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SECOND MALIGNANCY – OUR ONE YEAR EXPERIENCE "THE EXPECTED" AND "THE SURPRISES"

Oncology

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ABSTRACT

Early diagnosis and treatment lead to improved survival in cancer patients. A major concern in such patients with improved survival is the risk of second primary malignancy. We report our experience, managing cancer patients with second primary malignancy. Second malignancies can be attributed to common etiological agents with primary malignancy, field cancerization, a consequence of treatment of primary malignancy, genetic syndromes and can be totally unrelated to the primary malignancy. Watchful expectancy with site-specific screening can detect the second primary without delay may help in reducing the morbidity and mortality associated with the second primary.

KEYWORDS

Second Primary Malignancy, Synchronous, Metachronous, Field Cancerization.

Introduction

Early diagnosis and treatment have led to improved survival in cancer patients. Among the various long-term physical and psychosocial consequences of the disease, a major concern among cancer survivor is the risk of developing a second primary malignancy (SPM). According to SEER data second primary malignancy accounts for 16% of incident cases[1]. Second primary malignancy is attributed to prior cancer treatment, shared etiological factors, environmental factors, host characteristics, the gene to gene and gene-environment interaction. In addition to this well defined clinical genetic syndromes like Neurofibromatosis are associated with increased risk of SPM.

Patients and Methods

During the one year period (November 2015 to October 2016) data was gathered from patients managed in our institution. This is a prospective descriptive study were data analysed with the primary intention to know the incidence of SPM among the patients, to know which site contributes to the incidence of SPM and to analyse possible ways for prevention of the second primary as well as early detection of the second primary.'

Patients developing second malignancy during follow up and patients presenting with double primary malignancies are included in the study. Recurrences and residue are excluded from the study. Recurrences are considered within 2 cm of the primary malignancy. Synchronous SPM is those developing simultaneously with or within 6 months after an index tumour, out of this time period is metachronous SPM. All clinical data including the site, pathology, treatment and time duration between the first and the second malignancy were analysed. We have made analysis to establish the correlation between first and second malignancies.

Results

During the study period of one year, totally of 2135 patients were registered in our department of which 25 patients had a second double primary, an incidence of 1.01. Of the 25 patients, 9 patients had synchronous second primary and the rest were metachronous.

Head and neck malignancies were the most common primary site to develop a SPM (n=10) followed by Gynaecological malignancies (n= 6), breast (n=5), Urological malignancies (n=2), GIT (n=1) and Soft tissue tumors (n=1) (Table 1).

Also, head and neck region was the most common site for second primary malignancy (n=7) followed by endometrial carcinoma and carcinoma breast.

Among the Head and neck malignancies, the oral cavity subsite first primary is associated with higher chance of developing a second primary followed by subsite hypopharynx and larynx. Among the head and neck malignancies, five cases presented with synchronous SPM. The time gap between the index and the SPM ranged from synchronous to 8 years. Five cases developed the second primary away from the head and neck region.

Among patients with carcinoma breast as the first primary, 2 patients developed carcinoma endometrium, 1 patient contralateral breast cancer, and the other patient developed radiation-induced pleomorphic sarcoma of the chest wall. Longest time gap to develop SPM is 8 years, all the patients who developed endometrial SPM were on tamoxifen.

Among the gynaecological first primary cancers, cervix comprised of the most common site followed by endometrial carcinoma to develop SPM. Among the patients with endometrial cancers, one patient developed papillary carcinoma thyroid and the other carcinoma ovary synchronously.

One case with higher order malignancy deserves special mention, a case of carcinoma cervix treated with radiotherapy developed carcinoma gastro-oesophageal junction sieverts type III (adenocarcinoma) after a time gap of 11 years, treated with total gastrectomy. The same patient developed carcinoma upper and middle third oesophagus (squamous cell carcinoma) 8 years later, treated with external beam radiotherapy.

A case of neurofibromatosis treated for leiomyosarcoma of the urinary bladder, partial cystectomy done developed malignant peripheral nerve sheath tumour of stomach 12 years later for which radical distal gastrectomy was done.

Another case of extraskeletal chondrosarcoma of thigh treated with wide local excision with positive posterior margin treated with adjuvant EBRT and adjuvant chemotherapy developed carcinoma endometrium surgical staging done.

