

# Squamous cell oesophageal cancer in retinoblastoma survivor: does germinal *RB1* mutation influence chemo- and radiosensitivity?

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## ABSTRACT

The case of complete response of squamous cell oesophageal cancer to radiochemotherapy in patient previously operated due to hereditary retinoblastoma is presented. Second cancers in retinoblastoma survivors are the main cause of death in that group of patients in developed countries. There is little data on the outcome of treatment in those patients but the few papers available suggest rather poor prognosis. However, it is not clear whether the biology of cancer determined by *RB* gene mutation is responsible for that. The data suggesting decreased radio- and chemoresistance in cancers with decreased *RB* gene expression is discussed in the present paper. The role of that gene in the response to cancer treatment was showed in lung, breast and bladder cancer. Moreover, laboratory studies seem to confirm clinical observations and show that *RB* gene inhibition leads to increased cytotoxic effect of cisplatin, etoposide and 5-fluorouracil. It seems that without the incorporation of gene expression profiling into clinical practice further improvement in cancer treatment will be difficult to achieve.

**KEY WORDS:** retinoblastoma, case report, second malignancy, squamous cell esophageal cancer, radiosensitivity, chemoresistance

## INTRODUCTION

Retinoblastoma is an ocular cancer which develops from the immature cells of the retina. Its incidence in Poland is 3.7 cases per one million children [1]. Being the most frequent paediatric ocular neoplasm, it mostly affects children between one and two years of age. Some of the early symptoms suggestive of retinoblastoma include strabismus, hyperaemia, and an inflammatory condition of the eye. The characteristic symptom of the cat's eye accompanied by exophthalmos is one of the late manifestations of the disease. For the tumour to develop, there has to be a biallelic *RB* gene mutation present. In 60% of the patients, the disease develops as a result of somatic mutations in the retinal cells, leading to a non-hereditary form of the cancer, affecting a single eyeball only. In 40% of the cases, the neoplasm is a result of a constitutive mutation in one allele, followed by another somatic mutation in the retinal cells. In the latter scenario, the disease usually develops in both eyes.

The *RB1* gene is located in the 13q14 chromosome band. The protein encoded by the gene is one of the basic cellular cycle regulators. Its dephosphorylated form binds with the E2F family of transcription factors, making it impossible for the cells to pass through the G1 phase, and move into the S phase. That effect is presently considered to be its fundamental function. To date, however, over 100 proteins have been discovered to interact with the retinoblastoma protein, which points to the coordinating role it takes upon in the processes of proliferation, differentiation, biosynthesis, and apoptosis [2].

## CASE DESCRIPTION

In 1975, at the age of 1, binocular enucleation was performed in a retinoblastoma patient. Histopathology examination ruled out infiltration of the optic nerves. Genetic tests confirmed the presence of *RB1* mutation.

In December 2010, the 35-year old patient presented with aphagia and hoarse voice. Fiberscopy visualized an almost entirely occluded lumen of the oesophagus, with the mucous membrane bleeding under palpation. The histopathology specimen revealed the G1 keratinizing squamous cell carcinoma. Chest CT showed a 39 × 39 × 18 mm oesophageal infiltration, different from the trachea wall, but with no clear signs of the infiltration involving the surrounding adipose tissue. Laryngological examination, however, showed immobilization of the left vocal cord. The patient was qualified for radical radiochemotherapy at the Gliwice Institute of Oncology. Radiotherapy was planned based on the PET-CT scan, raising suspicion of a left level IV lymph node metastasis. The tumour and the suspected lymph node received the full dose of

50.4 Gy of radiation, with the regional lymphatic system irradiated with the dose of 41.4 Gy. In the course radiotherapy, 2 chemotherapy cycles were administered, involving cisplatin, dosed at 80 mg/m<sup>2</sup>, on day 1., and 5-fluorouracil, dosed at 800 mg/m<sup>2</sup>, on days 1–4. A 2nd degree post-radiation reaction was observed in the throat, as well as neutropenic fever (treated with good result). Due to the poor tolerance of the treatment regimen, the third cycle doses were first reduced to 80%, and then withdrawn altogether, aborting the fourth chemotherapy cycle. The patient is followed up by the Gliwice Institute of Oncology. By June 2013, there were no signs of relapse in the imaging tests, including oesophageal fiberoscopy as well as chest and abdominal CT.

