospective nature of our research.

6. Summary, conclusions

6.1. We found prone-positioned pelvic IMRT can be properly carried out in case of high risk PC patients. It decreases the irradiated bowel volumes, and contributes to rectal sparing. The relative dose reduction in the rectal exposure might be a consequence of the slight departure between the prostate wall and the rectal wall, as consistent with the literature, and the increasing volume and diameters of the rectum generated by the displacement of rectal gases.

6.2. IMRT radiotherapy in the prone position can be properly carried out in case of high risk PC patients. Using belly board and mask fixation, vertical and lateral setting accuracy detected with CBCT is similar to the literature.

6.3. GU/GI side effects of this therapy were tolerable. Change of patients' quality of life is insignificant during RT, while improvement 3 and 6 months after RT may be due to rapid recovery from side-effects and effectiveness of therapy. Late toxicities need further examination.

6.4. We suggest that performance status, PSA response, ERG, only biochemical or oligo-progression were associated with better clinical outcomes. Large multicentric, prospective studies are would be necessary to further investigation the role of ERG and other biomarkers in identifying mHSPC patients who would have benefit from the addition of early docetaxel to ADT.

7. Acknowledgements

At the end of my thesis I would like to thank all those people who made this work possible and provided an unforgettable experience for me.

First of all I am most grateful to my supervisor, Anikó Maráz, whose encouragement and generous support helped me in the completion of this thesis. Her patience, guidance and motivation helped me all the time during the research and writing this dissertation.

I wish to express my special thanks to Professor Zsuzsanna Kahán the former, and to Professor Judit Oláh the current director of the Department of Oncotherapy, University of Szeged, who provided excellent working condition for me at the institute.

I would like to express my sincere gratitude to Katalin Hideghéty, Adrienn Cserháti, whose invaluable support significantly contributed my scientific work, and Zoltán Varga, for the guidance in statistical analysis.

Special thanks are due to Zsófia Küronya, Renáta Kószó, Kitti Müller, Emese Fodor, Barbara Darázs, Emőke Borzási, Zoltán Végváry, without whom this task would never have been fulfilled.

Particular thanks to all the Colleagues at the Department of Oncotherapy, University of Szeged. Although they were very busy with their daily tasks, they have always been available to support and guide me, sometimes even in the form of fatherly advice.

I am grateful for the contribution of the colleagues at the uro-oncological board, at the Department of Pathology and Department of Urology, University of Szeged, and the National Institute of Oncology, Budapest.

I greatly appreciate all the support and work of high standard provided by physicians, technicians and physicists of the Department of Oncotherapy, University of Szeged.

Lastly, but most importantly I wish to thank to my family and friends for their unconditional love, care and measureless patience; my gratitude to them is beyond words.