Five index cases where radiation was a part of the primary modality of treatment developed SPM. One case of Carcinoma oral cavity operated and adjuvant radiation given developed carcinoma Maxilla, One case of carcinoma cervix treated with radiation developed carcinoma vulva, another case of carcinoma cervix developed granulose cell tumor of the ovary, one case of bilateral carcinoma breast treated with surgery and adjuvant radiation developed pleomorphic sarcoma of the chest wall during follow up. Another case of carcinoma breast treated with

surgery and radiation developed contralateral breast cancer.

Discussion

First case report on multiple primaries was reported as early as 1869 by Billroth, but he experienced difficulty in differentiating double primary from metastatic disease. Warren and Gates later in 1932 defined the criteria for multiple primary. According to the criteria,

1. Both tumours should be malignant as evidenced by histology
2. Each a tumour should be geographically separate and distinct with intervening areas of normal and non-neoplastic mucosa
3. The possibility of a second tumour being metastatic should be excluded.

Second Primary Malignancy in Head and Neck region

Second Primary Malignancy is the leading cause of mortality following a primary head and neck squamous cell carcinoma (HNSCC) [2]. About one-third of the death in head and neck squamous cell carcinoma is attributed to SPM [3][4]. Head and neck squamous cell carcinoma best illustrate the concept of field cancerization. Slaughter et al was the first to describe the concept of field cancerization. Tobacco and alcohol increase the cancer risk of the exposed mucosa of the aerodigestive tract. HPV virus is also associated oropharyngeal cancers. The common sites of SPM after an index case of HNSCC are head and neck, lung and oesophagus[5][6].

Oral cavity cancers are more commonly associated with SPM of HNSCC[7][8]. Laryngeal cancer appears most commonly associated with SPM in the head and neck [7][8]. There is no data regarding the risk of SPM in HPV positive and negative data except for Ang et al have reported a lower rate of second head and neck and lung cancers among patients with HPV positive tumours[9].

Surveillance for SPM of Head and Neck second malignancy includes a regular follow up 1 to 2 months for 2 years, every 3 months for the 3rd year, every 6 months for the 4th and 5th years, and annually thereafter. Chest radiography and thyroid function tests are to be done annually. Fibre optic endoscopy should be done as and when clinically indicated.

Second Primary malignancy after Breast cancer.

The incidence of contralateral breast cancer is around 2 to 15 % in a treated case of breast cancer [10]. Synchronous or metachronous bilateral cancer occurs approximately in 0.3% – 12% and in 5% – 10% of the patients, respectively[11][12]. It is imperative to distinguish bilateral tumours from metastasis as obviously the outcome after recurrence is poor compared to second primary malignancy in the contralateral breast. The risk factors associated with bilateral occurrence are: familial or hereditary breast cancer, young age at primary breast cancer diagnosis, lobular invasive carcinoma, multicentricity and radiation exposure.

Chaudary et al [13] proposed criteria for the diagnosis of second primary breast cancer in 1984 as follows:

(i) there must be in situ change in a contralateral tumour,
(ii) a tumour in the second breast is histologically different from cancer in the first breast,
(iii) the degree of histological differentiation of a tumour in the second breast is distinctly greater than that of the lesion in the first breast,
(iv) there is no evidence of local, regional, or distant metastases from cancer in the ipsilateral breast.

Above criteria are the most widely accepted method to differentiate second primary lesion from the metastatic lesion.

Survival analysis shows that bilateral breast cancer is not associated with impaired survival. Patients with bilateral breast cancer were more likely to have bone metastasis and visceral metastasis than those with unilateral breast cancer [14].

The risk of ovarian malignancy increases in women with BRCA1-associated cancers, the lifetime risk of second breast cancers is 40% to 60% and the lifetime risk of ovarian malignancy is 15% to 45%. Similarly, the risk of second breast cancers among women with BRCA2-associated cancers is also 40% to 60%, whereas the risk of ovarian cancers is 10% to 20%.

The risk of endometrial malignancy following a primary breast cancer is increased 2- to 4-fold in postmenopausal women who use tamoxifen. Patients with endometrial cancer after breast cancer who received tamoxifen treatment for five years for breast cancer have greater endometrial cancer mortality risk than those who did not receive tamoxifen. This can be attributed to non-endometrioid histological subtypes with poorer prognosis among long-term tamoxifen users.

