Trends in Cancer Research
Vol. 9, 2013

Original Communication

A personalised treatment with image guided intensity modulated radiotherapy for high-very high risk and metastatic prostate cancer patients: preliminary results

Elisabetta Garibaldi[1,*], Gabriella Cattari[1], Domenico Gabriele[4], Elena Delmastro[1], Barbara Carau[5], Claudia Cutaia[2], Sara Bresciani[2], Cinzia Ortega[3] and Pietro Gabriele[1]

[1]Radiotherapy, [2]Medical Physics and [3]Medical Oncology Units, IRCCS – FPO Candiolo, Torino, Italy, [4]Physiology Institute, Neuroscience Department, University of Torino, Italy, [5]Radiotherapy Unit, Businco Oncology Hospital, Cagliari, Italy

ABSTRACT

83 patients with histologically confirmed high-very high risk prostate cancer or with nodal or distant metastatic disease were treated at IRCCS – FPO Cancer Institute of Candiolo, Torino, Italy, with definitive IMRT-SIB-IGRT technique using Tomotherapy in association with long-term hormone therapy in all patients excluding three. Cohort median follow-up is 14 months. Pre-treatment diagnostic evaluation was performed by multiparametric-MRI and choline-PET/CT in a high percentage of patients. The treatment consisted of extensive field irradiation of pelvic prophylactic nodes, positive nodes or distant metastasis if apparent, and in some patients also prophylactic lumbar-aortic nodes, in addition to prostate bed. Toxicity is acceptable with acute severe GU and GI toxicities respectively of 8% and 1%, and late severe GU and GI toxicities of 0% and 3%. Regarding the outcome, the median PSA nadir after radiotherapy is 0.03 ng/mL and, on considering the 69 patients with a follow-up for longer than 6 months, 66 patients are free from biochemical relapse, two are in clinical progression confirmed by choline-PET/CT, but none in RT treatment fields, and one is dead by cause other than prostate cancer. Hence in this group of patients we favour a personalized treatment thanks to the present day availability of extensive functional imaging in staging and tailored image-guided irradiation.

KEYWORDS: personalised medicine, IMRT, IGRT, high-very high risk, metastatic, prostate cancer

ABBREVIATIONS

PSA, Prostatic Specific Antigen; ADT, Androgen Deprivation Therapy; GU, Genito-Urinary; GI, Gastro-Intestinal; NCCN, National Comprehensive Cancer Network; RT, RadioTherapy; 3D-CRT, 3D Conformational Radiation Therapy; IMRT, Intensity Modulated Radiation Therapy; IGRT, Image Guided Radiation Therapy; MV, MegaVoltage; KV, KiloVoltage; SIB, Simultaneous Integrated Boost; TURP, Trans-Urethral Resection of the Prostate; HIFU, High Intensity Focused Ultrasounds; DCE, Dynamic Contrast-Enhanced; DWI, Diffusion-Weighted Imaging; PTV, Planning Target Volume; RP, Radical Prostatectomy; MAB, Maximal Androgen Blockade

INTRODUCTION

Prostate cancer is the most prevalent malignancy in males worldwide. A prognostic group with high risk of biochemical recurrence includes patients with T3a staging or those with biological characteristics of aggressiveness (GS $\geq$ 8 and/or PSA > 20 ng/mL), while patients with T3b to T4

*Corresponding author: elisabetta.garibaldi@ircc.it

staging are considered as very high risk. Patients with nodal disease, N1, are judged metastatic [1]. Androgen deprivation therapy (ADT) or radiation therapy plus long-term ADT (≥ 2 years) are efficient therapeutic options in these cases [2-7], while ADT is the standard therapy for distant metastatic prostate cancer, possibly associated to a palliative radiotherapy for symptomatic metastases.

The results of treatments in N+ patients are still disappointing, with a 20-50% biochemical progression free survival (b-PFS) at 5-10 years and a 35-60% overall survival (OS) at 10 years, with a median survival for androgen-independent metastatic carcinoma of only 18 months [8].

However, up-to-date technological advances both in the fields of imaging and radiotherapy can help to improve these results. Indeed, the availability of morphological and functional imaging, like multi-parametric MRI and choline-PET/CT, allows nowadays to visualize the disease sites in the prostate, showing the extra-capsular extension, and in the lymph nodes, the most frequent metastatic locations together with bones. However conventional RT techniques, like 3D-CRT, do not allow adequate treatment of a high risk or locally advanced disease requiring high doses both on prostate and on any positive node in addition to a prophylactic irradiation onto the pelvis, and sometimes lumbar-aortic lymphatic drainage. In fact, the existence of a close correlation between radiation dose and tumor control in prostate cancer is well known [9-16]. A recent study suggests that the plateau in the dose-response curve for prostate cancer may lie beyond 80 Gy [15]. Besides several studies confirm the usefulness of pelvic lymphatic prophylactic irradiation in patients with a significant risk of nodal involvement (≥ 15%, from Roach's equations [17-18]).

