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ROLE OF TRASLATIONAL RESEARCH IN SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK: IS IT POSSIBLE TO IMPROVE THE THERAPEUTIC SCENARIO?

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ABSTRACT – *Squamous cell carcinoma of the head and neck (SCCHN) represent a group of malignancies arising from the first tract of both respiratory and digestive ways. Being very similar with regard to pathology, etiology and clinical outcome, SCCHN have been often approached with similar therapy strategies in clinical trials. Recent studies have demonstrated the existence of different entities among the SCCHN, in particular, some neoplasms have been shown to behave differently from others. Human papilloma virus (HPV) related SCCHN show very peculiar features, as like good prognosis and good response to both chemo and radiotherapy. On the other hand, alcohol and tobacco related ones show the opposite features. Immunoistochemistry (IHC) and polymerase chain reaction (PCR) methodologies may help us to identify the biological characteristics which strongly divide HPV related SCCHN from the tobacco and alcohol related ones.*

Moreover, another subgroup of SCCHN may be recognized, namely those related to a loco-regional immune suppression status. Some oral cavity and soft palate carcinomas often recur after standard treatment and this feature may be related to a local immune system impairment, often due to the microenvironment and tumour characteristics.

On the basis of these findings, we can conclude that the very heterogeneous category of SCCHN should be better studied and divided in several subgroups, characterized by different biological and clinical features. A step forward may be to administer a well shaped therapy starting from these biological features.

KEY WORDS: *Squamous cell carcinoma of the head and neck, Human papilloma virus, Cancerogenesis, P16, P53, EGFR, Cyclin D1, Immune system.*

BACKGROUND

Squamous Cell Carcinoma of the Head and neck (SCCHN) are not rare diseases, accounting for 5-7% of all malignancies. Historically, they are associated to smoke and alcohol consumption and often have been diagnosed at 6-7 decade of age[1-3], but in the last years, a strike change in their epidemiology has been observed. In fact, incidence of some SCCHN, in particular oropharyngeal carcinomas has shown a sensible increase, especially with regard to some oropharyngeal sites, namely tonsil and base of tongue[4,5]. This phenomenon has been explained with a strong increase of Human

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Papilloma Virus (HPV) related tumours. HPV often colonizes epithelium which covers the pharynx and it may induce in some patients neoplastic transformation. HPV related neoplasms often strike the young adult, at 4/5 decade of age, never or slight smokers and with anamnesis of several sexual partners[5].

Some SCCHN, in particular those originating from oral cavity and soft palate show poor prognosis after primary therapy both surgery and radiation therapy, being characterized by frequent locoregional failure and new primitives incidence. The history of these tumours may be influenced by immune status, as demonstrated in some clinical trials[6,7].

On the basis of the findings, we can conclude that SCCHN are a very heterogeneous group of tumours, related to different etiologies and characterized by different prognosis and response to therapy.

In this review, we will try to expose the possible future therapeutic approaches based on the different biological features which characterize the SCCHN.

DIFFERENT CAUSES LEADING TO SCCHN DEVELOPMENT

Cancerogenesis process in SCCHN is mainly due to the mutagens present in smoking and alcohol. It has been postulated that these mutagens may alter DNA in some specific loci, causing neoplastic transformation and progression[8,9]. Smoking, alcohol and smokeless tobacco related neoplasms often show typical genetic features, as like CCND1 gene changes, TP53 mutations, severe over expression of EGFR protein on cell membrane, disregulation of PI3K/Akt pathway, down regulation of p16 and several chromosomal abnormalities[10-14]. On the other hand, HPV related tumours, show the opposite features, as like, a low number of chromosomal abnormalities, over expression of p16 and p21, low EGFR expression, wild type CCND1 and an often high nuclear proliferating index (Ki-67)[15-17]. These genetic differences may reflect two totally different cancerogenesis routes. On these findings we could distinguish between an HPV driven cancerogenesis and a smoke and alcohol driven one (Figure 1).

HPV related SCCHN show better prognosis if compared with the non-HPV related ones in clinical trials[18,19], and, more interestingly, they might better respond to therapies. A subgroup analyses carried out in the TAX 324 study, has demonstrated that HPV related SCCHN better respond to induction TPF followed by chemoradiation, if compared to HPV negative counterpart[20]. A very similar feature has been shown in the ECOG 2399 study, being observed the best response to induction therapy only in the HPV related neoplasms[21]. These features may authorize to think that HPV driven cancerogenesis leads to the genesis of more chemo-sensitive tumours, which are more suitable for an "early" chemotherapy.

