

ATM variant P1054R and risk of radiation-induced morbidity in patients treated with permanent interstitial brachytherapy for early stage prostate cancer

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Background

Prostate cancer is associated with defective DNA strand break repair after DNA damage leading to genetic instability and prostate cancer progression [1]. The ATM (ataxia-telangiectasia mutated) gene product is known to play an important role in cell cycle regulation and maintenance of genomic integrity. Angele et al. [2] previously reported that the ATM substitution P1054R could be associated with inherited prostate cancer risk.

Additionally, at least in ataxia-telangiectasia patients ATM mutations lead to an increased normal tissue response to radiotherapy. Cesaretti et al. [3] reported that heterocygote carriers of ATM gene variants treated with I-125 brachytherapy for prostate cancer were predictive of adverse radiotherapy reactions.

We investigated whether the prevalence of the P1054R variant is increased in prostate cancer patients and if carriers are at increased risk for treatment-related side effects.

1. Fan R, Kumaravel TS, Jalali F, et al. Defective DNA strand break repair after DNA damage in prostate cancer cells: implications for genetic instability and prostate cancer progression. *Cancer Res.* 2004; 64: 8526-8533

2. Angele S, Falcner A, Edwards SM, et al. ATM polymorphisms as risk factors for prostate cancer development. *Br J Cancer.* 2004; 91: 783-787

3. Cesaretti JA, Stock RG, Lehrer S, et al. ATM sequence variants are predictive of adverse radiotherapy response among patients treated for prostate cancer. *Int J Radiat Oncol Biol Phys.* 2005; 61: 196-202

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Material and Methods

A hospital-based series of 261 patients treated for early-stage prostate cancer with I-125 brachytherapy (permanent seed implantation) between 10/2000 and 04/2006 at our institution was screened for the presence of the ATM missense variant P1054R. Allele frequencies of this polymorphism were assessed using restriction fragment length polymorphism (RFLP) analysis with AlwI after polymerase chain reaction (PCR) amplification of a genomic DNA fragment.

Outcome of therapy regarding morbidity and late effects was compared between carriers vs. non-carriers prospectively with the International Prostate Symptoms Score (IPSS-15), a Quality-of-Life-index (QoL) and the International Index of Erectile Function (IIEF-15) with its subgroups (IIEF-5: short version and EF: erectile function).

For comparison a series of 460 genomic DNA samples were collected from random male blood donors representative for the healthy general population.

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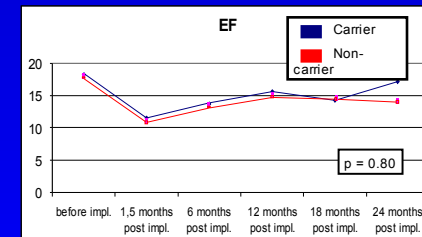
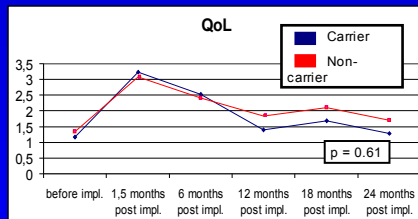
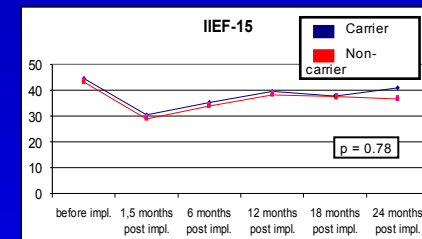
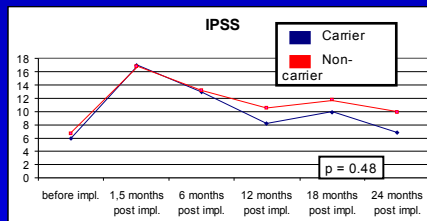
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Results

We identified 25 prostate cancer patients (9.6 %) being heterozygous carriers of the ATM sequence variant P1054R. The proportion of carriers was significantly higher among prostate cancer patients than in the general population (25 out of 261 vs. 22 out of 460; $p < 0.01$, OR 2.1, 95% CI: 1.2-3.8).

After median follow-up of 18 months mean IPSS score for carriers vs. non-carriers was 9.9 vs. 11.7 ($p = 0.48$), QoL 1.7 vs. 2.1 ($p = 0.61$), IIEF-15 score 37.7 vs. 37.0 ($p = 0.78$), IIEF-5 score 11.5 vs. 11.5 ($p = 0.83$), and EF score 14.2 vs. 14.4 ($p = 0.80$), respectively (Figure 1-4). One carrier developed a proctitis vs. 7 non-carriers ($p = 0.78$).



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Conclusion

3. We found an increased prevalence of the ATM sequence variant P1054R in prostate cancer patients compared to the general population.
5. We could not demonstrate that heterozygosity for the ATM sequence variant P1054R is predictive for the development of increased adverse radiotherapy response.
7. Analysis of other potential candidate gene variants are in progress for determination of their potential relevance for clinical radiosensitivity in prostate cancer patients.