On the contrary, until now no literature data show a prognostic advantage in biochemical recurrence for patients treated with lumbar-aortic prophylactic irradiation. However, the inclusion of lumbar-aortic nodes in the radiotherapy fields in prostate cancer was already suggested in the seventies by Bagshaw. Unfortunately the study was stopped due to toxicity [19], probably related to the use of obsolete radiotherapy techniques, with large volumes of treatment including a large part of abdominal organs such as small bowel, kidneys, liver, stomach, pancreas and spinal cord.

Therefore an intensity modulated radiation technique (IMRT) can be useful to pursue a curative intent in high-very high risk patients, in which high doses have to be administered to extensive volumes. IMRT, indeed, can obtain a higher dose-conformation to the target volume and steeper dose gradients, allowing a dose-escalation to the tumor reducing concurrently the dose to the organs at risk (not only rectum and bladder but also small bowel, the critical organ in abdominal irradiation).

The result is an improved tumor control with reduced treatment toxicity, as already shown in literature [20-25]. Moreover IMRT allows a concomitant administration of different dose levels on prostate and nodal volumes by simultaneous integrated boost (SIB) technique, due to the implementation of hypo-fractionation protocols [26] based on prostate cancer radiobiology [27]. In literature, there are several prostate hypo-fractionation trials (retrospective and prospective) with whole pelvic irradiation, that show low rates of severe acute and late toxicity: G3-4 genitourinary acute toxicity 0-6%; G3-4 genitourinary late toxicity 0-6%; G3-4 gastrointestinal acute toxicity 0%; G3-4 gastrointestinal late toxicity 0-2% [28-32]. However, IMRT requires improved procedures to control treatment accuracy, achievable through Image-Guided Radio-Therapy (IGRT). An IGRT method is the use of MV or KV-CT before irradiation to check patient set-up and organ motion (mainly due to rectum and bladder filling) [33].

Several linacs are equipped with volumentric IGRT systems: in particular Tomotherapy devices realize a helical IMRT due to the rotational movement of the gantry and to the concomitant translational movement of the couch, with an onboarding integrated CT megavoltage system, to perform a daily IGRT. Literature regarding new imaging tools to guide the delivery of higher radiation doses in a wide abdominal area while minimizing radiation toxicity is increasing fast.

So we have developed at our center a clinical protocol in order to treat patients with IMRT with

simultaneous integrated boost (SIB) and IGRT by Tomotherapy onto an extended volume including prostate bed and pelvic ± lumbar-aortic nodes (as showed by MRI/choline-PET imaging) with the maximum avoidance of organs at risk (rectum, bladder, small bowel, kidneys, liver, stomach etc), realizing a very personalized treatment. The aim of this paper is to present the preliminary results of our protocol, in terms of toxicity and outcome.

MATERIALS AND METHODS

Between October 2010 and June 2013, 93 patients with histologically confirmed high-very high risk prostate cancer or with nodal or distant metastatic disease were treated at IRCCS – FPO Cancer Institute of Candiolo, Torino, Italy, with definitive IMRT-SIB-IGRT technique using Tomotherapy ± ADT. Patients were stratified in high-very high risk and metastatic prognostic groups according to NCCN guidelines. Ten patients were lost at the follow-up and so the cohort of the study is composed by 83 patients assessable in terms of toxicity and outcome with a median follow-up of 14 months.

Demographics and anamnestic characteristics of the cohort are shown in Table 1, while staging statistics are illustrated in Table 2. Four patients had conservative treatment on the prostate before radiotherapy (2 TURP and 2 HIFU). Urinary symptoms, mainly dysuria, were present before radiotherapy in the 37% of the cohort. Initial PSA average was 30.82 and median 12.96 ng/mL. In 17 patients before RT a zenith-PSA higher than initial PSA was also assessable with a median of 18.8 ng/mL and in 13 patients a post-neoadjuvant hormone-therapy pre-RT PSA was evaluated with a median of 1.27 ng/mL.

Pre-treatment diagnostic evaluation was performed by multiparametric-MRI (including DCE and DWI series), in order to evaluate extra-prostatic extension and/or nodal involvement. If unavailable, in ongoing ADT patients, a CT scan and/or an endorectal ultrasound were used. Bone scan was performed to evaluate a bone involvement. A choline-PET/CT was performed in patients with suspected positive lymph nodes at CT or MRI

Table 1. Demographics and anamnestic characteristics.