Breast cancer patients treated with radiation show 16 fold increase in the risk of development of Angiosarcoma and 2 fold of increase of all soft tissue sarcoma [15]. Overall Radiation-induced sarcoma constitutes 3% of all sarcomas [16]. Malignant Fibrous Histiocytoma and undifferentiated sarcoma not otherwise specified are the most common subtype [17][18].

Criteria for defining Radiation Induced sarcoma was proposed by Cahan and modified by Arlen et al [19].

1. Treatment with therapeutic irradiation at least three years prior to development of sarcoma
2. Sarcoma arising within the field of previous therapeutic irradiation
3. Differing histology between the sarcoma and the primary tumour that required radiotherapy

Properly structured screening aimed at detection of contralateral breast cancer and possible second primary sites as described above can lead to early detection of the second primary and hence appropriate treatment.

Second Primary Malignancy in Gynaecological malignancies

The risk of the second primary is increased in the following sites breast (relative risk, 4.1), ovary (relative risk, 11.6), cervix (relative risk, 5.1), and colon (relative risk, 5.9) after a primary endometrial carcinoma associated with HNPCC [20]. HNPCC may explain some of the excess risks of second intestinal, stomach, kidney, and bladder carcinomas. HNPCC also may contribute to the association between endometrial and ovarian carcinomas. In a recent study, the risk of ovarian carcinoma increased 17-fold during the first 4 years after women were diagnosed with endometrial carcinoma, but that risk was limited to women who were diagnosed with endometrial carcinoma before age 50 years. Scully et al proposed a more detailed method of differentiating endometrial tumours metastatic to ovary, ovarian tumour metastatic to endometrium, and independent primary cancers [21].

Cowden syndrome is part of the PTEN hamartoma tumour syndrome. It is characterized by a high risk of both benign and cancerous tumours of the breast, follicular neoplasm of thyroid, endometrium, colorectal, kidney, and skin (melanoma). Follicular neoplasm of thyroid and Endometrial carcinoma are components of major criteria defining Cowden Syndrome. The risk of thyroid cancer in men and women with Cowden Syndrome is estimated to be 35%. Thyroid cancer in Cowden Syndrome is most commonly the follicular type but may also be the papillary type. The risk of endometrial cancer in women with CS is 28% [22].

Well-known contributing factors for cervical cancer include the human papillomavirus (HPV) and smoking. HPV-related cancers, including those of the vagina, vulva, or anus, and smoking-related cancers, such as cancers of the lung and bronchus, bladder, or oesophagus cancer are increased. Following radiotherapy for cervical cancer treatment, the risk for all second cancers continues to increase over time and remains elevated for more than 40 years. Risks for second cancers of the rectum/anus, colon, urinary bladder, ovary, and female genital sites other than cervix remain elevated to a statistically significant extent for at least 40 years after radiotherapy. Compared with risk in the general population, risk for cancers of the stomach and colon was increased to a statistically significant levels for women treated with radiotherapy [23].

Neurofibromatosis-associated Malignancy

Benign and malignant neoplasms may arise in the abdomen in both pediatric and adult patients with Neurofibromatosis NF1. The abdominal neoplasms in NF1 can be divided into five basic categories: neurogenic tumours, neuroendocrine tumours, non-neurogenic gastrointestinal mesenchymal tumours, embryonal tumours, and miscellaneous tumours. The lifetime risk of developing an MPNST for a person with NF1 is 4%–5% [24].

Genitourinary tract is rarely involved in NF1. The bladder is the commonest affected organ in the urinary tract, in which the manifestation of the disease is either as an isolated mass or a diffuse infiltrative process. One case report of leiomyosarcoma of urinary bladder in Neurofibromatosis was reported as early as in 1977 [25].

Radiation and Second Primary

It is well established that radiation increases the chances of SPM. Management of tumours which necessitate radiation as part of the combined modality of treatment is prone to the development of SPM. In certain cases, radiation cannot be avoided but in cases wherein both surgery and radiation offer a similar response, cure and survival rates it is better to treat surgically rather than by radiation. So it is wise to gauge the after-effects of radiation and surgical morbidity in treating early lesions of the oral cavity, an operable subset of cancer cervix and in early breast cancer patients undergoing BCT.

