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CYTOLOGIC EXAMINATION USING SWAB METHOD TO EVALUATE RADIOLOGIC OUTCOME IN NASOPHARYNGEAL CARCINOMA PATIENTS POST-RADIOTHERAPY

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ABSTRACT

Blind biopsy is still a standard procedure for the evaluation of NPC patients after radiotherapy in Oncology Clinic at ENT Department, Dr Soetomo Hospital. There is a problem in this procedure for patients because blind biopsy method could make bleeding and pain. The swab method was conducted by scraping nasopharyngeal area. This method has minimal injury, bleeding and painless. The result was quicker, cheaper as compared to blind biopsy. Swab method had been reported as having low accuracy as compared to blind biopsy to diagnose NPC. The purpose of this study was to analyze of different results of swab method and blind biopsy in patients of NPC after radiotherapy. The diagnostic test study was done by cross sectional comparative design. The population was NPC patients who had total dose of radiotherapy in Radiotherapy Installation, Dr Soetomo Hospital. The samples were taken by consecutive sampling to incoming patients at Oncology Clinic, ENT Department, Dr. Soetomo Hospital during the period of January to May 2005. There were 40 samples to study. The results of cytology and histopathology of the swab method and the blind biopsy in seven patients had a result of positive swab and positive biopsy. Two patients had a result of positive swab and negative biopsy. Three patients had a result of negative swab and positive biopsy. Twenty-eight patients had a result of negative swab and negative biopsy. Statistical analysis of the results with McNemar's test was $p = 1.000$. This means that there was no significant difference ($p > 0.05$) between the results of swab method and blind biopsy. The swab method had the sensitivity of 70%, the specificity of 93.3%, the positive predictive value was 77.8%, the negative predictive value was 90.3%, and the accuracy was 87.5%. The conclusion of this study was that the swab method can be a substitution of blind biopsy to evaluate NPC patients after radiotherapy.

Keywords: *Nasopharyngeal carcinoma, post radiotherapy, swab, blind biopsy*

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INTRODUCTION

Nasopharyngeal biopsy in patients with nasopharyngeal carcinoma (NPC) post-radiotherapy is intended to evaluate the results of therapy or as an effort to establish the diagnosis of tumor recurrence. This procedure provides a particular problem for the patients since it may be painful. In addition, although it rarely occurs, the procedure may also result in profuse bleeding, which is worrisome and even threatening the life of the patient. The occurrence of bleeding during biopsy is a considerable risk since the effect of radiotherapy may result in tissue atrophy and mucocytis that is easy to bleed (Stanley & Fong, 1997). In addition, post-radiotherapy biopsy procedure could increase the risk of radionecrosis in re-radiation (Hussey 1993).

Today, histopathological examination of tissue resulting from nasopharyngeal biopsy is regarded as the gold standard for establishing the diagnosis of nasopharyngeal carcinoma or post-radiotherapy tumor recurrence (Kentjono 2001). Although more sophisticated endoscopic instrument has been found, nasopharyngeal biopsy with blind biopsy is still frequently undertaken. In advanced stage (III and IV), the success of this technique is high, about 95% (Bambang 1977; Hadi 1998; Kentjono 2001). The failure to obtain representative tumor tissue for histopathological examination is reported to be only 10% - 25%, particularly if the tumor is small and located at anterior or submucosal part of the nasopharynx (Chew 1987). In ENT Clinic, Dr Soetomo Hospital, blind biopsy remains the standard procedure to diagnose nasopharyngeal carcinoma (Mulyarjo et al. 2001).