Age	Average (yy) Median (yy) Range (yy)	71 73 56 to 84
Anti-aggregation or anticoagulant therapy	YES NO	27% 73%
Diabetes	YES NO	8% 92%
Hemorrhoids	YES NO	13% 87%
Obesity	YES NO	1% 99%
Diverticulosis	YES NO	8% 92%
Cardiovascular diseases	YES NO	33% 67%
Hypertension	YES NO	46% 54%
Pre-RT urinary symptoms	YES NO	37% 63%
Pre-RT major abdominal surgery	YES NO	27% 73%
Pre-RT prostate conservative surgery (not RP)	YES NO	5% 95%

Table 2. Staging statistics.

iPSA	Average (ng/mL)	30.82
	Median (ng/mL)	12.96
	SD (ng/mL)	59.74
	Min (ng/mL)	2.3
	Max (ng/mL)	386
Gleason score	3 + 3	14%
	3 + 4	14%
	4 + 3	16%
	4 + 4	33%
	3 + 5	2%
	5 + 3	7%
	4 + 5	11%
	5 + 4	0%
	5 + 5	2%
Clinical and radiological staging	I	1%
	IIA	0%
	IIB	39%
	III	30%
	IV	30%
Prognostic classes	High risk	59%
	Very high risk	10%
	Metastatic	31%

imaging or with positive bone scan. MRI was performed in 59 (71%) patients and PET/CT in 31 (37%), and both exams were performed in 22 (27%) patients.

Hormone therapy was administered only to 80 patients, because 3 patients refused it. Hormonal therapy is still ongoing in 66 patients, while in 14 patients it is already finished with a median last of 25 months. In 72 patients hormone-therapy consisted of long term LH-RH analogues alone. Long term anti-androgen alone was used in 5 patients and a Maximal Androgen Blockade (MAB) in 3 patients.

Patients were treated by IMRT-SIB-IGRT using Tomotherapy Hi-Art system from October 2010 and Tomotherapy HD System from March 2012 (Accuray, Inc., Madison, Wisconsin, USA). Set-up was in supine position, using Pro-Step (Q-Fix) system, with an empty rectum and a comfortably full bladder. In patients requiring an upper abdominal irradiation, like lumbar-aortic nodes, the Harm Shuttle system was also used to keep arms above the head, away from irradiation fields. A dietary education was imparted by the nursing staff in order to get a proper intestinal and bladder preparation.

The protocol volumes and prescribed doses were the following (see also Figure 1):

1) Prostate target volume including prostate gland with an adequate margin, relating to the presence of extra-capsular extension (PTV-P). The total dose to PTV-P was 75.2 Gy in 32 fractions using a moderate hypo-fractionation of 2.35 Gy per die;

2) Seminal vesicles target volume, including the seminal vesicles with an adequate margin, relating to the presence of extra-vesicle extension (PTV-SV). The total dose to PTV-SV was 75.2 Gy in 32 fractions (dose per fraction 2.35 Gy) if an involvement was confirmed by imaging (MRI, ultrasound, CT or choline-PET/CT), or 67.2 in 32 fractions (2.1 Gy per fraction) if vesicle involvement was not apparent;

3) Positive nodal volumes, as showed by imaging, including a margin of 8 mm (PTV-N+). The total dose delivered to PTV-N+ ranged between

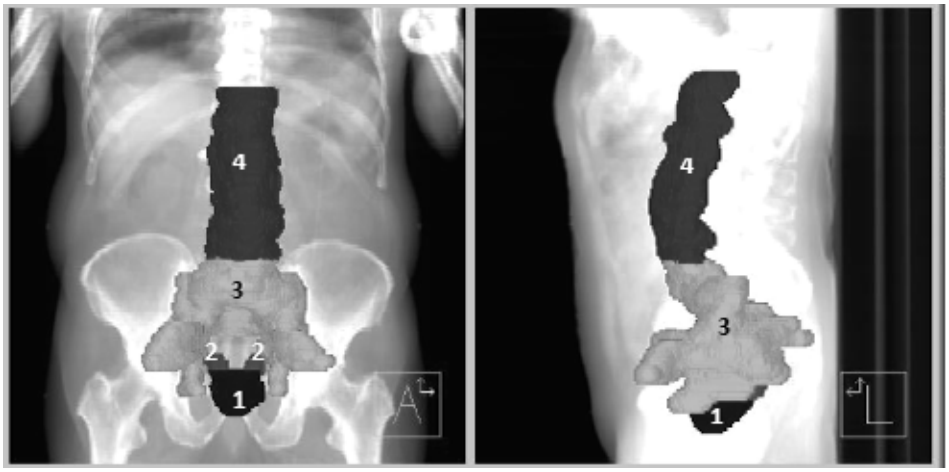

Figure 1. Irradiated volumes: prostate (1), seminal vesicles (2), pelvic prophylactic nodes (3), lumbar-aortic prophylactic nodes (4).

