PROTON THERAPY CENTER

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Regular news from proton therapy

No disease recurrence in patients with prostate cancer treated with proton therapy in Prague

From December 2012 to December 2014, the Proton centre in Prague used the proton radiotherapy in the stereotactic mode in 86 patients with non-metastatic prostate cancer without previous surgical intervention. The whole group of the monitored **patients included no cases of PSA relapse. The toxicity level is still very good, usually below the published values for the IMRT radiotherapy.**

The demographic characteristics are shown in the Table 1. The patients were treated with single radiotherapy or the its combination with hormonal therapy. The therapeutic characteristics are shown in the Table 2. The results of the initial treatment assessment are provided in the Table 3.

Demographic characteristics		
N		86
Age (median)		63,1 years
Risk group (NCCN)	1	57 (66%)
	2	29 (34%)
Initial PSA (median)		5,75
Adenocarcinoma	GS 6	63 (73,2%)
	GS 7	22 (25,6%)
	GS not specified	1 (1,2%)

Therapeutic characteristics		
Dose		36.25 CGE/5 fractions
Target volume	Prostate	86 patients (100%)
Total treatment duration (median)		9 days
Hormonal therapy	Neoadjuvant	16 (18,6%)
	Adjuvant	0 (0%)

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Results		
FU (median)		11 m (5-26)
PSA relapse		0 (0%)
Acute GU toxicity	Gr 0	29 (33,7%)
	Gr 1	45 (56,9%)
	Gr 2	13 (15,1%)
Acute GI toxicity	Gr 0	76 (88,3%)
	Gr 1	7 (81,3%)
	Gr 2	3 (3,4%)
Late GU toxicity	Gr 0	72 (83,7%)
	Gr 1	14 (16,2%)
	Gr 2	0 (0%)
Late GI toxicity	Gr 0	76 (88,3%)
	Gr 1	8 (9,3%)
	Gr 2	2 (2,3%)

Proton radiotherapy in prostate cancer:
5-10% better survival rate without biochemical relapse and 2-3-fold lower incidence of late adverse events

The proton or particle radiotherapy has an important position in the treatment of prostate cancer. Its advantage, compared to the photon therapy techniques, is the more favourable dose distribution in the tissues in the treatment of the prostate cancer. This dosimetric advantage increases with the increasing size of the target volume and in the target volumes of a complex shape (for example, irradiation of seminal vesicles or lymph nodes).

Particle irradiation therapy has been used in the treatment of prostate cancer for decades. Its dosimetric benefits are well documented and there is a significant reduction of the dose to the critical organs and the integral dose, as confirmed by long-term data on its high efficiency and safety. Recent results of prospective studies are summarized in the Table 1.

Author	Number of patients	Mode	FU (median)	5 year survival without biochemical relapse	Toxicity	Note
Mendenhall et al., 2014 (1)	211 (89 low risk, 82 intermediate risk, 40 high risk)	78-82 CGE/ 39-41 fr	5,2 y	Low risk - 99 % Intermediate risk - 99 % High risk - 76 %	CTCEA v.4 (grade 3+) GI - 0,5 % GU - 1 %	High risk in combination with HORT and CHT
Henderson et al., 2015 (2)	228 (122 low risk, 106 intermediate risk)	70 CGE/28 fr or 72,5/29 fr	4,9 y	Low risk - 99,2 % Intermediate risk - 92,6 %	CTCEA v.4 (grade 3+) GI - 0,9 % GU - 0,9 %	Without adjuvant HORT
Takagi et al., 2015 (3)	1375 (249 low risk, 602 intermediate risk, 499 high risk)	74 CGE/ 37 fr	5,8 y	Low risk - 98,7 % Intermediate risk - 90,8 % High risk - 85,6 %	CTCEA v.4 (grade 2+) GI - 4,1 % GU - 5,4 %	Only 4% of patients with adjuvant hort

These results are better than the recent work published in the field of the photon radiotherapy. For example, Spratt et al. (4) describe 5-year biochemical relapse-free survival in intermediate-risk prostate cancer treated with either external radiotherapy using the IMRT technique or the combination of IMRT and brachytherapy at the level of approximately 90% for IMRT (81.4% after 7 years) and approximately 95% in the combination of IMRT and BRT (92% after 7 years). Grade 2 toxicity or higher (CTCAE v. 4) reached the following levels at the evaluation after 7 years: GU (genitourinary) – 19.6% for IMRT and 21.2% for the combined treatment; grade 3 GU toxicity was 3.1 and 1.4%, respectively; GI (Gastrointestinal) – grade 2 and above 4.6 and 4.1%, respectively; grade 3 0.4% and 1.4%, respectively.