Blind biopsy is usually undertaken by using a large biopsy plier, so that it may induce pain and bleeding. Pain is a reality experienced by anyone as a physiological response against trauma. In post-radiotherapy NPC patients, the pain is aggravated by the presence of mucocytis as the side effect of radiation in

airway mucosa, particularly the nasopharynx. Mucocytis is the side effect of radiation which was most commonly found, in 48.57% of NPC patients who received radiation (Roezin 1994). Similarly, there is a risk of post-biopsy profuse bleeding post-radiotherapy NPC patients due to easy-to-bleed tumor residual and the presence of radiation effect that results in tissue atrophy, including the atrophy of muscular tunics of capillary vessels (Stanley & Fong 1997). Therefore, another less-painful method that may prevent the risk of bleeding, but with a high sensitivity and specificity, should be found.

Several authors reported that examination using swab may detect the presence or absence of malignant cells. This method induces only painless minimum trauma and the risk of bleeding will be least (Sutjipto 1983). In addition to its rapidity in determining the presence of malignant cells, the cost of swab examination is far cheaper as compared to biopsy. Sutjipto (1983) studied swab method to establish NPC diagnosis (pre-radiotherapy), by which he obtained accuration rate of 14.3%. Djojopranoto (quoted by Sutjipto 1983) found an accuracy rate of 26.1%, Ali and Shanmugaratnam (1967) 44.3%, Cakra et al. (1977) 83.3%, Lau et al (1991) found the sensitivity rate 71% with accuracy of 86%. Morrison (quoted by Sutjipto 1983) found the sensitivity rate of 87.5%. Angelaksis et al (1980) conducted a study on cytological results (using index finger) which was compared to histopathological results (taken using biopsy) in NPC patients who were receiving radiotherapy. From 30 studied patients, 27 with positive histopathological results also had positive cytological results (sensitivity 100%). There were even three patients whose histopathological results in the first biopsy was negative, but cytological results revealed malignant cells. Until recently, there has been no report on sensitivity and specificity rate, predictive value and accuracy in swab examination among post-radiotherapy NPC patients. This paper was aimed to compare the results of swab with blind biopsy and to obtain sensitivity and specificity rates, predictive value, and accuracy of swab examination among NPC patients post-radiotherapy.

MATERIALS AND METHODS

This was a diagnostic test using comparative cross-sectional design. The study was undertaken in ENT Oncology Clinic, Dr Soetomo Hospital, Surabaya, to obtain samples and to undertake swab examination and blind biopsy and at the Department of Anatomic Pathology, Dr Soetomo Hospital, for cytological and histopathological examination. The duration of study lasted between January and May 2005, observing post-radiotherapy NPC patients visiting ENT Oncology Clinic, Dr Soetomo Hospital, Surabaya, who met the inclusion criteria. The inclusion criteria were having received total dose radiotherapy (minimally 6000 – 7000 cGy, meeting the standard procedure of NPC therapy in Radiotherapy Installation, Dr Soetomo Hospital, Surabaya), the last radiation was minimally 4 weeks, cooperative, and willing to participate in the study. The exclusion criteria were having abnormalities or diseases in nasal cavity, such as polyp or severe deviated septum that are not allowing swab examination and/or blind biopsy in the nasopharynx. The other inclusion criterion was weakness (Karnofsky scale < 40). Samples were taken using consecutive sampling. All post-radiotherapy NPC patients who met the criteria were included as samples.

The results of cytological examination or nasopharyngeal secrete obtained with swab were the results of cytological reading of the tissue or left and right nasopharyngeal secrete obtained by cotton application after swab and Papanicolaou staining. Results of cytological examination were presented as swab (+) if malignant cells were found, and swab (-) if no malignant cells were found. Results of histopathological examination from tissue or nasopharyngeal tumor obtained with blind biopsy were the results of histopathological reading from tissue or tumor at right and left nasopharyngeal side taken blindly after Hematoxylin-Eosin staining. The results were presented as biopsy (+) if malignant cells were found, and biopsy (-) if no malignant cells were found.