60 and 70.4, according to constraints at OARs (with dose per fraction ranging between 2 and 2.35 Gy);

4) Pelvic prophylactic nodal volume, with a margin of 5 mm (PTV-pelvis). The total dose to PTV-pelvis was 54.4 Gy in 32 fractions (1.7 Gy per die);

5) Lumbar-aortic prophylactic nodal volume, with a margin of 5 mm (PTV-LA). The total dose to PTV-LA was 54.4 Gy in 32 fractions (with 1.7 Gy per die);

6) Distant metastatic sites were treated, delivering the higher radical doses compatible with constraints observance, with an average of 50 Gy and a standard deviation of 8 Gy.

All patients were irradiated prophylactically onto the pelvis. Four patients received a prophylactic dose onto the lumbar-aortic lymph nodes too; 22 patients had increased doses on positive nodes and 5 were treated also for distant metastases.

All organs at risk were contoured including rectum, bladder, femoral heads, anus, penile bulb, sigma-colon, small bowel (defined as intestinal cavity), right and left ureters and, for upper abdominal irradiation, liver, kidneys, pancreas, stomach, spinal cord, spleen. Tumor coverage and dose constraints to organs at risk were evaluated according to ICRU Report No. 62 and 83 [34-35] and QUANTEC recommendations [36]. A daily megavoltage CT imaging (MVCT) was performed to verify treatment reproducibility.

All patients were clinically evaluated during radiotherapy weekly for acute toxicity and every 3 months after the end of treatment for acute and late toxicity, according to RTOG-EORTC scale. If a lumbar-aortic irradiation was required, haematological, hepatic, renal and pancreatic functions were assessed by laboratory exams. In patients with a persistent toxicity during follow up, diagnostic examinations were performed, including proctoscopy and/or colonscopy and cystoscopy.

In patients with biochemical rising during follow-up, in presence of a definite biochemical relapse (Phoenix criteria) or of suspicious prognostic clues like a high PSA doubling-time, a diagnostic evaluation (bone scan, choline-PET/CT, MRI, CT scan) was performed.

The outcome was evaluated as biochemical control. A biochemical relapse was defined according to the Phoenix system and clinical relapse was defined as demonstrated recurrence by imaging.

RESULTS

All patients but 3 received the prescribed doses of our protocol. For one patient, affected by a cT2c cN1 M0 prostate cancer, a conventional fractionation (with 2 Gy per die) was used due to constraints to small bowel, that was too close to prostatic bed. Total doses for this patient were 54 Gy on the pelvic volume, 60 Gy on the seminal

vesicles and positive nodes, and 78 Gy on the prostatic volume. Two patients stopped treatment after 30th session for intolerance.

Overall patient compliance was acceptable with a mean interruption of 2 days (SD 2.17). One patient required an interruption of 16 days due to a Herpes Zoster Virus infection in the treated area; he completed radiotherapy after healing. Tomotherapy treatment sessions lasted 7.5 min on average with a SD of 1.8 min.

Average doses and volumes on PTVs are reported in Table 3 and on OAR in Table 4, while acute and late toxicity data are shown in Table 5.

Fourteen patients of the 83 of the cohort still have a follow-up lower than 6 months; hence only the remaining 69 patients were evaluated for late toxicity.

Severe acute toxicity (≥ G3) was observed in six patients for genitourinary (GU) and in one patient for gastrointestinal (GI) symptoms.

Four patients had an acute urinary obstruction, requiring bladder catheter. For three patients the obstruction appeared after few sessions of treatment and it resolved in a week with antibiotics, cortisones and alpha-lytic therapy. Of these 3 patients, two had previous episodes of acute urinary obstruction in their clinical history. In the fourth patient the acute urinary obstruction appeared 5 months after the end of radiotherapy requiring bladder catheter and it persisted for 1 month and a half. He had in his clinical history a benign prostatic hypertrophy which was treated, 6 years earlier, by trans-urethral resection of the prostate.

Table 3. Delivered doses and volumes of treatment.

Prostate	D95% ± SD (Gy) Dmean ± SD (Gy)	73.8 ± 2.6 75.9 ± 5
Seminal vesicles	D95% ± SD (Gy) Dmean ± SD (Gy)	68.8 ± 3.7 72.7 ± 2.7
Prophylactic pelvic nodes	D95% ± SD (Gy) Dmean ± SD (Gy)	54.1 ± 2.3 56.2 ± 2.4
N positive nodes	Mean volume ± SD (mL) D95% ± SD (Gy) Dmean ± SD (Gy)	67 ± 72 62.5 ± 3 64.5 ± 3

Table 4. OAR doses and volumes.