## DISCUSSION

### Second neoplasm as a clinical problem in retinoblastoma patients

Second neoplasms in survivors of hereditary retinoblastoma are now the chief cause their death in developed countries [3, 4]. Mortality related to the second cancer in patients suffering from the hereditary form of the *RB* gene mutation amounts to 17–36% 50 years from the diagnosis of retinoblastoma, and can reach even up to 56% throughout a person's lifetime [4–6]. In the USA, where a considerable number of retinoblastoma patients have been treated with radiotherapy, the second neoplasms are usually sarcomas, and develop in the irradiated area, i.e. in the region of the base of the skull [4, 7]. In the European population, on the other hand, in which the use of radiotherapy was much more limited, a significant number of the second neoplasms involves lung and urinary bladder tumours [6]. There are very few papers discussing second cancer treatment outcomes in the latter group of patients [8–12]. The outcomes presented so far suggest that prognosis is poor for those patients, with the 10-year overall survival fluctuating between 20% and 40%. The 15-year overall survival, following second cancer treatment, is around 22% [13]. However, it is difficult to state beyond any doubt that it is the tumour biology, determined by the *RB* gene mutation, which is responsible for it. An equally probable cause might be the location of the second neoplasm in the region of the cranial basis, frequently encountered in retinoblastoma survivors, as well as the limited therapeutic options, due to the earlier radio- and chemotherapy. The thesis appears to be supported by European studies. Rodjan and collaborators demonstrated that it is the possibility of a radical surgical procedure which is decisive as for the treatment outcome of skull base sarcomas in that group of patients [9]. 5-year survival in the patients who underwent an R0 resection was reported as 80%, as

compared with the 40% in the remaining groups of patients. On the other hand, Marees and collaborators, analysing the Dutch population, pointed to a considerably higher percentage of deaths, following second cancer treatment, amongst the irradiated retinoblastoma patients [5]. It is fair to assume that the reason for it is the location of the second neoplasms in the region of the skull base, which is more frequent in the irradiated group of patients. A source of interesting information is also the work of Fletcher and collaborators, looking into the second cancer morbidity in the British population of retinoblastoma survivors born in the years 1873–1950. A great majority of those patients (contrary to the previously mentioned studies) were treated without radiotherapy. The paper presents both second cancer morbidity and mortality in the population of patients suffering from the familial and sporadic forms of retinoblastoma. Even though second cancer incidence was much lower in the group of patients with the sporadic form of mutation, the death rate was 70% for the sporadic *RB* gene mutation carriers, and around 82% for the patients with the hereditary mutation. It was not determined, though, whether the difference was statistically significant or not. To the best knowledge of the authors of the present paper, the presented case is the first description of the treatment outcome of squamous cell carcinoma in a patient with the hereditary form of the *RB* gene mutation. In the case discussed, the second neoplasm involved was oesophageal cancer, i.e. the type of cancer whose prognosis is generally poor. The good tumour response to treatment, leading to complete remission, lasting for over 2 years now, might bring to mind the question of whether or not the good treatment outcome is related to the *RB* gene mutation carrier state. As has already been mentioned, based on the above quoted epidemiological studies, it is difficult to rule out such possibility once and for all. It would appear, on the other hand, that translation studies confirm the impact of the *RB* gene mutation on treatment outcomes.

### Presence of the *RB* mutation and response to cytotoxic treatment

Lower *RB* gene expression in squamous cell oesophageal cancer was found to be related to poorer patient prognosis in two independent studies looking into the treatment outcomes of stand-alone oesophageal cancer surgery [14, 15]. However, the interrelationship was not demonstrated in the cases, where surgical treatment