Patients who met the study criteria were given with the objectives of the study and examinations to be undertaken. If they were willing to participate, they were asked to sign the informed consent. Each patient (sample) was subjected to two treatments at once, swab and blind biopsy, conducted by the author himself. The results of cytological and histopathological examination were entered into data collection sheet and arranged into tables. To find whether there was difference between the results of swab and those of blind biopsy, we undertook McNemar comparative test. We also undertook cross-tabulation to obtain sensitivity rate, specificity rate, and predictive value. Accuracy rate was estimated using the formula TP + TN / Total sample. TP was sample with positive swab and negative biopsy result, while TN was sample with negative swab and negative biopsy result.

RESULTS

From January to May 2005, there were 43 patients who met the research criteria. Three patients (7%) were not

included as sample, two due to non-representation of histopathological examination from blind biopsy, and one had too-thin cytological examination, not allowing evaluation. The youngest age was 13 years, and the eldest was 62. Twenty-one patients (52.5%) aged between 41-60 years, six (15%) aged less than 30 years, ten (25%) aged 31-40 years, three (7.5%) aged more than 60 years. As many as 25 patients (62.5%) were male and 15 (37.5%) female. After swab and blind biopsy in each sample, we obtained the results of cytological and histopathological examinations from 40 samples as can be seen in Table 1.

Table 1. Comparison of cytological and histopathological examination of he samples taken using swab and blind biopsy

	Blind Biopsy		Total
	Malignant cells (+)	Malignant cells (-)	
Swab: Malignant cells (+)	7	2	9
Swab: Malignant cells (-)	3	28	31
Total	10	30	40

The result of statistical analysis on the data in Table 1 using McNemar comparative test revealed p = 1.000, indicating that the results of swab and blind biopsy had no significant difference (p > 0.05). Based on cross-tabulation, these values from swab were obtained: sensitivity 70%, specificity 93.3%, positive prediction rate 77.8%, and negative prediction rate 90.3%. Using the formula, the accuracy rate obtained was 87.5%. During the procedures, we found 2 patients (5%) who had profuse bleeding, requiring the placement of anterior tampon in nasal cavity. These two profuse bleeding cases occurred in post-blind biopsy (Table 2). Regarding comfort, most of the samples (92.5%) subjectively stated that blind biopsy was more painful than swab.

Table 2. Comparison of profuse bleeding during swab and blind biopsy procedures

	Profuse bleeding	
	Yes	No
Swab	0	40
Blind biopsy	2	38

DISCUSSION

This study was a diagnostic test, although it was used to evaluate radiotherapy results in NPC patients. The design used was cross-sectional comparative design to compare the results of swab and blind biopsy in NPC patients post-radiotherapy with one-time measurement at once. The performance of diagnostic test in clinical setting was assessed by comparing the results of test in a 2 x 2 table (cross-tabulation). This assessment was presented as sensitivity, specificity, and predictive value. To obtain a reliable test results, we used a gold standard for comparison (Soeparto 1998). In practice, there are only few ideal gold standards, so that not infrequently we use the best diagnostic test as gold standard. The best here refers to the available diagnostic test with highest sensitivity and specificity. However, it is often unavailable so that a certain method should be agreed to be used as gold standard (Pusponegoro dkk, 1995). In the case of NPC diagnosis, the result of histopathological examination of nasopharyngeal tissue with biopsy, particularly with nasopharyngoscopy guidance, is regarded as the best, primarily in developed countries. However, in ENT Department, Dr Soetomo Hospital, Surabaya, blind biopsy remains the most practical method with a success rate around 95% (Kentjono 2001), so that it was assumed that blind biopsy was the best method and the standard procedure to establish NPC diagnosis, to evaluate post-radiotherapy NPC, and to determine post-radiotherapy tumor recurrence. Therefore, blind biopsy was used as gold standard in this study. The result of swab was compared with blind biopsy in post-radiotherapy NPC patients.

