

FINE NEEDLE ASPIRATION CYTOLOGY IN LESIONS OF GALL BLADDER - EXPERIENCE IN A PRIMARY CARE SETTING.

ABSTRACT

Aims: Cancer of gall bladder (GBCa) is a common malignancy in certain parts of India. In the Gangetic belt, its incidence is up to 10 times greater than in some other parts of the country. The aim of the present retrospective study is to study the utility of guided fine needle aspiration cytology (FNAC) in patients of GBCa; to analyze whether use of this technique helps in detecting patients requiring palliative care only and to study the demographic profile of patients of GBCa in a primary care setting.

Study design: All patients referred with a gall bladder mass underwent guided fine needle aspiration procedure for purpose of morphological diagnosis. An ultrasonographic examination for staging was used to delineate inoperable cases.

Place and Duration of Study: The study was conducted at Ama diagnostic centre, Lucknow, in collaboration with the department of Pathology, Integral Institute of Medical Sciences, Lucknow, India. The period of study is from August 2010 to March 2016.

Methodology: FNAC was performed under ultrasound guidance on all patients with a gall bladder mass clinically suspicious of malignancy. Clinical details of the patient were recorded and their demographic profile was studied.

Results: Forty five patients with gall bladder mass underwent FNAC for diagnosis of malignancy. Adequate material was obtained in 44 patients. It was possible to provide a definite diagnosis in 38 cases (86.3 % of cases). Adenocarcinoma NOS was the commonest diagnosis (86.8% of cases). Amongst patients with malignancy, 73.7% of cases were in advanced stage. Palliative care represents suitable treatment option in such patients in our clinical set up.

Conclusion: Utilizing guided FNAC, it was possible to provide a definite diagnosis in 86.3% cases. It was also possible to delineate inoperable cases.

Keywords: Cancer of gall bladder, Adenocarcinoma gall bladder, Aspiration cytology of gallbladder.

1. INTRODUCTION

Cancer of the gall bladder (GBCa) - although uncommon in many parts of the world – happens to be a common malignancy in India [1]. Even within India, it shows marked regional variation. Amongst female population, it is about 10 times commoner in North India as compared to southern parts of the country [2]. Frequency of GBCa in north Indian males is about 4 times greater than in south Indian male population. Of greater significance is the universally dismal prognosis of this disease [3]. Reasons cited for poor prognosis of GBCa are - the nature of the malignancy itself and the fact that patients of GBCa usually present at an advanced stage. Reasons proposed for late presentation - apart from medical resource deficiency and lack of awareness - is that patients of GBCa often remain asymptomatic for a long period of time or they have non-specific symptoms or symptoms that mimic benign gall bladder disease. Correct diagnosis is suspected only when invasion of surrounding structures takes place [4].

Now days, staging of cancer is easily feasible using non-invasive radiological and radio-isotopic techniques. As survival of patients with GBCa in advanced stages, is usually less than a year, realization of correct diagnosis and provision of palliative care, often becomes the rational objective for a clinician [5, 6]. Therefore feasibility of delineating patients requiring definitive treatment from those needing palliative care only - at the level of primary medical care service - is a judicious option.

Such an approach to patient management, apart from providing relief to the sufferer, helps in conserving scarce medical resources of our country.

Therefore the present study was planned to -

1. Study the utility of guided FNAC in diagnosing GBCa at the level of primary medical care service.
2. Analyzing whether use of guided FNAC helps in delineating the two groups of patients outlined above.
3. Study the demographic profile of patients of GBCa presenting for FNAC.

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38 MATERIAL AND METHODS

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40 2.1 STUDY AREA

41 The study was conducted at Ama diagnostic centre, Lucknow, in collaboration with the department of
42 Pathology, Integral Institute of Medical Sciences and Research, Lucknow, India. The period of study
43 is from August 2010 to March 2016.