SPM Prevention and Early detection

13 cis Retinoic acid in cases of prior HNSCC significantly reduces second primary tumours at 32 and 55 months various agents tried were of no significant benefit. Combination of beta-carotene, Vitamin D and selenium showed a significant decrease in stomach cancer death. Results have shown that NSAIDs reduce the recurrence as well as delayed development of polyps and regression of polyps. Also, there is a role for surgery in cancer prevention.

Recent research has found that HPV vaccination administered for Carcinoma cervix confers strong protection against oral HPV infections known to be associated with cancer of oropharynx and tonsil. HPV vaccination could make an important contribution to the reduction of the risk for cervical cancer and could also prevent about half the vulvar carcinomas in younger women and about two-thirds of the intraepithelial lesions in the lower genital tract [26].

All Cancer patients should be screened thoroughly with a higher degree of suspicion for the development of SPM. Though screening is of value only in cervix and colorectal, it should be extended for all systems relevant to the index case. No screening exists for HNSCC but these cases are more prone to the development of SPM such index cases should be followed up with triple endoscopy and imaging at regular intervals. It is high time to develop separate screening modality and guidelines for cancer survivors and this will definitely help in early detection of SPM and improved survival.

The incidence of SPM currently is around 16 -18 % worldwide but our incidence is much lesser compared to world data. This may be due to the advanced presentation of first primary leading to decreased survival rates hence decreased chances of developing a second primary. Second, lack of awareness and motivation about surveillance and screening among the cancer survivors.

Conclusion

The burden of Second Primary Malignancy cannot be underestimated in the era of improved cancer therapeutics. HNSCC followed by breast and gynaecological malignancies constitute the majority of index cases developing SPM. Keeping these patients under close surveillance and testing for genetic abnormality may help in detecting second malignancy at the earliest. Screening as per guidelines should be insisted. Watchful expectancy with site-specific screening modalities may help in reducing morbidity and mortality due to SPM in these unfortunate victims of successful cancer therapy.

Table 1: Showing site, treatment of first primary and second primary and time gap between index and second primary malignancy.

S NO	First Primary	Treatment	Second Primary	Treatment	Time gap	Follow up months
1	Carcinoma Left Lateral Tongue(T1)	Left Hemiglossectomy	Carcinoma Right Lateral Tongue(T1)	Wide Local Excision	8 years	5
2	Carcinoma Right lateral tongue	Wide Local excision(Margins negative)	Carcinoma Right buccal mucosa	Wide Local Excision	3years	7
3	Carcinoma Left Lower Alveolus(T3)	Composite Resection	Carcinoma left Lateral tongue	Composite resection	Synchronous	7
4	Carcinoma Right Buccal Mucosa	Right Composite Resection	Carcinoma Right Maxilla	Radical chemo radiation	2 years	Lost follow up
5	Carcinoma Left Lower Alveolus	Defaulted treatment	Non-Hodgkins Lymphoma	Defaulted treatment	Synchronous	Lost follow up
6	Carcinoma Lip(T1)	Wide local excision	Multifocal HCC	Palliative	3 years	Lost follow up
7	Carcinoma Post Cricoid region	Radical Chemo radiation	Papillary carcinoma thyroid	Defaulted treatment	Synchronous	8
8	Carcinoma Right lateral border tongue	Wide local excision	Carcinoma left buccal mucosa	Wide excision	Synchronous	2
9	Carcinoma Supra Glottis	Defaulted RT	Carcinoma OG junction	Palliative Feeding Jejunostomy	Synchronous	Lost follow up
10	Carcinoma Hypopharynx	Radical Chemoradiation/ Laryngo Pharyngo Oesophagectomy	Carcinoma Right Breast	Modified Radical Mastectomy	1 year	7
11	Leiomyosarcoma Of Urinary Bladder(Neurofibromatosis)	Partial Cystectomy	Carcinoma Distal Stomach (MPNST)	Radical Distal Gastrectomy D2 Lymphadenectomy	12 years	6 months
12	Carcinoma Oesophagus (Adenocarcinoma)	Chemoradiation	Carcinoma middle third Rectum	Low anterior resection	Synchronous	12
13	Carcinoma Right Breast	Modified Radical Mastectomy	Carcinoma Left Breast	Modified Radical Mastectomy	2 years	4
14	Carcinoma Right breast(T4b N2a M0)	Neoadjuvant Chemotherapy	Carcinoma Left breast (T2 NO M0)	Neo-Adjuvant Chemotherapy	Synchronous	Started treatment
15	Carcinoma Right Breast	Modified Radical Mastectomy	Carcinoma Endometrium	Staging/EBRT	2 years	8
16	Bilateral Carcinoma Breast	Bilateral Modified Radical Mastectomy/ Radiation	Pleomorphic Sarcoma Chest wall	Wide excision / Brachytherapy	3years	8
17	Carcinoma Right Breast	Right Modified radical mastectomy/ Adjuvant Chemotherapy	Carcinoma Endometrium	Staging laparotomy	8 years	4