Statistical analysis of both method of examinations using McNemar test revealed p = 1.000, indicating no significant difference (p > 0.05) between the result of swab and blind biopsy. Since diagnostic test should be able to separate subjects with disease from those with disease, so that other consideration was needed to interpret the result of the diagnostic test (Pusponegoro et al. 1995). Results data were entered into 2 x 2 table (table 3) and then subejcted to statistical estimation. The table reveals characteristics values of swab examination, presenting as sensitivity rate, specificity rate, positive predictive value, negative predictive value, and accuracy.

Sensitivity is an index (percentage) indicating the capability of a diagnostic test to detect the presence of a disease if the disease is indeed present. The formula to obtain sensitivity rate in 2 x 2 table was a/(a + c). A test with high sensitivity (almost 100%) should be used not to lose the detected disease (Soeparto 1988). In this study, we obtained a sensitivity rate of 70%, indicating

that the use of swab method can detect 70% patients who definitely had post-radiotherapy NPC (residual or recurrent tumor). Swab has several advantages as compared to blind biopsy, which was more comfortable to the patients (less painful), lower risk of profuse bleeding, more immediate results, and cost saving. In addition, cross-tabulation data (2 x 2 table) in box c, where there are two patients, statistically reveals false positive result, but clinically it is the result of cytological examination, in which positive malignant cells were definitely found and has been used as a reference for subsequent management (re-radiation). This is a fact showing that there is a possibility to find negative blind biopsy in patient who also showed positive swab result. Therefore, although sensitivity rate from blind biopsy is slightly higher, swab method can be used to substitute blind biopsy in evaluating the presence of malignant cells in post-radiotherapy NPC patients.

Table 3. 2 x 2 table, the result of cytologic and histopathological examination

		Blind biopsy			
		Ca cells (+)		Ca cells (-)	
Swab	Ca cells (+)	(a)	7	(b)	2
	Ca cells (-)	(c)	3	(d)	28

Specificity is an index indicating the capability of diagnostic test to detect the absence of disease if the disease is indeed absent. The specificity formula is d / (b + d). A highly specific test is needed particularly if false positive result can be harmful for patients, either physically, psychologically or financially (Soeparto, 1988). In this study, the specificity of swab method was 93.3%, indicating that swab method in post-radiotherapy NPC evaluation can detect the absence of residual or recurrent tumor in 93.3% in whom they definitely do not have residual or recurrent tumor, while only 6.7% who will show false positive result. The specificity of the swab method has been sufficiently high, but in order to establish the diagnosis of residual or recurrent tumor in post-radiotherapy NPC patients, it was wise to choose diagnostic test with a very high sensitivity. This was because the risk of false negative result was more dangerous than false positive.

Sensitivity and specificity are two important elements that should be considered in deciding which diagnostic test (method of examination) that will be used. However, once the result is obtained, whether it is positive or negative, sensitivity and specificity become unimportant. This is because the result has probability, that a test may provide positive or negative results in individuals either with or without disease. Probability of disease based on a test is designated as predictive value (Fletcher 1986). Positive predictive value is an index to find how capable a diagnostic test in predicting the real presence of a disease if the test reveals positive result. The formula is a/(a + b). In this study, the positive predictive value in swab method was 77.8%, indicating that positive result obtained with swab method in post-radiotherapy NPC patients had probability of 77.8%, meaning that in those patients it was true that there was residual or recurrent tumor. Negative predictive value is an index to find how capable a diagnostic test in predicting the real absence of a disease if the test reveals negative result. The formula is d/(c + d). In this study, the negative predictive value in swab method was 90.3%, indicating that negative result obtained with swab method in post-radiotherapy NPC patients had probability of 90.3%, meaning that in those patients it was true that there was no residual or recurrent tumor.

Predictive value is affected by sensitivity, specificity, and prevalence of the disease in tested population setting (Soeparto 1988). The lower the prevalence of studied population, the lower the positive predictive value, the higher the negative predictive value. Contrastingly, the higher the prevalence of studied population, the higher the positive predictive value, and the lower the negative predictive value. Prevalence is a pre-test probability, which in 2 x 2 table the formula is (a + c)/(a + b + c + d). The prevalence in studied population was 25%, in line with reported post-radiotherapy NPC prevalence (recurrent) rate, which is 19% - 56% (Kentjono 2001).

