



Treatment of nasopharyngeal carcinoma in unique scenarios

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Abstract: Nasopharyngeal carcinoma (NPC) is a type of malignant tumor originated from nasopharyngeal mucosa. According to statistics, there were about 129,000 new cases of NPC in 2018, of which more than 70% were in East and Southeast Asia. Due to its radiosensitive behavior and deep-seated anatomic location, NPC almost exclusively rely on radiotherapy for local disease control and chemoradiotherapy (CCRT) is established as the standard treatment protocol for advanced-stage NPC. However, some NPC patients were under unique scenarios on admission, in which the principles of diagnosis and treatment may be different from conventional cases. These special patients bring difficulties and challenges to clinicians, so that it is necessary to analyze and summarize the management methods for these kinds of patients. In this study, we discussed the following three types of NPC, including dermatomyositis-associated NPC, NPC identified during pregnancy and elderly patients with NPC. As the physiological state of these three kinds of patients is different from others, physicians need to pay special attention to them in the application of chemotherapy, imaging examination and the management of side effects, etc. In order to help clinicians take effective measures in the management of these patients, we refer to the previous studies and summarize the relevant conclusions in the review.

Keywords: Nasopharyngeal carcinoma (NPC); treatment; dermatomyositis; pregnancy; elderly

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Introduction

Nasopharyngeal carcinoma (NPC) is a malignancy arising from the nasopharyngeal mucosal lining. In 2018, there were approximately 129,000 newly diagnosed cases of NPC all over the world, accounting for 0.7% of all cancers. Notably, the geographical global distribution of NPC is extremely unbalanced, and 70% of cases were in East and Southeast Asia (1). In endemic areas such as southern China, World Health Organization (WHO) type III (non-keratinizing subtype) was the most common pathological type (>95%), and this type is primarily associated with Epstein-Barr virus (EBV) infection (2-4). Due to the proximity to multiple critical structures, such as brainstem,

optic apparatus and spinal cord, cure of NPC almost entirely relies on safely delivery of high dose radiotherapy (RT), and often combined with chemotherapy in most presentations. However, safely delivery of RT and chemotherapy may be challenging in some unique setting where treatment decision and regimen needs to be delicately planned. In this review, we presented a summary of NPC presented under unique setting: dermatomyositis, pregnancy and elderly, which help clinicians better deal with these patients.

Dermatomyositis-associated NPC

Dermatomyositis (DM) is a multisystem inflammatory

disease with distinctive cutaneous manifestations. Through an autoimmune mechanism, DM primarily affects the skin and muscle fibers (5,6). Up to now, the pathogenesis of DM remained unclear. A previous study reported that some immune factors such as human leukocyte antigen-subregion DR3 (HLA-DR3) and tumor necrosis factor (TNF) might take part in the pathophysiology of DM. The first case of DM-associated malignancy was reported in 1916, and the first case of DM associated with NPC was reported in 1969 (7). Since then, there were continuous reports regarding the relationship between DM and different malignancies such as carcinoma of the breast, lung, uterus, colorectal region, and non-Hodgkin lymphoma (8). One possible explanation for this association was that tumor cells secreted a series of cross-reacting substances, which further lead to the immune reactions to the skin and muscle (9). Under this theory, DM could be defined as a kind of paraneoplastic syndrome.

It should be noted that DM is not a cancer-specific disease. Instead, it is related to different types of malignancy in different populations. For example, ovarian, lung, and pancreatic cancers were reported as the three most common types of cancers associated with dermatomyositis in Sweden, Denmark, and Finland, whereas DM is closely related to NPC in Asia (10-12). In addition to the mechanism of paraneoplastic syndrome mentioned previously, the association between DM and NPC in endemic areas might also be explained by the infection of EBV. It has been clearly verified that EBV infection is associated with the pathogenesis of NPC. However, whether the EBV could lead to the occurrence of DM remains to be confirmed (13). A previous study demonstrated a positive correlation between DM and EBV infection, and this correlation is stronger among the Southern China population. Further, in our previous study, which retrospectively analyzed a total of 112 patients with NPC combined with DM from 1964 to 2007, patients with NPC combined with DM had a higher serum EBV viral capsule antigen-immunoglobulin A (VCA-IgA) level compared with the control group (14). Similarly, Yamashita *et al.* also reported a case of EBV-associated gastric cancer in a patient with DM. We can speculate from these studies that EBV-associated malignancy causes DM as a paraneoplastic syndrome in which EBV may somehow play a role (15).