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45 2.2 SAMPLE COLLECTION

46 FNAC was performed under ultrasound guidance on all patients with a gall bladder mass that was
47 clinically suspicious of malignancy. After explaining the risks associated with the procedure, a written
48 consent was obtained from the patient. Prior to performing the procedure the patient was investigated
49 for any hemorrhagic diathesis. FNAC was performed using a 21 or 23 gauge needle attached to a 10
50 ml syringe. Skin overlying the site of aspiration was thoroughly cleaned to achieve asepsis. Under
51 ultrasonographic (US) guidance, the needle was inserted into the lesion by the radiologist. All efforts
52 were made to place the needle in the peripheral part of the lesion, avoiding necrotic or hemorrhagic
53 areas. The patient was asked to withhold breath and the aspiration was performed by the pathologist.

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55 2.3 LABORATORY PROCEDURE

56 Aspirated material was smeared onto glass slides. Air dried smears for MGG stain and wet fixed
57 smears for H&E and Papanicolaou stain were prepared. An initial on site evaluation of a smear was
58 carried out using Leishman stain. If the aspirate was found inadequate, re-aspiration was performed
59 in the same sitting. A maximum of three attempts were made to obtain adequate material. Every case
60 was examined individually by both pathologists and results were recorded separately. In a case where
61 discordant opinion existed, a final consensus diagnosis was attempted for purpose of analysis of the
62 results. Diagnosis was rendered based on cytological criteria enumerated in standard textbooks of
63 cytology [7].

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65 3. RESULTS

66 FNAC was performed on 45 cases presenting with a gall bladder mass. In one case, insufficient
67 material was obtained and it is excluded from further analysis. The diagnosis rendered in remaining
68 44 patients is shown in figure 1.

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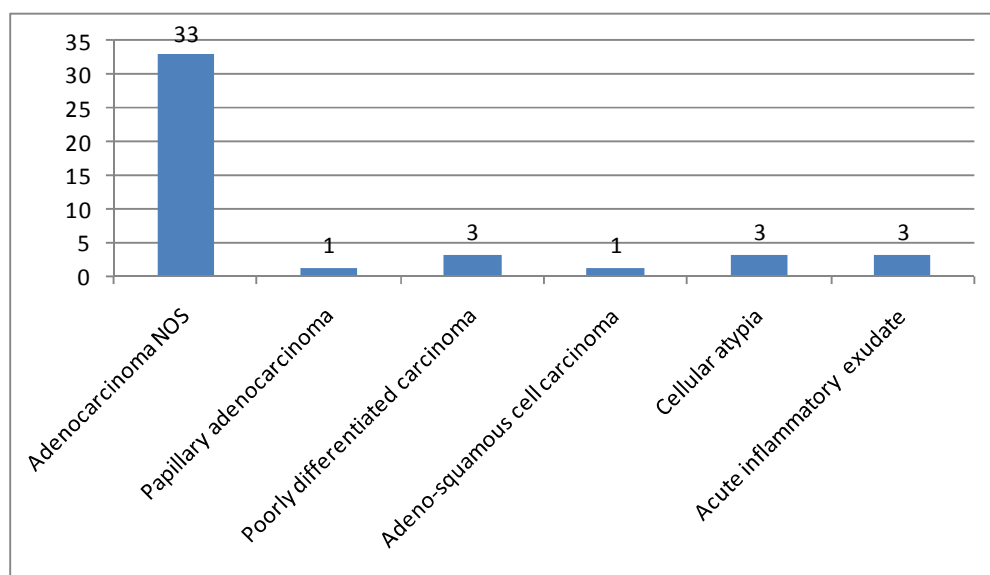
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Fig 1: Disease distribution of 44 patients with gall bladder mass