18	Carcinoma Endometrium	Staging / EBRT / Brachytherapy	Differentiated Carcinoma Thyroid	Total thyroidectomy Paratracheal dissection	2 years	12
19	Carcinoma endometrium	Surgical Staging	Carcinoma Ovary	Staging Laparotomy	Synchronous	4
20	Carcinoma Cervix	Radiotherapy	Malignant Granulosa Cell Tumor (Inoperable)	Palliative Chemotherapy	25 years	3
21	Carcinoma Cervix	Radical Chemoradiation	Carcinoma Vulva	Wide local excision / Inguinofemoral Lymph node dissection	8 years	8
23	Carcinoma Cervix IIIB	Radiotherapy	OG Junction Tumor Involving Fundus/ 3rd Primary Carcinoma Upper and Middle third Oesophagus	Total gastrectomy/ Chemoradiation 50 Gy EBRT	11 years 8 Years	Lost follow up
24	Carcinoma Prostate	ADT/Radiotherapy	Carcinoma Left Buccal Mucosa, Pterygoids	Palliative	3 years	Lost follow up
25	Extraskeletal Chondrosarcoma of left thigh	Wide excision/ EBRT/ Adjuvant Chemotherapy	Carcinoma Endometrium	Surgical Staging	2	1 month

REFERENCES

1. Travis LB. The Epidemiology of Second Primary Cancers. Cancer Epidemiol Biomarkers Prev [Internet]. 2006 Oct 20 [cited 2017 Dec 12];15(11):2020–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17057028
2. Vikram B. Changing patterns of failure in advanced head and neck cancer. Arch Otolaryngol [Internet]. 1984;110(9):564–5. Available from: http:// www. ncbi. nlm. nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=6477272
3. León X, Quer M, Diez S, Orús C, López-Pousa a, Burgués J. Second neoplasm in patients with head and neck cancer. Head Neck. 1999;21(3):204–10.
4. Sturgis EM, Miller RH. Second primary malignancies in the head and neck cancer patient. Ann Otol Rhinol Laryngol [Internet]. 1995;104(12):946–54. Available from: http://www.ncbi.nlm.nih.gov/pubmed/7492066
5. Chuang S-CC, Scelo G, Tonita JM, Tamaro S, Jonasson JG, Kliewer E V, et al. Risk of second primary cancer among patients with head and neck cancers: A pooled analysis of 13 cancer registries. Int J cancerJournal Int du cancer. 2008;123(10):2390–6.
6. Lin K, Patel SG, Chu PY, Matsuo JMS, Singh B, Wong RJ, et al. Second primary malignancy of the aerodigestive tract in patients treated for cancer of the oral cavity and larynx. Head Neck. 2005;27(12):1042–8.
7. Haughey BH, Gates GA, Arfken CL, Harvey J. Meta-analysis of second malignant tumors in head and neck cancer: the case for an endoscopic screening protocol. Ann Otol Rhinol Laryngol [Internet]. 1992;101(2 Pt 1):105–12. Available from: http:// www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=1531402
8. Yamamoto E, Shibuya H, Yoshimura R, Miura M. Site specific dependency of second primary cancer in early stage head and neck squamous cell carcinoma. Cancer [Internet]. 2002;94(7):2007–14.
9. Ang KK, Harris J, Wheeler R, Weber R, Rosenthal DI, Nguyen-Tân PF, et al. Human papillomavirus and survival of patients with oropharyngeal cancer. N Eng J Med. 2010;363:24–35.
10. Banelli B, Casciano I, di Vinci A, Gatteschi B, Levaggi A, Carli F, et al. Pathological and molecular characteristics distinguishing contralateral metastatic from new primary breast cancer. Ann Oncol. 2009;21(6):1237–42.