As there have been very few randomized controlled trials targeting DM, its clinical management has been based primarily on case reports and retrospective studies. An agreement had been reached that corticosteroids

were the cornerstone of DM treatment (16). Recently, some scholars suggested that a more aggressive therapy, which added immunosuppressive drug to steroids, could result in a better outcome (17-20). Considering that the immunosuppressive agent could exacerbate malignancy to some extent, this therapy was not recommended in patients with DM-associated malignancy. Thus, corticosteroids are still the alternative treatment method for patients with NPC combined with DM. However, different researchers held different views in the application of corticosteroids. A single-arm study of 45 patients with NPC with DM indicated that prednisone treatment is not only quite effective in symptom control, but also does not lead to a significantly increased rate of distant metastasis. Whereas, other scholars considered that glucocorticoid treatment had no effect on DM-associated malignancy, and could promote the progression of malignancy because of its immune suppression (21,22). Our previous study verified that chemotherapy application was an independent prognostic factor in cases of NPC with DM, but the addition of glucocorticoid could not further improve the survival outcome. Interestingly, many authors found a phenomenon that the symptoms of DM showed different degrees of improvement accompanying the elimination of NPC without any specific treatment for DM (23). These results indicated to us that the application of corticosteroids was not necessary in patients who were sensitive to treatment, as the symptoms of DM may improve after tumor remission. Conversely, if the tumor cannot be treated quickly and radically, the corticosteroid treatment might be required to control the skin symptom (24). Because of the low incidence of NPC with DM, it is very difficult to launch a prospective research, and there is no agreement on the therapeutic value of corticosteroids in these patients. The clinician should use corticosteroids with caution based on the specific circumstances of each patient.

In addition, the side effect of RT is also a notable problem for patients with NPC combined with DM. According to a previous study, acute mucositis, sore throat, and neck dermatitis were more frequent and serious in the DM group, and could affect the quality of life of patients, and even cause delay or interruption of treatment (14,25). The primary treatment strategies included nutritional supplementation, oral cleansing, the application of a mucosal protector, and antibiotics (26-29). In addition, better family care and nursing care were needed for these patients. Our previous study demonstrated that early use of controlled-release oxycodone at the moderate pain stage could provide

better pain relief, reduced weight loss during treatment, and improved quality of life for these patients (25).

Nasopharyngeal cancer identified during pregnancy

Pregnancy-associated nasopharyngeal cancer (PANPC) has been defined as NPC diagnosed not only during pregnancy but also up to 1 year after delivery (30). With the tendency of women delaying childbearing into their late reproductive years (31), we would like to focus on the care of women with PANPC for the desire to diagnose and treat them effectively but also ensure the safety of the fetus.

After comparing the percentage of patients diagnosed with advanced-stage NPC (60% of patients with NPC shown by Li *et al.* vs. 83.3% of patients with PANPC, and even 92.3% of patients with PANPC according to Cheng *et al.*), we indicated that pregnancy might delay the diagnosis and evaluation of NPC (32,33). Timely nasopharyngoscopy examinations and biopsies should be provided if indicated. For non-pregnant patients, magnetic resonance imaging (MRI) and/or computed tomography (CT), chest radiography, abdominal ultrasound, a whole-body ECT, and an EBV DNA test were conventionally used to assess, and PET/CT was recommended if economy permitted. However, for those pregnant patients, MRI with teratogenic gadolinium-based contrast, which has been shown to pass through the placenta, should be limited only when the advantages outweigh the disadvantages with the lowest dose (34). For those patients who are lactating, because these low protein binding and water soluble contrast agents are excreted into breast milk, it is a preventive strategy to suspend breastfeeding for 12 hours after the injection of gadolinium (35). Furthermore, we need to minimize radiation exposure during diagnosis. Chest radiography results in lower fetal radiation exposure than chest CT scan (0.02–0.07 mrad vs. 0.02 rad) (36,37). Systemic staging studies accepted by the public include abdominal ultrasound, chest radiography with abdominal shielding and non-contrast skeletal MRI due to the risk of radiation and contrast agents on the vulnerable fetus (38,39). Neither PET/CT scan or bone scintigraphy cannot be recommended; but when necessary, reducing radioactive administration with increasing imaging time or catheterizing the bladder is an alternative way to reduce fetal exposure (40,41). An EBV DNA test has been used for population screening, prognostication, predicting treatment response for therapeutic adaptation, and disease

surveillance, whereas normal pregnancy, which means acquired immune suppression, may be associated with reactivation of EBV. Thus, the role of EBV reactivation in PANPC warrants further attention (42–45).