Summary

Recent published results for proton radiotherapy indicate 5-10% better survival rate without biochemical relapse and 2-3-fold lower incidence of late adverse events.

Refuting the myths about the proton therapy in the treatment of prostate cancer and the arguments for its use

Particle radiotherapy in prostate cancer provides the best dose distributions of all the available radiotherapy techniques. Prospective, non-randomized studies document its high efficiency and very low toxicity. When used in accelerated modes, its cost is comparable to modern photon radiotherapy techniques.

Whether out of ignorance or intentionally, there are occasional arguments against against the proton therapy in the treatment of prostate cancer. However, they are not based on valid data and provide a misleading interpretation of the facts.

- **The first example is the fact that the American Society for Radiation Oncology did not recommend the proton therapy. This argument is completely false.**
- **Conversely, ASTRO supported the use of the proton radiotherapy in the treatment of prostate cancer within clinical trials or registries in 2013 – "While proton beam therapy is not a new technology, its use in the treatment of prostate cancer is evolving. ASTRO strongly supports allowing for coverage with evidence development for patients treated on clinical trials or within prospective registries. ASTRO believes that collecting data in these settings is essential to informing consensus on the role of proton therapy for prostate cancer, especially insofar as it is important to understand how the effectiveness of proton therapy compares to other radiation therapy modalities such as IMRT and brachytherapy."**

- **In its model, the same ASTRO committee recommended proton therapy reimbursement from health insurance in 2014.**

- **The argument against the proton radiation therapy based on a relatively low dosimetric benefit of the proton radiotherapy in comparison with IMRT is also problematic. This statement is true only partially for passive modes of proton radiotherapy, already considered obsolete. Pencil beam scanning techniques (IMPT) lead to about 50% improvement in the dose distribution for the rectum and bladder (6). Using data applicable to passive modes of proton radiotherapy is therefore misleading and incorrect.**

- **According to another argument, the proton radiotherapy of the prostate cancer is not performed in the proton centres world-wide. This argument is completely false. On the contrary, all the centres (and these are the leaders of the world of oncology) include it in their basic indications. See, for example:**

- **MD Anderson Cancer Center**
- **MGH Boston**
- **UPENN**
- **University of Florida**

- **Another argument, basically the only clinical argument, is the work of Sheets et al. (5) which shows a higher incidence of late gastrointestinal toxicity in the proton radiotherapy compared to IMRT (17.8% vs. 12.2%). This study has a number of methodological problems.**
- **First of all, it was only a comparison of data of health insurance companies – on the one hand, radiotherapy with protons or photons, the second parameter was the rectoscopy number. The higher number of rectoscopy examinations in the group treated with protons lead perhaps to the hypothesised higher toxicity of the proton radiotherapy. However, we may assume that patients treated with protons form a specific group of patients who care more about their health and thus undergo more frequent examinations, including the rectoscopy. Likewise, radiation oncologists working with protons indicate the control examinations more frequently as a part of the monitoring. In addition, the population study was performed in a time period when the proton radiotherapy in the monitored data was available only in one proton centre using higher doses than for IMRT. This paper cannot be consider a valid and powerful source of data against the proton radiotherapy.**

- **The final argument against proton therapy is a disproportionate price. This argument is also no longer valid. The cost of proton radiotherapy are mainly dependent on the number of irradiation fractions. The standard procedures used in most centres in the past were based on the modes of normo-fractionated or moderately accelerated radiotherapy (i.e. 30-40 fractions). To reduce the costs, proton radiation therapy is now used in accelerated procedures or as stereotactic radiotherapy (7). This way, it is possible to achieve a comparable or lower cost than the contemporary techniques of photon radiotherapy.**

The facts about the proton therapy:

1. Particle radiation therapy does not have a higher toxicity than modern IMRT – the long term results shown in the Table 1 demonstrate a very low long-term toxicity of the particle radiotherapy. The quality of life of patients is affected to the minimal extent.

2. Particle radiotherapy is highly effective – in the absence of randomized data, the results from prospective, non-randomized studies are more favourable for this treatment than for most other modalities.

3. Particle therapy is not significantly more expensive than other modalities – using the accelerated fractionation / the stereotactic radiotherapy, the costs of the proton radiotherapy are comparable to the costs of advanced IMRT.

4. Proton radiotherapy is not associated with a higher risk of secondary malignancies due to a higher secondary neutrons load – conversely, the proton radiotherapy with the active scanning technology has significantly lower secondary neutron contamination compared to the techniques of photon radiotherapy. Even when using obsolete methods of passive scattering, the incidence of secondary malignancies is lower (5.2% vs. 7.5%, statistically not significant, (8)) for protons than for photons.

References

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