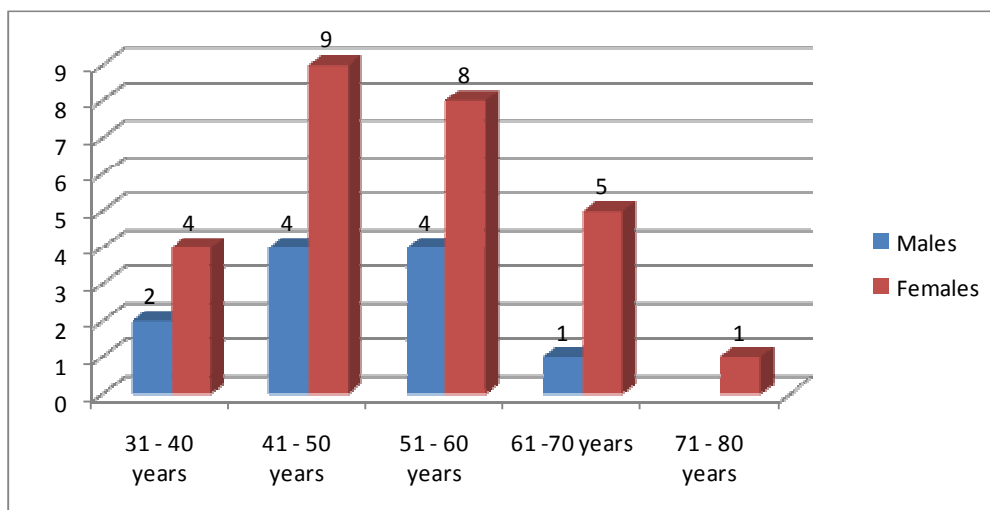


The above figure shows that definite diagnosis of malignancy was possible in 38 cases. Cellular atypia and acute inflammatory exudate was seen in 3 cases each. Amongst 38 cases of gall bladder malignancy, adenocarcinoma- not otherwise specified, was seen in 33 patients (86.8 % of cases). Poorly differentiated malignancy was present in three patients. Papillary adenocarcinoma and adenosquamous cell carcinoma was seen in one patient each. Cases of adenocarcinoma NOS showed three dimensional cell clusters. Cell nuclei were irregular and pleomorphic with increased N/C ratio. Nucleoli were prominent. The solitary case of adenosquamous cell carcinoma seen in our series, apart from having features of adenocarcinoma, showed squamous differentiation of some cells in form of pyknotic nuclei, thick cytoplasm, angulated cell borders and orangeophilia on Pap staining. Patient with poorly differentiated carcinoma showed dispersed cell population with presence of highly pleomorphic cells. The case of papillary adenocarcinoma showed papillae formation. Cell pleomorphism was minimal in this case.

In our series, no case of mucinous carcinoma, signet ring carcinoma, pure squamous cell carcinoma, small cell carcinoma or neuroendocrine tumour was seen. In cases where only cellular atypia or mixed inflammatory exudate was present, we were unable to confirm the diagnosis as histological correlation was unavailable.

The age and sex distribution of patients with gall bladder malignancy is shown in figure 2. The youngest patient in our series was a 35 years old female and the oldest was 75 years of age. Our results indicate that gall bladder malignancy is seen more often in 5th and 6th decade of life (65.8% of cases). 15.8% cases were seen in 4th and 7th decade each. In our series, GBCa is about 2.5 times more common in females as compared to males.

Fig 2: Age and sex distribution of gall bladder malignancy (n=38)



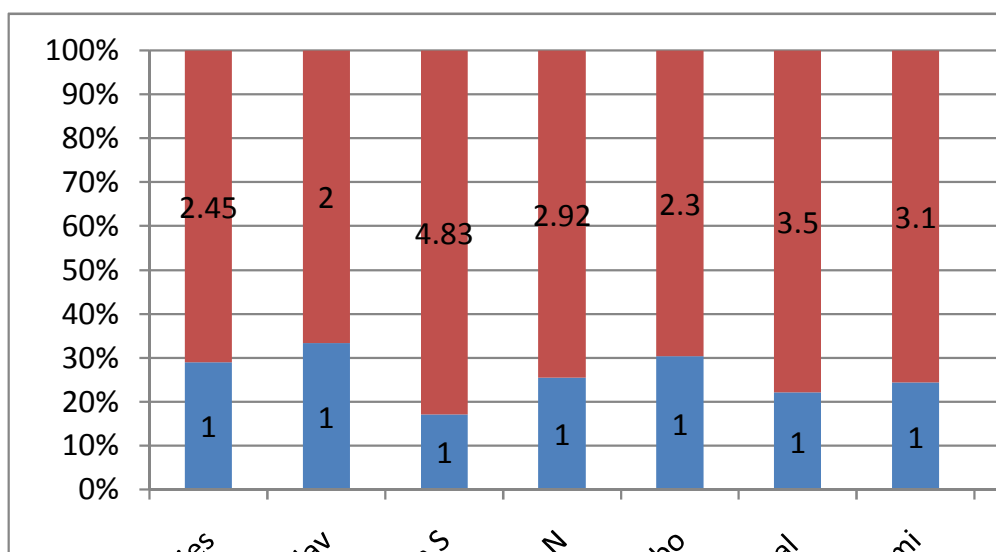
In 28 out of 38 cases of malignancy, ultrasound examination showed presence of metastasis in liver. In other cases, no metastasis was detected.