In the treatment of NPC, RT has been recognized as the radical treatment modality, while systemic chemotherapy providing benefits to patients forms an integral component (46). However, for pregnant patients, how and when to treat is a therapeutic dilemma. There have been some case reports concerning the treatment of pregnant women. A case by Felix Wong in 1986 reported the delivery of a healthy infant NPC after irradiation treatment during the second trimester of pregnancy with an abdominal shield (47). A case by Tsung-I Lin in 2007 reported a woman (staged T4N2M0) who was cured by a combination of chemotherapy and RT after cesarean section at 33 weeks (48). Successfully, the patient received a second healthy infant with a 3-year birth interval. A case by Jami Star in 1999 reported a woman (staged T4N2–3M1 with mediastinal metastases) underwent four courses of chemotherapy and radiation therapy after spontaneous delivery but died of tumor within 6 months (49). As the development of the human fetus is extremely sensitive to ionizing radiation (causing lethal effects, malformations, growth disturbances, or childhood cancer), some authors recommend the tailored use of RT, especially during the first trimester; however, Mazeron and his colleague reported that irradiation below the threshold of 0.1 Gy and subdiaphragmatic treatments are possible during pregnancy (50–52). A shield can reduce the fetal radiation in IMRT era (53). To date, the safety of RT is not conclusive. In this setting, we suggest to evaluate the fetal dose of RT. As for chemotherapy, it is contraindicated during the first trimester of pregnancy because of the normal organogenesis, and the use of cytotoxic chemotherapy is well tolerated and feasible during the second and third trimesters (51). Chemotherapy should be halted before 34-week gestation for the possibility of fetal myelosuppression (36,39). More, pregnancy physiologically leads to volume expansion with maternal blood dilution, hepatic metabolism, distribution and excretions of drugs, all of which can have an influence on the appropriate delivery of chemotherapy (54).

Although a disastrous outcome was reported by Yan *et al.* in 1984, in that eight concurrent patients died within 1.5 years after radiation with only 11% (1/9) 5-year survival rate, previous studies draw a conclusion that pregnancy itself may not cause inferior survival with the evolution of diagnostic and therapeutic technology (33,55,56).

Interestingly, in the retrospective case-control analysis (36 PANPC patients: 36 matched non-pregnant women) by Cheng *et al.* (33), patients who developed NPC during pregnancy may have a poorer outcome than those who developed NPC within 1 year after labor. Whereas, in the matched cohort analysis (51 PANPC patients: 51 matched non-pregnant females), there was no difference between the early pregnant group (defined as the patients during pregnancy or within 6 months after delivery) and the late pregnant group (defined as the patients at least 6 months after delivery but within 1 year) (4). Last but not the least, neither of these authors provide information about pregnancy outcome.

All in all, PANPC, which has been regarded as hope after the storm, brings ethical and professional challenge for both the women patients and the healthcare providers. We need to take the timing of the pregnancy and the mothers' wishes into consideration to generate individualized treatment plans for maximizing benefits and minimizing harm to the mother and newborns or fetus. We suggested the careful decision based on trimester. During the first trimester, the treatments should be deferred to the second trimester if possible or after therapeutic abortion; during the second and third trimesters, treatments can be delayed depending on the maternal stages or initiated with close monitoring (37,57). There is no need for iatrogenic premature delivery defer therapy (58).

Elderly patients with NPC

At what age, does the term “elderly” applies cannot be universally decided, since it varies according to the situation. Most studies agree that persons 65 years of age or older can be considered elderly. However, some research has set the age at 60 years. As yet another group of NPC patients, the elderly represent a unique challenge for RT and/or chemotherapy because of decreased physical function and comorbidities. Common tools to measure the comorbidities include the Adult Comorbidity Evaluation-27 (ACE-27) and the Charlson Comorbidity Index (CCI). In a recently published study, the incidence of comorbidities in elderly NPC patients was reported to be 22.4%, which is critical to predicting a decline in OS (59).