Moreover, Feng et al have demonstrated that wild type status of CCND1, which is the gene encoding for Cyclin D1, may be considered as a predictive of response to induction chemotherapy followed by chemoradiation, if compared with upfront surgery followed by adjuvant chemoradiotherapy[22]. This feature suggests a more chemosensitivity of SCCHN characterized by wild type CCND1, if compared with CCND1-mu-

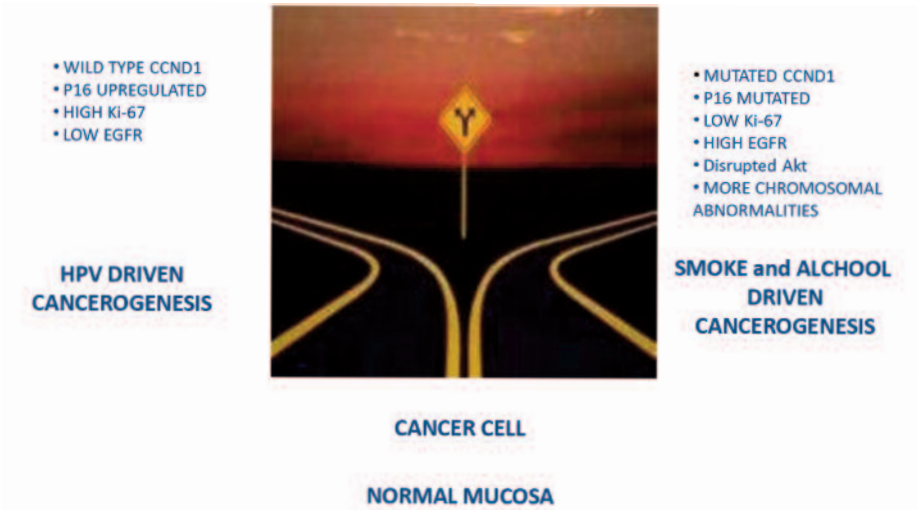

Figure 1. Different features between HPV related SCCHN and smoke and alcohol related ones.

tated SCCHN. HPV related neoplasms often present wild type CCND1 in addition to p16 and p21 over expression and TP53 wild type status[18,19], thus results of this last trial reinforce the hypothesis of a good chemo and radiosensitivity of HPV related SCCHN.

HPV RELATED SCCHN: IMPLICATIONS ON THERAPY

Given the high chemo and radiosensitivity shown by HPV related SCCHN, a number of clinical trials aimed to perform conservative strategies in locally advanced SCCHN, are ongoing. Recently, Cmelak et al have presented at ASCO 2014 the preliminary results of a phase II trials enrolling HPV positive SCCHN. Patients were treated with induction chemotherapy followed by two different regimens of concurrent cetuximab-radiotherapy (RT). In particular, an underpowered RT regimen, consisting in 50Gy in site of the standard 70, was administered only in patients which completely responded to induction chemotherapy, while concurrent cetuximab and 70 Gy RT was offered to those which have obtained only a partial response. As result, Patients treated with the underpowered radiotherapy experienced a better outcome if compared with those treated with standard RT[23]. This was only a small phase II trial, but further analyses are strongly warranted.

SMOKE AND TOBACCO RELATED SCCHN: IMPLICATIONS ON THERAPY

As the opposite, smoke and tobacco related tumours, often present poor prognosis and poor response to chemo and radiotherapy in clinical trials. Tumours which present PI3K/Akt disregulation show scarce response to chemotherapy and are often radioresistant. Mutation of TP53, which leads to a de-regulation of p53 production, identifies a group of tumours poorly responsive to chemo and radiotherapy, and the same feature regards SCCHN which highly express EGFR at immunostaining[24,25].

Given the high number of genetic abnormalities, it has been hypothesized that this category of SCCHN could be characterized by several neoplastic clones, a features strongly linked to both chemo and radioresistance. Unfortunately, conservative therapeutic strategies may easily fail in these patients and few other therapy options remain available. A possible approach may be to selectively target the disrupted pathways detected in them.

IMMUNE SYSTEM AND SCCHN

The strong linkage between immunosuppression and neoplastic progression has been repeatedly demonstrated, given the high frequency of some malignancies in patients affected by immunodeficiency syndromes[26,27].