Rectum	V75 (%), mean ± SD V70 (%), mean ± SD V50 (%), mean ± SD Dmax (Gy), mean ± SD	3.2 ± 4.6 14.3 ± 7.4 40.1 ± 7.5 75.9 ± 4.2
Small bowel	Volume (mL), mean ± SD V45 (mL), mean ± SD	2956 ± 1380 118 ± 52
Urinary bladder	Volume (mL), mean ± SD V70 (%), mean ± SD Dmean (Gy), mean ± SD Dmax (Gy), mean ± SD	274 ± 164 18.2 ± 9.7 47.7 ± 6.6 78.3 ± 1.5
Ureters	Dmean (Gy), mean ± SD Dmax (Gy), mean ± SD	30.5 ± 6.5 68.9 ± 5
Femoral heads	Dmean (Gy), mean ± SD	28.6 ± 6.2
Penile bulb	Dmean (Gy), mean ± SD	62.9 ± 10.3

Table 5. Acute and late toxicity (RTOG-EORTC scale).

Acute genito-urinary	0	24%
	1	54%
	2	14%
	3	3%
	4	5%
Acute gastro-intestinal	0	44%
	1	40%
	2	15%
	3	1%
	4	0%
Acute skin toxicity	0	90%
	1	6%
	2	4%
	3	0%
	4	0%
Late genito-urinary	0	72%
	1	22%
	2	6%
	3	0%
	4	0%
Late gastro-intestinal	0	70%
	1	20%
	2	7%
	3	3%
	4	0%

Concerning late toxicity, 2 patients have severe late GI toxicity (≥ G3), precisely histologically documented proctitis requiring local treatment (Figure 2). No patient had small bowel late toxicity or showed severe hematological toxicity or liver, renal or pancreatic dysfunctions, as reveled by hematochemical evaluation; moreover no patient until now shows severe GU late toxicity.

Evaluating the outcome, the median of PSA nadir after radiotherapy is 0.03 ng/mL, the mean 0.15 and the SD 0.34 ng/mL.

Regarding the clinical status of the 69 patients with a follow-up longer than 6 months, 66 are free from biochemical relapse (Figure 3), two are in clinical progression confirmed by PET/CT and one is dead by other cause, that is not by prostate cancer.

The first relapsed patient was a cT3a cN0 M0, GS 9 (4 + 5), iPSA 98.4 treated on prostate, seminal vesicles and with a prophylactic pelvic irradiation. 16 months after the end of radiotherapy the patient had a biochemical relapse confirmed clinically by bone scintigraphy and PET/CT demonstrating a single lumbar bone metastasis, then treated by RT with a good biochemical control. The second one, cT2c cN1 M0 at staging with a PET-positive pelvic node, GS 10 (5 + 5), iPSA 47, had an RT treatment on the prostate associated to a prophylactic pelvic irradiation with a boost on the positive node, according to our protocol. Thirteen months after the end of treatment he had a biochemical comeback and PET/CT showed positive lumbar-aortic nodes, where later on a second salvage RT treatment was performed with a good biochemical control.

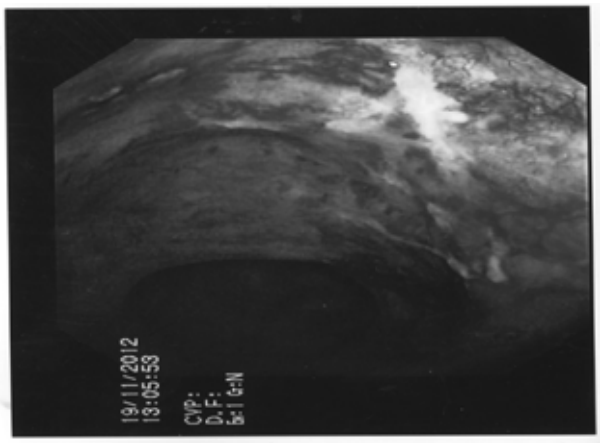

Figure 2. Actinic proctitis at proctoscopy.

Interestingly none of the 3 patients treated only by RT without androgen deprivation therapy has shown relapse.

DISCUSSION

The prognosis of high-very high risk and metastatic prostate cancer is until now disappointing and an up-to-date multimodal approach is essential to offer the maximum chances of cure [37]. Often failure is caused by unknown metastasis at diagnosis. In the past predictive formulae like Roach ones could only predict statistically the probability of ECE and nodal metastatization. But these days, modern imaging, mainly functional MRI and PET/CT, can greatly help to disclose the presence of nodal and bone metastasis, and lead to earlier irradiation of lymphatic drainage and even metastatic