The treatment of elderly NPC patients remains blurry, although concurrent chemoradiotherapy is the cornerstone treatment modality for NPC patients. Whether the elderly can benefit from chemotherapy is controversial, since chemotherapy is associated with significantly increased

toxic effects that induce treatment-related mortality and is unlikely to improve survival.

In clinical practice, RT alone or concurrent chemoradiotherapy were applied to elderly patients. Sze *et al.* demonstrated that compared with those aged less than 70 years, those aged 70 and above displayed significantly higher incidences of acute adverse effects, RT incompleteness, and mortality at 90 days with a percentage of 7.8%. The 5-year OS rates of those aged greater than 70 years dramatically decreases, and ACE-27 was the only prognostic factor for mortality at 90 days with a hazard ratio of 15.86 [95% confidence interval (CI): 2.68–93.95, $P=0.002$]. This research indicates that elderly patients should be treated when their comorbidities are well-controlled, and patient selection and treatment modality should be chosen with reference to ACE-27 (60). Wen and colleagues reported that the 3-year cancer-specific survival in elderly NPC patients who were 70 years of age and older in the RT alone group was comparable with that in the concurrent chemoradiotherapy group (64.3% *vs.* 65.2%, $P=0.764$) by using propensity score matching and creating a balanced cohort. Similar with previous studies, they also showed that a high ACE-27 score instead of the addition of chemotherapy was the independent prognostic factor for cancer-specific survival (61). In accordance with the aforementioned results, Mi elucidated that the additional concurrent chemotherapy could not significantly increase the OS of elderly patients (72.5% *vs.* 72.1%, $P=0.799$). However, the frequencies of grade 3 acute adverse effects including vomiting/nausea, leukopenia/neutropenia, thrombocytopenia, and anemia significantly increase in the intensity-modulated radiotherapy (IMRT) in combination with chemotherapy group (62). Regarding the choice of chemotherapy modalities, concurrent chemoradiotherapy is the most common method. Zeng *et al.* conducted a cohort study investigating the survival rates in elderly NPC patients treated by induction chemotherapy and RT alone compared with concurrent chemoradiotherapy using a propensity score matching method. They demonstrated that no significant survival differences were obtained between the two groups. However, in comparison with the patients in the concurrent chemotherapy group, patients who received induction chemotherapy followed by RT alone had significantly fewer acute adverse effects, including leucopenia, anemia, mucositis, and weight loss. They recommended that induction chemotherapy followed by RT alone as the better modality for elderly patients (63). With regard to antibody against epidermal growth factor

receptor (EGFR) in elderly NPC patients, Wang and his collaborators found that the administration of nimotuzumab plus RT with or without chemotherapy in elderly NPC patients was safe, and the adverse effects were tolerated. Nimotuzumab may be a preferable option for elderly NPC patients who cannot tolerate chemotherapy, but this result needs to be validated by larger randomized controlled clinical trials (64).

Elderly NPC patients often present with decreased performance status and have poorer tolerance to chemotherapy. RT alone seems to be the most agreeable and widely applied treatment modality for this population. Whether induction chemotherapy followed by RT alone or RT in combination with nimotuzumab could be superior to RT alone remains unequivocal, and more evidence is needed. Despite a worse survival rate compared with the young, a rather satisfactory disease control rate could still be achieved in the IMRT era. The comorbidities measured by ACE-27 have been shown to be predictive for mortality. Therefore, decisions on the treatment modality should be made on the basis of ACE-27 or the CCI score. And, intensive support and care should be provided to elderly NPC patients.