4. DISCUSSION

In many parts of the world, GBCa is an uncommon malignancy. In USA, its frequency is 1.43/hundred thousand population [4]. However in certain parts of the world, it ranks amongst ten commonest malignancies. High incidence of GBCa is seen in persons living in western parts of the Andes, in North American Indians, in Mexican Americans and amongst inhabitants of northern India. In these areas, the incidence may reach up to 7.5/hundred thousand for men and 23/hundred thousand for women [8]. In northern parts of India, the cancer registry of Indian Council of Medical Research, records an incidence of 4.5/ hundred thousand for men and 10.1/hundred thousand for women [1]. In Delhi, GBCa with an incidence rate 6.6/ hundred thousand females is the fourth most common cancer overall and the most common gastrointestinal cancer in females [9]. In Lucknow, in north India, GBCa was the most common cause of malignant obstructive jaundice [10]. That this cancer shows marked geographical variation is further illustrated by the fact that in southern India, its incidence is only 1.2/ hundred thousand females. Incidence rates of 1.6 and 2.3 per hundred thousand people are reported in men and women respectively from Mumbai in western India [11]. However, one thing that is common about this disease all over the world is that it shows a definite predilection for the female population.

In our study, it was possible to provide a definite diagnosis of malignancy in 38 out of 45 patients in whom aspiration was performed. Thus the success rate of aspiration in our series is 84.4%. Success rate of guided aspiration for cases of GBCa as reported by some other workers from India varies from 60% to 90% [12, 13]. Out of 38 cases of confirmed malignancy in our series, 27 cases were seen in females and 11 cases were present in males; giving a female to male ratio of 2.45:1. Figure 3 illustrates female to male ratio in some other series from India. In all series, females are found to be more commonly affected by GBCa. In one series, figures show nearly five times greater propensity of this disease in females [8]. Reasons proposed for female preponderance include - higher incidence of gall stone disease in this population group and possibly the role of oestrogen/progesterone receptors within the gall bladder epithelium. That cholelithiasis plays a role in pathogenesis of GBCa is based on observations which show high incidence GBCa in populations with higher prevalence of gall stone disease [8, 9]. However the causal role of gall stone disease is not entirely clear. Role of oestrogen/progesterone receptors is suspected based on observations which show that the disease is more common in females exhibiting - younger age of menarche, early age of first pregnancy, multiple pregnancies, and prolonged fertility span with higher number of live births [13, 14,15]. All these conditions are associated with increased duration of exposure to estrogens and progesterone [8]. If this hypothesis happens to be true, then anti-oestrogen therapies like tamoxifen should play a role in treatment of this disease.