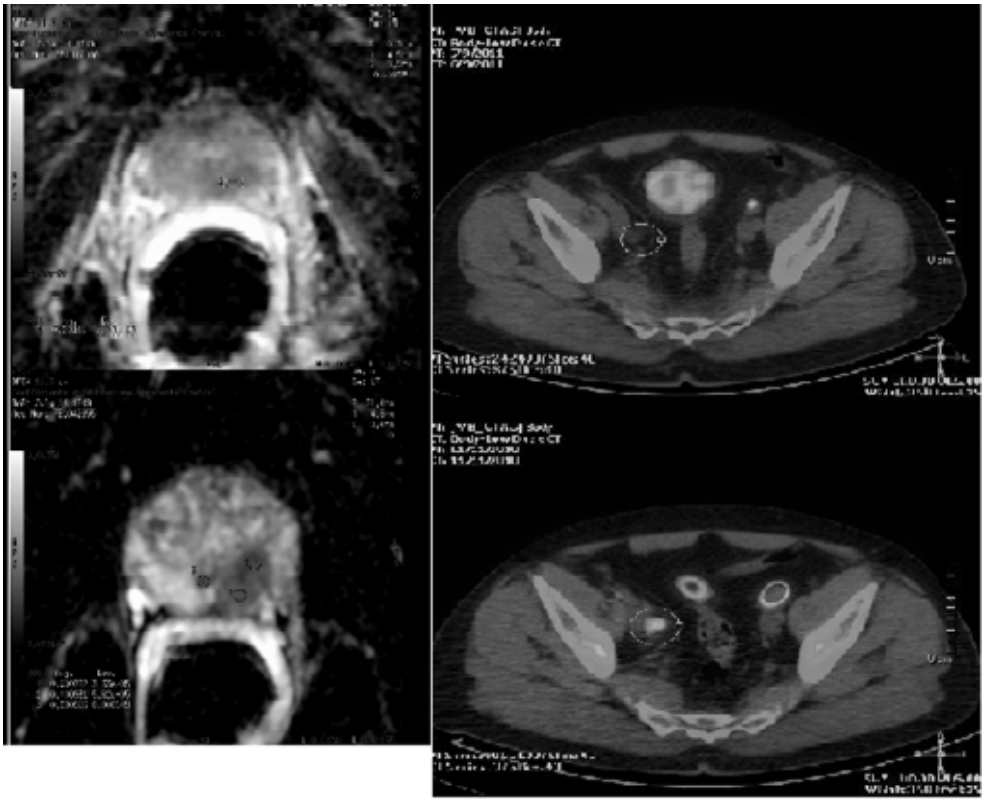

Figure 3. Clinical Case: iPSA 121 ng/mL, GS 8 (5 + 3), staging cT3b cN1 M0, MRI and CT-PET before (below) and after (above) RT treatment.

sites with a radical intent. The advantage of prophylactic nodal irradiation in high-very high risk prostate cancer patients has already been demonstrated in some literature studies [38-40], while regarding N+ irradiation literature is scarce. Besides, literature regarding MRI or PET/CT guided radiotherapy is increasing in head and neck, lung and gynecologic cancers, and offers wide perspectives also in prostate tumors [41]. Moreover modern RT techniques like IMRT-IGRT allow a more precise irradiation, possibly combining wide fields, higher doses on positive nodes and sparing organs at risk [42].

In our cohort a high percentage of patients was staged with MRI (71%) and with PET/CT (37%) allowing to disclose 20 N+ patients and 5 M+ patients. Thanks to the high RT doses delivered even in the metastatic sites, no patient has until now relapsed in the RT fields; however it should be taken into consideration that the result is only preliminary due to the short 14 months median follow-up and the ongoing ADT in a high percentage of patients. Acute and late toxicities are acceptable and, apart from nausea, no collateral effect has been observed on bowel or upper abdomen.

CONCLUSION

Our study shows the feasibility of wide field, high dose radiotherapy on high-very high and metastatic prostate cancer patients treated with radical intent in association with long term hormone-therapy; in fact irradiation included pelvic prophylactic nodes, positive nodes or distant metastasis if apparent, and in some patients also prophylactic lumbar-aortic nodes.

In our series we observed 2 recurrent patients, one of whom, with lumbar-aortic recurrence, was at diagnosis pelvic N1. We irradiated lumbar-aortic nodes only when imaging became positive in this area. Perhaps patients with pelvic N1 at diagnosis could benefit from a prophylactic lumbar-aortic irradiation. Studies are needed to define the utility of such irradiation.

At last modern imaging is fundamental to recognize the correct disease extension so as to help the precise dose delivery for a highly shaped treatment. The main pitfall of the study is the short follow up, but we foresee to update our cohort follow-up within 18 months with an extended median follow-up of about 30 months.

ACKNOWLEDGMENTS

The authors would like to thank the 5/1000 program of the Italian Association for Cancer Research (AIRC).

CONFLICT OF INTEREST STATEMENT

None to declare.