Lately, it has been discovered that tumours cell, in addition to hormones and pro coagulant agents (which provoke paraneoplastic syndromes and thrombosis), are able to secrete also cytokines. Some of these cytokines, in particular TGF-α and TGF-β have an immunosuppressive function[28,29]. In alternative, tumour cells may induce the macrophages infiltrating tumour to produce several cytokines, among which TGF, leading to an immunosuppression status. A subgroup of SCCHN, in particular oral cavity and soft palate primitives, which seem to be related only to smoke and oral trauma, are characterized also by a loco-regional immunosuppression status, which is responsible for a poor outcome and an high rate of local recurrences.

Clinical phase II trials have employed a mixture of several cytokines, mainly constituted by IL-2, IL-1 and TNF, which have been administered as peritumoral injection, associated to standard therapy in patients with locally advanced oral cavity carcinomas. The aim of these trials was to restore the immune status in the oral cavity, favoring the immune response against the tumour. In both these phase II trials, intratumoral injection of a combination of cytokines (Multikine), added to the standard surgery followed by radiotherapy has reached a promising activity and a favorable toxicity spectrum[30,31]. Phase III randomized trials exploring Multikine efficacy are ongoing. Further similar analyses are warranted to confirm these data.

CONCLUSIONS AND FUTURE PERSPECTIVES

SCCHN are very heterogeneous with regard of outcome and response to therapy. Recent data are in favor of a better response to both chemo and radiotherapy for HPV related carcinomas. It has been hypothesized that HPV driven cancerogenesis might lead to the genesis of tumours characterized by chemosensitivity and radiosensitivity, perhaps due to their mono or oligoclonality. On the other hand, smoke and alcohol related ones poorly respond to conservative treatments. DNA mutations which characterize this last entity, as like TP53 mutation, PI3KCA changes and CCND1 amplification lead to scarce response to both chemo and radiotherapy.

Possible therapeutic strategies which may be employed in smoke and alcohol related SCCHN, are the selective targeting of the main disrupted pathways, as like p53, PI3K/Akt and EGFR. A number of clinical trials have tested several strategies restoring p53 function, but results are discordant[32-35], moreover, a lot of PI3K selective inhibitors are available for clinical trials, and some of that have been tested in SCCHN. Perifostine, a strong Akt inhibitor, was tested in phase II clinical trials enrolling SCCHN, but results are not very encouraging, mainly due to its toxicity[36,37].

HPV related SCCHN show low expression of EGFR at immunostaining, if compared with smoke and alcohol related ones, that instead are characterized by severe over expression of EGFR. EGFR over expression is the main responsible for radio-resistance, leading to an accelerated cell repopulation after each dose of RT. Highly EGFR expressing SCCHN might be suitable for an accelerated and/or hyperfractionated RT regimen. In a phase III clinical trial, patients with locally advanced SCCHN have been treated with two RT regimen given concomitantly with cetuximab. In the standard RT arm, RT was administered using a conventional fractionating regimen, while in the experimental arm, a combined hyperfractionated accelerated radiation therapy (CHART) was given[38,39]. Interestingly, patients treated with concomitant CHART-cetuximab showed a better survival, but only in a subgroup characterized by high levels of EGFR at immunostaining. In the future we could take advantage of the over expression of EGFR, which is a feature frequent in smoke and alcohol related SCCHN.

Finally, the possibility to restore loco-regional immune response in some locally advanced oral cavity tumours may lead to an outcome improvement in these poor prognosis patients.

We can conclude that, given the strike heterogeneity of SCCHN, we should not treat all them at the same way, but a future possible approach may be to identify the specific genetic signature which often characterize them, and to perform a well shaped therapy based on this signature[40] (Figure 2).