11. ROBBINS GF, BERG JW. BILATERAL PRIMARY BREAST CANCER; A PROSPECTIVE CLINICOPATHOLOGICAL STUDY. Cancer [Internet]. 1964 Dec [cited 2017 Dec 12];17:1501–27. Available from: http:// www. ncbi. nlm. nih. gov/pubmed/14239677
12. Pomerantz RA, Murad T, Hines JR. Bilateral breast cancer. Am Surg. 1989;55(7):441–4.
13. Chaudary MA, Millis RR, Hoskins EO, Halder M, Bulbrook RD, Cuzick J, et al. Bilateral primary breast cancer: a prospective study of disease incidence. Br J Surg. 1984;71(9):711–4.
14. Chen SF, Du CW, Yang P, Zhang HW, Kwan M, Zhang GJ. The molecular and clinicopathologic characteristics of bilateral breast cancer. Sci Rep. 2013;3.
15. Huang J, Mackillop WJ. Increased risk of soft tissue sarcoma after radiotherapy in women with breast carcinoma. Cancer. 2001;92(1):172–80.
16. Yap J, Chuba PJ, Thomas R, Aref A, Lucas D, Severson RK, et al. Sarcoma as a second malignancy after treatment for breast cancer. Int J Radiat Oncol Biol Phys. 2002;52(5):1231–7.
17. Gladdy RA, Qin LX, Moraco N, Edgar MA, Antonescu CR, Alektiar KM, et al. Do radiation-associated soft tissue sarcomas have the same prognosis as sporadic soft tissue sarcomas? J Clin Oncol. 2010;28(12):2064–9.
18. Bjerkehagen B, Smeland S, Walberg L, Skjeldal S, Sundby Hall K, Nesland JM, et al. Radiation-induced sarcoma: 25-Year experience from the Norwegian Radium Hospital. Acta Oncol (Madr). 2008;47(8):1475–82.
19. Arlen M, Higinbotham NL, Huvos AG, Marcove RC, Miller T, Shah IC. Radiation???induced sarcoma of bone. Cancer. 1971;28(5):1087–99.
20. Schwartz Z, Ohel G, Birkenfeld A, Anteby SO, Schenker JG. Second primary malignancy in endometrial carcinoma patients. Gynecol Oncol [Internet]. 1985 Sep [cited 2017 Dec 12];22(1):40–5. Available from: http:// www. ncbi. nlm. nih. gov/pubmed/4018660
21. Rappaport H. Atlas of Tumor Pathology. Atlas of Tumor Pathology. 1966. Section 3.
22. Cowden Syndrome | Cancer.Net [Internet]. [cited 2017 Dec 12]. Available from: https://www.cancer.net/cancer-types/cowden-syndrome
23. Chaturvedi AK, Engels EA, Gilbert ES, Chen BE, Storm H, Lynch CF, et al. Second Cancers Among 104 760 Survivors of Cervical Cancer: Evaluation of Long-Term Risk. Artic | JNCI [Internet]. 1634 [cited 2017 Dec 12];99(21).
24. D'Agostino AN, Soule EH, Miller RH. Primary malignant neoplasms of nerves (Malignant neurilemomas) in patients without manifestations of multiple neurofibromatosis (von Recklinghausen's disease). Cancer [Internet]. 1963 Aug 1 [cited 2017 Dec 12];16(8):1003–14.
25. Poleksic S. Leiomyosarcoma of urinary bladder in von recklinghausen's neurofibromatosis. Urology [Internet]. 1977 Oct 1 [cited 2017 Dec 12];10(4):341–2.
26. Hampl M, Sarajuuri H, Wentzensen N, Bender HG, Kueppers V. Effect of Human Papillomavirus Vaccines on Vulvar, Vaginal, and Anal Intraepithelial Lesions and Vulvar Cancer. Obstet Gynecol [Internet]. 2006 Dec [cited 2017 Dec 12];108(6):1361–8.