REFERENCES

1. NCCN guidelines 2013. www.nccn.com
2. Denham, J. W. and Steigler, A. 2013, Semin. Radiat. Oncol., 23, 206-214.
3. Pilepich, M. V., Winter, K., Lawton, C. A., Krisch, R. E., Wolkov, H. B., Movsas, B., Hug, E. B., Asbell, S. O. and Grignon, D. 2005, Int. J. Radiat. Oncol. Biol. Phys., 61, 1285-1290.
4. Bolla, M., Collette, L., Blank, L., Warde, P., Dubois, J. B., Mirimanoff, R. O., Storme, G., Bernier, J., Kuten, A., Sternberg, C., Mattelaer, J., Lopez Torecilla, J., Pfeffer, J. R., Lino Cutajar, C., Zurlo, A. and Pierart, M. 2002, Lancet, 360, 103-108.
5. Hanks, G. E., Pajak, T. F., Porter, A., Grignon, D., Brereton, H., Venkatesan, V., Horwitz, E. M., Lawton, C., Rosenthal, S. A., Sandler, H. M. and Shipley, W. U. 2003, J. Clin. Oncol., 21, 3972-3978.
6. Horwitz, E. M., Bae, K., Hanks, G. E., Porter, A., Grignon, D. J., Brereton, H. D., Venkatesan, V., Lawton, C. A., Rosenthal, S. A., Sandler, H. M. and Shipley, W. U. 2008, J. Clin. Oncol., 26, 2497-2504.
7. Bolla, M., De Reijke, T. M., Van Tienhoven, G., Van den Bergh, A. C., Oddens, J., Poortmans, P. M., Gez, E., Kil, P., Akdas, A., Soete, G., Kariakine, O., Van der Steen-Banasik, E. M., Musat, E., Pierart, M., Mauer, M. E. and Collette, L. 2009, N. Engl. J. Med., 360, 2516-2527.
8. Hansen, E. K. and Roach, M. III. 2010, Hand-book of evidence-based Radiation Oncology –Second Edition, Springer.
9. Dearnaley, D. P., Sydes, M. R., Graham, J. D., Aird, E. G., Bottomley, D., Cowan, R. A., Huddart, R. A., Jose, C. C., Matthews, J. H., Millar, J., Moore, A. R., Morgan, R. C., Russell, J. M., Scrase, C. D., Stephens, R. J., Syndikus, I. and Parmar, M. K. 2007, Lancet Oncol., 8, 475-487.
10. Hanks, G. E., Hanlon, A. L., Epstein, B. and Horwitz, E. M. 2002, Int. J. Radiat. Oncol. Biol. Phys., 54, 427-435.
11. Peeters, S. T., Heemsbergen, W. D., Koper, P. C., van Putten, W. L., Slot, A., Dielwart, M. F., Bonfrer, J. M., Incrocci, L. and Lebesque, J. V. 2006, J. Clin. Oncol., 24, 1990-1996.
12. Pollack, A., Zagars, G. K., Smith, L. G., Lee, J. J., von Eschenbach, A. C., Antolak, J. A., Starkschall, G. and Rosen, I. 2000, J. Clin. Oncol., 18, 3904-3911.
13. Zelefsky, M. J., Leibel, S. A., Gaudin, P. B., Kutcher, G. J., Fleshner, N. E., Venkatramen, E. S., Reuter, V. E., Fair, W. R., Ling, C. C. and Fuks, Z. 1998, Int. J. Radiat. Oncol. Biol. Phys., 41, 491-500.
14. Zietman, A. L., DeSilvio, M. L., Slater, J. D., Rossi, C. J. Jr., Miller, D. W., Adams, J. A. and Shipley, W. U. 2005, JAMA, 294, 1233-1239.
15. Eade, T. N., Hanlon, A. L., Horwitz, E. M., Buyyounouski, M. K., Hanks, G. E. and Pollack, A. 2007, Int. J. Radiat. Oncol. Biol. Phys., 68, 682-689.
16. Zelefsky, M. J., Yamada, Y., Fucks, Z., Zhang, Z., Hunt, M., Cahlon, O., Park, J. and Shippy, A. 2008, Int. J. Radiat. Oncol. Biol. Phys., 71, 1028-1033.
17. Roach, M. III., Marquez, C., Yuo, H. S., Narayan, P., Coleman, L., Nseyo, U. O., Navvab, Z. and Carroll, P. R. 1994, Int. J. Radiat. Oncol. Biol. Phys., 28, 33-37.
18. Lawton, C. A., DeSilvio, M., Roach, M. III., Uhl, V., Kirsch, R., Seider, M., Rotman, M., Jones, C., Asbell, S., Valicenti, R., Hahn, S. and Thomas, C. R. Jr. 2007, Int. J. Radiat. Oncol. Biol. Phys., 69, 646-655.
19. Bagshaw, M. A., Pistenma, D. A., Ray, G. R., Freiha, F. S. and Kempson, R. L. 1977, Cancer Treat. Rep., 61, 297-306.