REFERENCES

1. Newman JR, Connolly TM, Illing EA, Kilgore ML, Locher JL, Carroll WR. Survival trends in Hypopharyngeal cancer: a population-based review. Laryngoscope. 2015; 125: 624-629.
2. Megwalu UC1, Sikora AG1. Survival outcomes in advanced laryngeal cancer. JAMA Otolaryngol Head Neck Surg 2014; 140: 855-860.
3. Zhang H, Dziegielewski PT, Biron VL, Szudek J, Al-Qahatani KH, O'Connell DA, Harris JR, Seikaly H. Survival outcomes of patients with advanced oral cavity squamous cell carcinoma treated with multimodal therapy: a multi-institutional analysis. J Otolaryngol Head Neck Surg 2013; 42: 30.
4. Chai RC, Lambie D, Verma M, Punyadeera C. Current trends in the etiology and diagnosis of HPV-related head and neck cancers. Cancer Med 2015 Feb 1. doi: 10.1002/cam4.424.
5. Deschler DG, Richmon JD2, Khariwala SS3, Ferris RL4, Wang MB5. The "new" head and neck cancer patient-young, nonsmoker, nondrinker, and HPV positive: evaluation. Otolaryngol Head Neck Surg 2014; 151: 375-380.
6. Lukits J. [The effect of the microenvironment of head and neck cancers on tumor progression]. Magy Onkol 2009; 53: 51-59.
7. Barrera JL, Verastegui E, Meneses A, Zinser J, de la Garza J, Hadden JW. Combination immunotherapy of squamous cell carcinoma of the head and neck: a phase 2 trial. Arch Otolaryngol Head Neck Surg 2000; 126: 345-351.
8. Gollin SM. Cytogenetic alterations and their molecular genetic correlates in head and neck squamous cell carcinoma: a next generation window to the biology of disease. Genes Chromosomes Cancer 2014; 53: 972-990.

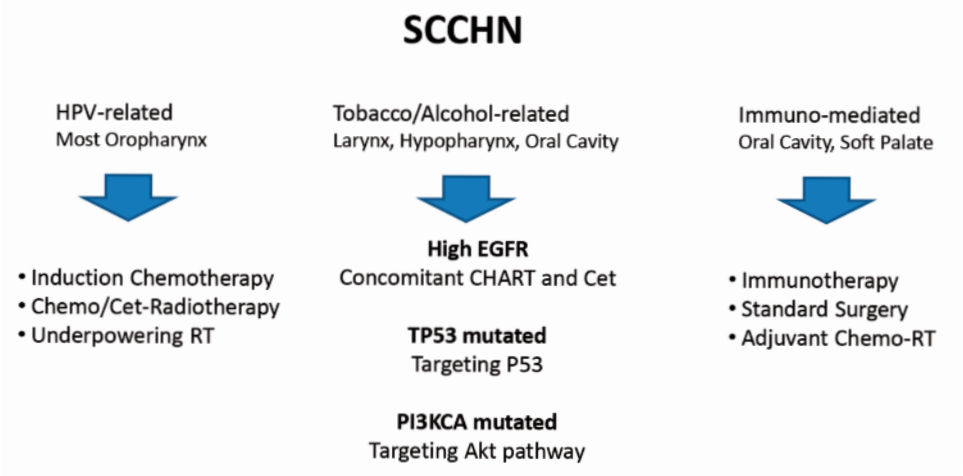

Figure 2. Possible future therapeutic approaches in SCCHN based on their biological features.