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Footnote

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References

1. Bray F, Ferlay J, Soerjomataram I et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018;68:394-424.
2. Wang HY, Chang YL, To KF et al. A new prognostic histopathologic classification of nasopharyngeal carcinoma. *Chin J Cancer* 2016;35:41.
3. Pathmanathan R, Prasad U, Chandrika G et al. Undifferentiated, nonkeratinizing, and squamous cell carcinoma of the nasopharynx. Variants of Epstein-Barr virus-infected neoplasia. *Am J Pathol* 1995;146:1355-67.
4. Chua ML, Wee J, Hui E, et al. Nasopharyngeal carcinoma. *Lancet* 2016;387:1012-24.
5. Mebazâa A, Boussen H, Nouria R, et al. Dermatomyositis and malignancy in Tunisia: a multicenter national retrospective study of 20 cases. *J Am Acad Dermatol* 2003;48:530-4.
6. Chakroun A, Guigay J, Lusinci A, et al. Paraneoplastic dermatomyositis accompanying nasopharyngeal carcinoma: diagnosis, treatment and prognosis. *Eur Ann Otorhinolaryngol Head Neck Dis* 2011;128:127-31.
7. Wong KO. Dermatomyositis: a clinical investigation of twenty-three cases in Hong Kong. *Br J Dermatol* 1969;81:544-7.
8. Tang MM, Thevarajah S. Paraneoplastic Dermatomyositis: A 12-year Retrospective Review in the Department of Dermatology Hospital Kuala Lumpur. *Med J Malaysia* 2010;65:138-42.
9. Maoz CR, Langevitz P, Livneh A, et al. High incidence of malignancies in patients with dermatomyositis and polymyositis: an 11-year analysis. *Semin Arthritis Rheum* 1998;27:319-324.
10. Chan HL. Dermatomyositis and cancer in Singapore. *Int J Dermatol* 1985;24:447-50.
11. Liu WC, Ho M, Koh WP, et al. An 11-year review of dermatomyositis in Asian patients. *Ann Acad Med Singapore* 2010;39:843-7.
12. Hill CL, Zhang Y, Sigurgeirsson B, et al. Frequency of specific cancer types in dermatomyositis and polymyositis: a population-based study. *Lancet* 2001; 357: 96-100.
13. Barzilai O, Sherer Y, Ram M, et al. Epstein-Barr virus and cytomegalovirus in autoimmune diseases: are they