Accuracy is the general compatibility between studied diagnostic test and gold standard diagnostic test. The formula is (a + d)/(a + b + c + d). In this study, the accuracy rate of swab method was 87.5%, indicating that, as compared to blind biopsy, swab method in post-radiotherapy NPC patients had validity rate of 87.5%. In clinical use to determine the choice of diagnostic test, this rate is less popular as it does not describe the characteristics of the test. However, this rate can be used as early consideration for considering other eligibility characteristics of a diagnostic test (Soeparto 1988).

Characteristic rates of swab method found in this study were almost similar to those obtained by Lau et al. (1991) in their study in Hongkong, in which they conducted nasopharyngeal swab using silk stick and obtained sensitivity of swab method of 71% and accuracy rate of 86%. This was different from the rate reported by Angelaksis et al. (1980) in their study in England who found sensitivity rate of 100%. The difference was present because the study conducted at the Department of Radiology used index finger to

directly palpate the tumor location of the patients who were undergoing radiotherapy, and it was highly probable to find primary tumor in the nasopharynx. However, highly different result was found in the accuracy rate in this study (87.5%) and that found by Sutjipto (1983) who conducted his study on swab method at the same place (Dr Soetomo Hospital, Surabaya) but with different target population (pre-radiotherapy). Reports from other authors on swab method among pre-radiotherapy patients, such as that by Ali and Shanmugaratnam (1967), reported accuracy rate of 44.3%, while Djojopranoto (quoted by Sutjipto 1983) found the accuracy rate of only 26.1%. Those rates indicated that swab method conducted to evaluate post-radiotherapy NPC patients was better than swab method carried out to establish NPC diagnosis (pre-radiotherapy). This was because pre-radiotherapy tumor condition and mucosal surface were different from post-radiotherapy condition.

In terms of comfort, based on history taking it was found that 37 patients (92.5%) reported that blind biopsy was more painful than swab. None of the patients stated that swab method was more painful than blind biopsy, and 3 patients (7.5%) stated that swab and blind biopsy were similarly painful. The data describe the advantage of swab method as compared to blind biopsy in post-radiotherapy NPC patients. Another advantage is that swab method has no risk of profuse bleeding. From 40 patients participating in this study, profuse bleeding was found in 2 patients (5%) after blind biopsy. Profuse bleeding was the bleeding that required particular procedure. Generally, post-biopsy bleeding can be overcome by placement of loose tampon. In both cases the placement of dense tampon band in left and right nasal cavity was provided along with antibiotics and analgesics. Tampon band was removed after 2 days.

This study has found encouraging characteristics values of swab examination (sensitivity 70%, specificity 93.3%, positive predictive value 77.8%, negative predictive value 90.3% and accuracy 87.5%). Although blind biopsy is more sensitive, swab method has advantages, i.e., more comfortable to the patients (less painful), lower risk of profuse bleeding, immediate results, and cost-saving. In addition, there was still possibility to obtain negative result from blind biopsy in patients with positive result from swab. These facts support the importance of swab to be used as diagnostic tool to substitute blind biopsy for evaluating post-radiotherapy NPC patients.

CONCLUSION

The result of swab and blind biopsy in post-radiotherapy NPC patients shows no difference. To determine the presence or absence of tumor residual and the presence or absence of tumor recurrence in post-radiotherapy NPC patients, the swab characteristics rates are as follows: sensitivity 70%, specificity 93.3%, positive predictive value 77.8%, negative predictive value 90.3%, and accuracy 87.5%.

REFERENCES

Ali, MY & Shanmugaratnam, K 1967, 'Cytodiagnosis of nasopharyngeal carcinoma', *Acta Citology*, vol. 11, no. 1, pp. 54-60.