was preceded with bleomycin-based chemotherapy [16]. It brings to mind the conclusion that pre-operative chemotherapy improves prognosis in the low *RB* gene expression tumours. Were it so in reality, it would testify to the greater chemosensitivity of those cancers. A number of studies devoted to other types of malignancies indeed appear to support the thesis. When assessing the degree of tumour regression upon treatment, increased chemosensitivity of the tumours lacking the *RB* gene expression has been demonstrated for the lung [17, 18] and breast cancer [19–21], and higher radiosensitivity has been shown for the urinary bladder carcinoma [22, 23]. Results of the above quoted clinical studies have been supported by laboratory studies, proving that blocking the *RB* gene expression leads to an enhanced cytotoxicity of cisplatin, etoposide and 5-fluorouracil [24, 25], while an increased expression of the gene has been observed upon adriamycin exposure [26]. Naturally, there are also studies, in which the impact of the *RB* gene expression on patient prognosis has not been demonstrated [27–29], and even isolated laboratory studies which appear to be suggesting quite the opposite, i.e. that lack of the *RB* gene expression might lead to poorer response to treatment [30, 31]. There are numerous potential causes behind the contradictory findings. For certain, the retrospective nature of the quoted clinical studies is not without significance, as is the use of different antibodies for the evaluation of the *RB* gene expression, the possible lack of direct correlation between the gene expression and the function of the protein produced, drawing conclusions on tumour biology on the basis of individual specimens, and many other inaccuracies. For those reasons, gene expression profiling is still applied only in scientific studies, and not as routine management. It seems, though, that without the incorporation of gene expression profiling into clinical practice further improvement in cancer treatment will be difficult to achieve.

### SUMMARY

A case of oesophageal squamous cell carcinoma in a bilateral retinoblastoma survivor has been presented. The review of theoretical and clinical studies in the field might suggest a correlation between the presence of the *RB* gene mutation and chemo- and radiosensitivity of tumour cells.

### References

1. Chybicka A, Sawicz-Birkowska K: Onkologia i hematologia dziecięca (Paediatric Oncology and Haematology). PZWL, Warsaw 2008.
2. Mittnacht S: The retinoblastoma protein – from bench to bedside. *Eur J Cell Biol* 2005; 84: 97-107.
3. Eng C, Li F, Abramson D. et al. Mortality from second tumors among long-term survivors of retinoblastoma. *J Natl Cancer Inst*. 1993; 85: 1121-8.
4. Kelinerman R, Tucker M, Tarone R et al. Risk of new cancers after radiotherapy in long-term survivors of retinoblastoma: an extended follow-up. *J Clin Oncol* 2005; 23: 2272-9.