20. Zelefsky, M. J., Chan, H., Hunt, M., Yamada, Y., Shippy, A. M. and Amols, H. 2006, J. Urol., 176, 1415-1419.
21. Ashman, J. B., Zelefsky, M. J., Hunt, M. S., Leibel, S. A. and Fuks, Z. 2005, Int. J. Radiat. Oncol. Biol. Phys., 63, 765-771.
22. Liu, Y. M., Shiau, C. Y., Lee, M. L., Huang, P. I., Hsieh, C. M., Chen, P. H., Lin, Y. H., Wang, L. W. and Yen, S. H. 2007, Int. J. Radiat. Oncol. Biol. Phys., 67, 1113-1123.
23. Su, A. W. and Jani, A. 2007, Am. J. Clin. Oncol. Cancer Clin. Trials, 30, 215-219.
24. Shih, H. A., Harisinghani, M., Zietman, A. L., Wolfgang, J. A., Saksena, M. and Weissleder, R. 2005, Int. J. Radiat. Oncol. Biol. Phys., 63, 1262-1269.
25. Wang-Chesebro, A., Xia, P., Coleman, J., Akazawa, C. and Roach, M. III. 2006, Int. J. Radiat. Oncol. Biol. Phys., 66, 654-662.
26. Li, X. A., Wang, J. Z., Jursinic, P. A., Lawton, C. A. and Wang, D. 2005, Int. J. Radiat. Oncol. Biol. Phys., 61, 1251-1257.
27. Fowler, J., Chappell, R. and Ritter, M. 2001, Int. J. Radiat. Oncol. Biol. Phys., 50, 1021-1031.
28. Hong, T. S., Tomé, W. A., Jaradat, H., Raisbeck, B. M. and Ritter, M. A. 2006, Acta Oncol., 45, 717-727.
29. Di Muzio, N., Fiorino, C., Cozzarini, C., Alongi, F., Broggi, S., Mangili, P., Guazzoni, G., Valdagni, R., Calandrino, R. and Fazio, F. 2009, Int. J. Radiat. Oncol. Biol. Phys., 74, 392-398.
30. Adkison, J. B., McHaffie, D. R., Bentzen, S. M., Patel, R. R., Khuntia, D., Petereit, D. G., Hong, T. S., Tomé, W. and Ritter, M. A. 2012, Int. J. Radiat. Oncol. Biol. Phys., 82, 184-190.
31. Quon, H., Cheung, P. C., Loblaw, D. A., Morton, G., Pang, G., Szumacher, E., Danjoux, C., Choo, R., Thomas, G., Kiss, A., Mamedov, A. and Deabreu, A. 2012, Int. J. Radiat. Oncol. Biol. Phys., 82, 898-905.
32. Fonteyne, V., De Gersem, W., De Neve, W., Jacobs, F., Lumen, N., Vandecasteele, K., Villeirs, G. and De Meerleer, G. 2009, Int. J. Radiat. Oncol. Biol. Phys., 75, 1013-1020.
33. van Herk, M. 2007, Semin. Radiat. Oncol., 17, 258-267.
34. ICRU: International Commission on Radiation Units and Measurements (ICRU). Prescribing, Recording and Reporting Photon Beam Therapy, ICRU Report 62.
35. ICRU: International Commission on Radiation Units and Measurements (ICRU). Prescribing, Recording, and Reporting Photon-Beam Intensity-Modulated Radiation Therapy (IMRT), ICRU Report 83.
36. Marks, L. B., Yorke, E. D., Jackson, A., Ten Haken, R. K., Constine, L. S., Eisbruch, A., Bentzen, S. M., Nam, J. and Deasy, J. O. 2010, Int. J. Radiat. Oncol. Biol. Phys., 76, S10-S19.
37. Rozet, F., Audenet, F., Sanchez-Salas, R., Galiano, M., Barret, E. and Cathelineau, X. 2013, Expert Rev. Anticancer Ther., 13, 811-8.
38. Morikawa, L. K. and Roach, M. III. 2011, Int. J. Radiat. Oncol. Biol. Phys., 80, 6-16.
39. Spiotto, M. T., Hancock, S. L. and King, C. R. 2007, Int. J. Radiat. Oncol. Biol. Phys., 69, 54-61.
40. Aizer, A. A., Yu, J. B., McKeon, A. M., Decker, R. H., Colberg, J. W. and Peschel, R. E. 2009, Int. J. Radiat. Oncol. Biol. Phys., 75, 1344-1349.
41. Würschmidt, F., Petersen, C., Wahl, A., Dahle, J. and Kretschmer, M. 2011, Radiat. Oncol., 6, 44.
42. Bresciani, S., Cattari, G., Garibaldi, E., Di Dia, A., Delmastro, E., Maggio, A., Stasi, M. and Gabriele, P. 2013, Abstract, 2nd ESTRO Forum 2013, 5451-2.