Angelaksis, P, Benakis, V, Pontifek, G 1980, 'Papanicolaou test of the nasopharynx in a Radiotherapy Departement', *British Journal Radiology*, vol. 53, no. 632, pp. 796-799.

Bambang, SS 1977, 'Karsinoma nasofaring', in *Cermin Dunia Kedokteran*, vol. 9, pp. 36-38.

Cakra, IGK, Losin, K, Soetomo, Soetarno 1977, 'Peranan swab nasofaring pada diagnosa kanker nasofaring', in *Kumpulan Naskah Kongres Nasional V PERHATI*, Semarang, October 1977, 27– 29, pp. 607-11.

Chew, CT 1987, 'Nasopharynx', in *Scott-Brown's Otolaryngology*, 5th edn, Butterworth, vol. 4, pp. 312-330.

Fletcher, RH, Flecher, SW, Wagner, EH 1988, *Clinical Epidemiology, The Essentials*, 2nd edn, Baltimore, William & Wilkins, pp. 1988.

Hadi, W 1998, 'Aspek klinis dan histopatologi karsinoma nasofaring di Lab/SMF THT FK Unair/RSU Dr Soetomo Surabaya tahun 1997', Lab/SMF THT FK Unair/RSU Dr Soetomo Surabaya, Final Paper.

Hussey, DH 1993, 'Principles of Radiation Oncology', in BJ Bailey (ed), *Head and Neck Surgery-Otolaryngology*, JB Lippincott Co., Philadelphia, pp. 1040-1060.

Kentjono, WA 2001, 'Pengaruh vaksinasi BCG dalam Meningkatkan Respons T Helper 1 (Th1) dan Respons Tumor terhadap Radiasi pada Karsinoma Nasofaring', Dissertation, Airlangga University Postgraduate Program, pp. 8-115.

Lau, SK, Hsu, CS, Sham, JS, Wei, WI 1991, 'The cytological diagnosis of nasopharyngeal carcinoma using a silk swab stick', in *Cytopathology*, vol. 5, no. 2, pp. 239-246.

Mulyarjo, et al. 2001, *Pedoman Pelayanan Medik Poliklinik THT, Diagnosis, Terapi dan Tindakan Praktis*, 2nd edn, SMF THT RSU Dr Soetomo, Surabaya, pp. 53.

Pusponegoro, HD, Wirya, IGN, Pudjiadi, AH, Bisanto, J, Zulkarnain, SZ, 'Uji diagnostik', in S Sastroasmoro, S Ismael, *Dasar-dasar Metodologi Penelitian Klinis*, Bina Aksara, Jakarta, pp. 126-142.

Roezin, A, Syafril, A 1997, 'Karsinoma nasofaring', in EA Soepardi, Iskandar, *Buku Ajar Ilmu Penyakit Telinga Hidung Tenggorok*, Jakarta, Fakultas Kedokteran Universitas Indonesia, pp. 149-153.

Sastroasmoro, S 1995, 'Pemilihan Subyek Penelitian', in S Sastroasmoro, S Ismael (eds), *Dasar-dasar Metodologi Penelitian Klinis*, Bina Aksara, Jakarta, pp. 42-51.

Soeparto, P 1998, 'Diagnosis', in P Soeparto, EP Soedibyo, J Soeroso, *Epidemiologi Klinis*, Gramik, FK Unair, Surabaya, pp. 21-48.

Stanley, RE, Fong, KW 1997, 'Clinical presentation & diagnosis', in VFH Chong, SY Tsao (eds), *Nasopharyngeal Carcinoma*, Loi Printing Pte Ltd, Singapore, pp. 29-41.

Sutjipto, 1983, *Peranan Swab dan Washing secara Avue pada Diagnosis Tumor Ganas Nasofaring*, Lab/SMF THT FK Unair/RSU Dr Soetomo, Surabaya, Final Paper.