9. Gollin SM. Chromosomal alterations in squamous cell carcinomas of the head and neck: window to the biology of disease. Head Neck 2001; 23: 238-253.
10. Giudice FS, Dal Vechio AM, Abrahão AC, Sperandio FF, Pinto-Junior Ddos S. Different expression patterns of pAkt, NF- B and cyclin D1 proteins during the invasion process of head and neck squamous cell carcinoma: an in vitro approach. J Oral Pathol Med 2011; 40: 405-411.
11. Mielcarek-Kuchta D1, Olofsson J, Golusinski W. p53, Ki67 and cyclin D1 as prognosticators of lymph node metastases in laryngeal carcinoma. Eur Arch Otorhinolaryngol 2003; 260: 549-554.
12. Namazie A, Alavi S, Olopade OI, Pauletti G, Aghamohammadi N, Aghamohammadi M, Gornbein JA, Calcaterra TC, Slamon DJ, Wang MB, Srivatsan ES. Cyclin D1 amplification and p16(MTS1/CDK4I) deletion correlate with poor prognosis in head and neck tumors. Laryngoscope 2002; 112: 472-481.
13. Weiss J, Hayes DN. Classifying squamous cell carcinoma of the head and neck: prognosis, prediction and implications for therapy. Expert Rev Anticancer Ther 2014; 14: 229-236.
14. Xu J, Gimenez-Conti IB, Cunningham JE, Collet AM, Luna MA, Lanfranchi HE, Spitz MR, Conti CJ. Alterations of p53, cyclin D1, Rb, and H-ras in human oral carcinomas related to tobacco use. Cancer 1998; 83: 204-212.
15. Hafkamp HC, Mooren JJ, Claessen SM, Klingenberg B, Voogd AC, Bot FJ, Klussmann JP, Hopman AH, Manni JJ, Kremer B, Ramaekers FC, Speel EJ. P21 Cip1/WAF1 expression is strongly associated with HPV-positive tonsillar carcinoma and a favorable prognosis. Mod Pathol 2009; 22: 686-698.
16. Li W, Thompson CH, Cossart YE, O'Brien CJ, McNeil EB, Scolyer RA, Rose BR. The expression of key cell cycle markers and presence of human papillomavirus in squamous cell carcinoma of the tonsil. Head Neck 2004; 26: 1-9.
17. Queiroz CJ, Nakata CM, Solito E, Damazo AS. Relationship between HPV and the biomarkers annexin A1 and p53 in oropharyngeal cancer. Infect Agent Cancer 2014; 9: 13.
18. Ang KK, Sturgis EM. Human papillomavirus as a marker of the natural history and response to therapy of head and neck squamous cell carcinoma. Semin Radiat Oncol 2012; 22: 128-142.
19. Ang KK, Harris J, Wheeler R, Weber R, Rosenthal DI, Nguyen-Tân PF, Westra WH, Chung CH, Jordan RC, Lu C, Kim H, Axelrod R, Silverman CC, Redmond KP, Gillison ML. Human papillomavirus and survival of patients with oropharyngeal cancer. N Engl J Med 2010; 363: 24-35.
20. Posner MR, Lorch JH, Goloubeva O, Tan M, Schumaker LM, Sarlis NJ, Haddad RI, Cullen KJ. Survival and human papillomavirus in oropharynx cancer in TAX 324: a subset analysis from an international phase III trial. Ann Oncol 2011; 22: 1071-1077.
21. Fakhry C, Westra WH, Li S, Cmelak A, Ridge JA, Pinto H, Forastiere A, Gillison ML. Improved survival of patients with human papillomavirus-positive head and neck squamous cell carcinoma in a prospective clinical trial. J Natl Cancer Inst 2008; 100: 261-269.
22. Feng Z, Guo W, Zhang C, Xu Q, Zhang P, Sun J, Zhu H, Wang Z, Li J, Wang L, Wang B, Ren G, Ji T, Tu W, Yang X, Qiu W, Mao L, Zhang Z, Chen W. CCND1 as a predictive biomarker of neoadjuvant chemotherapy in patients with locally advanced head and neck squamous cell carcinoma. PLoS One 2011; 6: e26399.
23. Cmelak A, Li S, Marur S, Zhao W, Westra WH, Chung CH, Gillison ML, Gilbert J, Bauman JE, Wagner LI, Ferris RL, Trevarthen DR, Colevas AD, Jahagirdar BN, Burtness B. Reduced-dose IMRT in human papilloma virus (HPV)-associated resectable oropharyngeal squamous carcinomas (OPSCC) after clinical complete response (cCR) to induction chemotherapy (IC). J Clin Oncol 2014; 32: 5s, (suppl; abstr LBA6006).
24. Perri F, Pacelli R, Scarpati GD, Cella L, Giuliano M, Caponigro F, Pepe S. Radioresistance in head and neck squamous cell carcinoma: Biological bases and therapeutic implications. Head Neck 2014 Jul 4. doi: 10.1002/hed.23837.
25. Horn D, Hess J, Freier K, Hoffmann J, Freudlsperger C. Targeting EGFR-PI3K-AKT-mTOR signaling enhances radiosensitivity in head and neck squamous cell carcinoma. Expert Opin Ther Targets 2015:1-11.
26. Chen CH, Chung CY, Wang LH, Lin C, Lin HL, Lin HC. Risk of cancer among HIV-infected patients from a population-based nested case-control study: implications for cancer prevention. BMC Cancer 2015; 15: 1099.
27. Clifford GM, Polesel J, Rickenbach M, Dal Maso L, Keiser O, Kofler A, Rapiti E, Levi F, Jundt G, Fisch T, Bordoni A, De Weck D, Franceschi S; Swiss HIV Cohort. Cancer risk in the Swiss HIV Cohort Study: associations with immunodeficiency, smoking, and highly active antiretroviral therapy. J Natl Cancer Inst 2005; 97: 425-432.
28. Schierl M, Patel D, Ding W, Kochhar A, Adhami K, Zhou XK, Dannenberg AJ, Granstein RD. Tobacco smoke-induced immunologic changes may contribute to oral carcinogenesis. J Investig Med 2014; 62: 316-323.
29. Costa NL, Valadares MC, Souza PP, Mendonça EF, Oliveira JC, Silva TA, Batista AC. Tumor-associated macrophages and the profile of inflammatory cytokines in oral squamous cell carcinoma. Oral Oncol 2013; 49: 216-223.
30. Tímár J, Forster-Horváth C, Lukits J, Döme B, Ladányi A, Remenár E, Kásler M, Bencsik M, Répássy G, Szabó G, Velich N, Suba Z, Elõ J, Balatoni Z, Bajtai A, Chretien P, Talor E. The effect of leukocyte interleukin injection (Multikine) treatment on the peritumoral and intratumoral subpopulation of mononuclear cells and on tumor epithelia: a possible new approach to augmenting sensitivity to radiation therapy and chemotherapy in oral cancer—a multicenter phase I/II clinical Trial. Laryngoscope 2003; 113: 2206-2217.
31. Feinmesser M, Okon E, Schwartz A, Kaganovsky E, Hardy B, Aminov E, Nageris B, Sulkes J, Feinmesser R. Histologic and immunohistochemical characterization of tumor and inflammatory infiltrates in oral squamous cell carcinomas treated with local multikine immunotherapy: the macrophage at the front line. Eur Arch Otorhinolaryngol 2004; 261: 359-368.
32. Lamont JP, Nemunaitis J, Kuhn JA, Landers SA, McCarty TM. A prospective phase II trial of ONYX-015 adenovirus and chemotherapy in recurrent squamous cell carcinoma of the head and neck (the Baylor experience). Ann Surg Oncol 2000; 7: 588-592.
33. Khuri FR, Nemunaitis J, Ganly I, Arseneau J, Tannock IF, Romel L, Gore M, Ironside J, MacDougall RH, Heise C, Randlev B, Gillenwater AM, Bruso P, Kaye SB, Hong WK, Kirn DH. a controlled trial of intratumoral ONYX-015, a selectively-replicating adenovirus, in combination with cisplatin and 5-fluorouracil in patients with recurrent head and neck cancer. Nat Med 2000; 6: 879-885.
34. Roh JL, Kang SK, Minn I, Califano JA, Sidransky D, Koch WM. p53-Reactivating small molecules induce apoptosis and enhance chemotherapeutic cytotoxicity in head and neck squamous cell carcinoma. Oral Oncol 2011; 47: 8-15.