- truly notorious? A preliminary report. *Ann N Y Acad Sci* 2007;1108:567-77.
14. Huang PY, Zhong ZL, Luo DH, et al. Paired study of 172 cases of nasopharyngeal carcinoma with or without dermatomyositis. *Acta Otolaryngol* 2014;134:824-30.
 15. Yamashita K, Hosokawa M, Hirohashi S, et al. Epstein-Barr virus-associated gastric cancer in a patient with dermatomyositis. *Intern Med* 2001;40:96-9.
 16. Gordon PA, Winer JB, Hoogendijk JE, et al. Immunosuppressant and immunomodulatory treatment for dermatomyositis and polymyositis. *Cochrane Database Syst Rev* 2012;2012:CD003643.
 17. Ruperto N, Pistorio A, Oliveira S, et al. Prednisone versus prednisone plus ciclosporin versus prednisone plus methotrexate in new-onset juvenile dermatomyositis: a randomised trial. *Lancet* 2016;387:671-8.
 18. Al-Mayouf SM, Laxer RM, Schneider R, et al. Intravenous immunoglobulin therapy for juvenile dermatomyositis: efficacy and safety. *J Rheumatol* 2000;27:2498-503.
 19. Al-Mayouf S, Al-Mazyed A, Bahabri S. Efficacy of early treatment of severe juvenile dermatomyositis with intravenous methylprednisolone and methotrexate. *Clin Rheumatol* 2000;19:138-41.
 20. Heckmatt J, Hasson N, Saunders C, et al. Cyclosporin in juvenile dermatomyositis. *Lancet* 1989;1:1063-6.
 21. Hu WJ, Chen DL, Min HQ. Study of 45 cases of nasopharyngeal carcinoma with dermatomyositis. *Am J Clin Oncol* 1996;19:35-8.
 22. Steff M, Le Corre Y, Penisson-Besnier I, et al. Cutaneous EBV-associated lymphoproliferative disorder in a dermatomyositis treated with immunosuppressive agents. *Rev Med Interne* 2009;30:720-3.
 23. Callen JP. Dermatomyositis and malignancy. *Clin Dermatol* 1993;11:61-5.
 24. Chandiramani M, Joyson C, Panchal R, et al. Dermatomyositis as a paraneoplastic syndrome in carcinosarcoma of uterine origin. *Clin Oncol (R Coll Radiol)* 2006;18:641-8.
 25. Hua X, Chen LM, Zhu Q, et al. Efficacy of controlled-release oxycodone for reducing pain due to oral mucositis in nasopharyngeal carcinoma patients treated with concurrent chemoradiotherapy: a prospective clinical trial. *Support Care Cancer* 2019;27:3759-67.
 26. Peterson DE, Bensadoun RJ, Roila F. Management of oral and gastrointestinal mucositis: ESMO Clinical Practice Guidelines. *Ann Oncol* 2011;22 Suppl 6:vi78-84.
 27. Liang G, Du W, Ke Q, et al. The effects of recombinant human granulocyte colony-stimulating factor mouthwash on radiotherapy-induced oral mucositis in locally advanced nasopharyngeal carcinoma patients. *Adv Clin Exp Med* 2017;26:409-13.
 28. Luo Y, Feng M, Fan Z, et al. Effect of Kangfuxin Solution on Chemo/Radiotherapy-Induced Mucositis in Nasopharyngeal Carcinoma Patients: A Multicenter, Prospective Randomized Phase III Clinical Study. *Evid Based Complement Alternat Med* 2016;2016:8692343.
 29. Zheng B, Zhu X, Liu M, et al. Randomized, Double-Blind, Placebo-Controlled Trial of Shuanghua Baihe Tablets to Prevent Oral Mucositis in Patients With Nasopharyngeal Cancer Undergoing Chemoradiation Therapy. *Int J Radiat Oncol Biol Phys* 2018;100:418-26.
 30. Voulgaris E, Pentheroudakis G, Pavlidis N. Cancer and pregnancy: a comprehensive review. *Surg Oncol* 2011;20:e175-85.
 31. Matthews TJ, Hamilton BE. Delayed childbearing: more women are having their first child later in life. *NCHS Data Brief* 2009;(21):1-8.
 32. Li WF, Sun Y, Mao YP, et al. Proposed lymph node staging system using the International Consensus Guidelines for lymph node levels is predictive for nasopharyngeal carcinoma patients from endemic areas treated with intensity modulated radiation therapy. *Int J Radiat Oncol Biol Phys* 2013;86:249-56.
 33. Cheng YK, Zhang F, Tang LL, et al. Pregnancy associated nasopharyngeal carcinoma: A retrospective case-control analysis of maternal survival outcomes. *Radiother Oncol* 2015;116:125-30.
 34. Nguyen CP, Goodman LH. Fetal risk in diagnostic radiology. *Semin Ultrasound CT MR* 2012;33:4-10.
 35. Webb JA, Thomsen HS, Morcos SK. The use of iodinated and gadolinium contrast media during pregnancy and lactation. *Eur Radiol* 2005;15:1234-40.
 36. Albright CM, Wenstrom KD. Malignancies in pregnancy. *Best Pract Res Clin Obstet Gynaecol* 2016;33:2-18.
 37. Pereg D, Koren G, Lishner M. Cancer in pregnancy: gaps, challenges and solutions. *Cancer Treat Rev* 2008;34:302-12.
 38. Tirada N, Dreizin D, Khati NJ et al. Imaging Pregnant and Lactating Patients. *Radiographics* 2015;35:1751-65.
 39. Shachar SS, Gallagher K, McGuire K et al. Multidisciplinary Management of Breast Cancer During Pregnancy. *Oncologist* 2017;22:324-34.
 40. de Haan J, Vandecaveye V, Han SN, et al. Difficulties with diagnosis of malignancies in pregnancy. *Best Pract Res Clin Obstet Gynaecol* 2016;33:19-32.
 41. Bural GG, Laymon CM, Mountz JM. Nuclear imaging of