5. Marees T, van Leeuwen F, de Boer M et al. Cancer mortality in long-term survivors of retinoblastoma. *Eur J Cancer* 2009; 45: 3245-53.
6. Fletcher O, Easton D, Anderson K et al. Lifetime risk of common cancers among retinoblastoma survivors. *J Natl Inst Cancer* 2004; 96: 357-63.
7. Woo K, Harbour J: Review of 676 second primary tumors in patients with retinoblastoma. *Arch Ophthalmol* 2010; 128: 865-70.
8. Dunkel I, Gerald W, Rosenfield N et al. Outcome of Patients with a history of Bilateral Retinoblastoma treated for a second malignancy: the sloan-kettering experience. *Med Pediatr Oncol* 1998; 30: 59-62.
9. Rodjan F, Graaf P, Brisse H. et al. Second cranio-facial malignancies in hereditary retinoblastoma survivors previously treated with radiation therapy: clinic and radiologic characteristics and survival outcomes. *Eur J Cancer* 2013; 49: 1939-47.
10. Aerts I, Pacquement H, Doz F et al. Outcome of second malignancies after retinoblastoma: a retrospective analysis of 25 patients treated at the Institute Curie *Eur J Cancer* 2004; 40: 1522-9.
11. Zubin C, Rosenfield N, Abramson S et al. The location and appearance of second malignancies in patients with bilateral retinoblastoma. *Sarcoma* 1997; 2: 89-93.
12. Mohney B, Robertson D, Schomberg P et al. Second non-ocular tumors in survivors of heritable retinoblastoma and prior radiation therapy. *Am J Ophthalmol* 1998; 128: 268-77.
13. Moll A, Imhof S, Bouter L et al: Second primary tumors in patients with hereditary retinoblastoma: a register-based follow-up study, 1945-1994. *Int J Cancer* 1996; 67: 515-9.
14. Ikeguchi M, Oka S, Gomyo Y et al. Clinical significance of retinoblastoma protein (pRB) expression in oesophageal squamous cell cancer *J Surg Oncol* 2000; 73: 104-8.
15. Guner D, Sturm I, Hemmati P et al. Multigene analysis of RB pathway and apoptosis control in esophageal squamous cell carcinoma identifies patients with good prognosis. *Int J Cancer* 2003; 103: 445-54.
16. Ishikawa T, Furihata M, Ohtsuki Y et al. Cyclin D1 overexpression related to retinoblastoma protein expression as a prognostic marker in human esophageal squamous cell carcinoma. *Br J Cancer* 1998; 77: 92-7.
17. Ludovini V, Gregorc V, Pistola L et al. Vascular endothelial growth factor, p53, Rb, Bcl-2 expression and response to chemotherapy in advance non-small cell lung cancer. *Lung Cancer* 2004; 46: 77-85.
18. Joseph M, Banerjee D, Kocha W et al: Metallothionein expression in patients with small cell carcinoma of the lung: correlation with other molecular markers and clinical outcome. *Cancer* 2001; 92: 836-42.
19. Derenzini M, Donati G, Mazzini G et al. Loss of retinoblastoma tumor suppressor protein makes human breast cancer cells more sensitive to antimetabolite exposure. *Clin Cancer Res* 2008; 14: 2199-209.
20. Trere D, Brighenti E, Donati G et al: High prevalence of retinoblastoma protein loss in triple-negative breast cancers and its association with a good prognosis in patients treated with adjuvant chemotherapy. *Ann Oncol* 2009; 20: 1818-23.
21. Witkiewicz A, Ertel A, McFalls J et al. RB-pathway disruption is associated with improved response to neoadjuvant chemotherapy in breast cancer. *Clin Cancer Res* 2012; 18: 5110-22.
22. Pollack A, Czerniak B, Zagars B et al. Retinoblastoma protein expression and radiation response in muscle-invasive bladder cancer. *Int J Radiat Oncol Biol Phys* 1997; 39: 687-95.
23. Agerbaeck M, Alsner J, Marcussen N et al. Retinoblastoma protein expression is an independent predictor of both radiation response and survival in muscle invasive bladder cancer. *Br J Cancer* 2003; 89: 298-304.
24. Zagorski W, Knudsen E, Reed M: Retinoblastoma deficiency increases chemosensitivity in lung cancer. *Cancer Res* 2007; 67: 8264-73.
25. Bosco E, Wang Y, Xu H et al. The retinoblastoma tumor suppressor modifies the therapeutic response of breast cancer. *J Clin Invest* 2007; 117: 218-28.
26. Yoo Y, Kang S, Kang Y: Cellular resistance to adriamycin conferred by enhanced Rb expression is associated with increased MDR1 expression. *Biochem Biophys Res Commun* 1998; 249: 6-10.
27. Moonen L, Ong F, Gallee M et al. Apoptosis, proliferation and p53, cyclin D1 and retinoblastoma gene expression in relation to radiation response in transitional cell carcinoma of the bladder. *Int J Radiat Oncol Biol Phys* 2001; 49: 1305-10.
28. Chakravarti A, Winter K, Wu C et al. Expression of the epidermal growth factor receptor and Her-2 are predictors of favorable outcome and reduced complete response rates, respectively, in patients with muscle-invasive bladder cancers treated by concurrent radiation and cisplatin-based chemotherapy: a report from the Radiation Therapy Oncology Group *Int J Radiat Oncol Biol Phys* 2005; 62: 309-17.
29. Otsuka H, Funai S, Tanaka A et al. Stratification of the biologic aggressiveness of non-small cell lung cancer using DNA flow cytometry and immunohistochemistry for the retinoblastoma protein. *Lung Cancer* 2004; 45: 307-16.
30. Waltersson M, Askmalm M, Nordenskjold B et al. Altered expression of cyclin E and the retinoblastoma protein influences the effect of adjuvant therapy in breast cancer *Int J Oncol* 2009; 34: 441-8.
31. Li W, Fan J, Hochhauser D et al. Lack of functional retinoblastoma protein mediates increased resistance to antimetabolites in human sarcoma cell lines. *Proc Natl Acad Sci USA* 1995; 92: 10436-40.

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