35. Miyachi M, Kakazu N, Yagyu S, Katsumi Y, Tsubai-Shimizu S, Kikuchi K, Tsuchiya K, Iehara T, Hosoi H. Restoration of p53 pathway by nutlin-3 induces cell cycle arrest and apoptosis in human rhabdomyosarcoma cells. Clin Cancer Res 2009; 15: 4077-4084.
36. Argiris A, Cohen E, Karrison T, Esparaz B, Mauer A, Ansari R, Wong S, Lu Y, Pins M, Dancey J, Vokes E. A phase II trial of perifosine, an oral alkylphospholipid, in recurrent or metastatic head and neck cancer. Cancer Biol Ther 2006; 5: 766-770.
37. Simpson DR, Mell LK, Cohen EE. Targeting the PI3K/AKT/mTOR pathway in squamous cell carcinoma of the head and neck. Oral Oncol 2015; 51: 291-298.
38. Bentzen SM, Atasoy BM, Daley FM, Dische S, Richman PI, Saunders MI, Trott KR, Wilson GD. Epidermal growth factor receptor expression in pretreatment biopsies from head and neck squamous cell carcinoma as a predictive factor for a benefit from accelerated radiation therapy in a randomized controlled trial. J Clin Oncol 2005; 23: 5560-7.
39. Gloghini A, Volpi CC, Gualeni AV, Cortellazzi B, Perrone F, Pilotti S. Defining the better algorithm for the accurate identification of HPV status among oropharyngeal squamous-cell carcinoma. Results from a pilot study. WCRJ 2015; 2: e497.
40. Berretta M, Di Francia R, Tirelli U. Editorial – The new oncologic challenges in the 3rd millennium. WCRJ 2014; 1: e133.