- a pregnant patient: should we perform nuclear medicine procedures during pregnancy? *Mol Imaging Radionucl Ther* 2012;21:1-5.
42. Chen YP, Chan ATC, Le QT, et al. Nasopharyngeal carcinoma. *Lancet* 2019;394:64-80.
 43. Luppi P. How immune mechanisms are affected by pregnancy. *Vaccine* 2003;21:3352-7.
 44. Sakamoto K, Greally J, Gilfillan RF, et al. Epstein-Barr virus in normal pregnant women. *Am J Reprod Immunol* 1982;2:217-21.
 45. Christian LM, Iams JD, Porter K, et al. Epstein-Barr virus reactivation during pregnancy and postpartum: effects of race and racial discrimination. *Brain Behav Immun* 2012;26:1280-7.
 46. Tan WL, Tan EH, Lim DW, et al. Advances in systemic treatment for nasopharyngeal carcinoma. *Chin Clin Oncol* 2016;5:21.
 47. Wong F, Sai-Ki O, Cheung F, et al. Pregnancy outcome following radiotherapy for naso-pharyngeal carcinoma. *Eur J Obstet Gynecol Reprod Biol* 1986;22:157-60.
 48. Lin TI, Lin JC, Ho ES, et al. Nasopharyngeal carcinoma during pregnancy. *Taiwan J Obstet Gynecol* 2007;46:423-6.
 49. Star J, Malee MP. Pregnancy complicated by nasopharyngeal carcinoma. *Obstet Gynecol* 1999;94:845.
 50. Mazzola R, Corradini S, Eidemueller M, et al. Modern radiotherapy in cancer treatment during pregnancy. *Crit Rev Oncol Hematol* 2019;136:13-9.
 51. Knabben L, Mueller MD. Breast cancer and pregnancy. *Horm Mol Biol Clin Investig* 2017;32.
 52. Mazon R, Barillot I, Mornex F, et al. Radiotherapy during pregnancy. *Cancer Radiother* 2016;20 Suppl:S264-8.
 53. Josipović M, Nyström H, Kjaer-Kristoffersen F. IMRT in a pregnant patient: how to reduce the fetal dose? *Med Dosim* 2009;34:301-10.
 54. Kohlhepp LM, Hollerich G, Vo L, et al. (Physiological changes during pregnancy). *Anaesthesist* 2018;67:383-96.
 55. Yan JH, Liao CS, Hu YH. Pregnancy and nasopharyngeal carcinoma: a prognostic evaluation of 27 patients. *Int J Radiat Oncol Biol Phys* 1984;10:851-5.
 56. Zhang L, Liu H, Tang LQ, et al. Prognostic effect of pregnancy on young female patients with nasopharyngeal carcinoma: results from a matched cohort analysis. *Oncotarget* 2016;7:21913-21.
 57. Peccatori FA, Azim HA Jr, Orecchia R, et al. Cancer, pregnancy and fertility: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2013;24 Suppl 6:vi160-170.
 58. Van Calsteren K, Heyns L, De Smet F, et al. Cancer during pregnancy: an analysis of 215 patients emphasizing the obstetrical and the neonatal outcomes. *J Clin Oncol* 2010;28:683-9.
 59. Huang Y, Chen W, Haque W, et al. The impact of comorbidity on overall survival in elderly nasopharyngeal carcinoma patients: a National Cancer Data Base analysis. *Cancer Med* 2018;7:1093-101.
 60. Sze HC, Ng WT, Chan OS, et al. Radical radiotherapy for nasopharyngeal carcinoma in elderly patients: the importance of co-morbidity assessment. *Oral Oncol* 2012;48:162-7.
 61. Wen YF, Sun XS, Yuan L, et al. The impact of Adult Comorbidity Evaluation-27 on the clinical outcome of elderly nasopharyngeal carcinoma patients treated with chemoradiotherapy or radiotherapy: a matched cohort analysis. *J Cancer* 2019;10:5614-21.
 62. Mi JL, Meng YL, Wu HL, et al. Comparison of intensity-modulated radiation therapy alone vs. intensity-modulated radiation therapy combined with chemotherapy in elderly nasopharyngeal carcinoma patients (aged >65 years). *Strahlenther Onkol* 2020;196:270-9.
 63. Zeng Q, Wang J, Lv X, et al. Induction Chemotherapy Followed by Radiotherapy versus Concurrent Chemoradiotherapy in elderly patients with nasopharyngeal carcinoma: finding from a propensity-matched analysis. *BMC Cancer* 2016;16:693.
 64. Wang F, Jiang C, Ye Z, et al. Efficacy and Safety of Nimotuzumab Plus Radiotherapy With or Without Cisplatin-Based Chemotherapy in an Elderly Patient Subgroup (Aged 60 and Older) With Nasopharyngeal Carcinoma. *Transl Oncol* 2018;11:338-45.

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