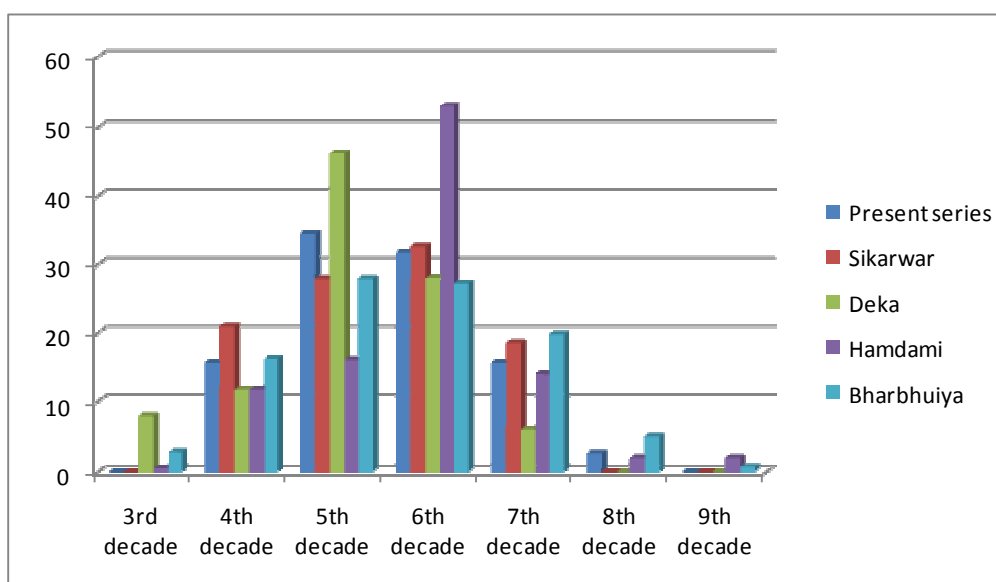
Fig 3: Comparison of sex ratio of carcinoma gall bladder in different series from India.



In our series, GBCa was seen more frequently in the age group of 41 to 60 years (65.8% of cases). Less commonly, it was seen in 4th and 7th decades of life (15.8% cases each). The decade wise incidence of GBCa in some other series from India [16, 17, 18, 19] is shown in figure 4. All these series show high incidence of GBCa in the age group 41 to 60 years.

The median age of patients with GBCa reported from India by some other workers ranges from 49 to 54 years [9, 13, 20, 21, 22]. This figure is much lower than what is reported in western literature. The median age reported from the UK is 70 -74 years [23], from USA - 73 years [24] and 66 years from Sweden [25] Poland [26] and Italy [27].

Figure 4: Comparison of distribution of GBCa in different decades of life in different series from India.



In our series, adenocarcinoma was the commonest form of GBCa (86.8% of cases). World over, adenocarcinoma is the most frequent histological subtype of the malignant gallbladder neoplasm,

representing approximately 90–95% of all cases [28]. Other workers from India have noted a similar finding in their series [8, 12, 18, 22].

It has been observed that GBCa is seen more commonly within migrant population from India to other countries like US, UK, Australia and Kuwait [29, 30]. Whether genetic factors or retention of cultural practices in migrant population are responsible for this phenomenon needs further elucidation. It may also shed light on role of dietary practices in causation of GBCa; like in case of carcinoma stomach where the study of dietary practices amongst migrant population from Japan to western countries facilitated discovery of the etiological factors for that disease. One study from India proposes the role of fried food as an aetiological factor for GBCa [22].

GBCa is regarded to have one of the poorest prognoses amongst all cancers. Mean survival of patients in TNM stage II, III, and IV is 7.5, 5.2, and 3.7 months, respectively [5] and the survival rate in stages II, III and IV are approximately 25%, 12%, and 1-2% respectively [6]. According to one of the largest studies from north India involving 490 cases, 52 % of patients with GBCa presented in stage IVB, 27% patients presented in stage IIIB and IVA and only 18% in stages I - IIIA [8]. In another large study from east India, 12.6% patients were in stage I, 16.2% in stage II, 14.1% in stage III and 57.1% in stage IV [18]. Reasons proposed for rapid spread of GBCa include - absence of submucosa in the GB wall and presence of important organs like liver, duodenum and pancreas in near vicinity to a very thin gall bladder wall (< 3mm). Also the hepatic surface of the gall bladder has no serosa; thereby a gall bladder tumour easily infiltrates the liver parenchyma [3].

In our series 28 out of 38 patients (73.7% of cases) were having metastatic deposits in liver. Palliative care only will serve best interests of the patient and his/her family in our set up.

5. CONCLUSION

FNAC is a useful diagnostic technique in patients presenting with a gall mass. In many patients with malignancy of the gall bladder, it obviates the need to perform surgery. As patients of GBCa in stage II – IV have a dismal prognosis with a short life span, palliative care becomes the treatment of choice in our country. For such patients, FNAC serves to provide a definitive morphological diagnosis and contributes in cancer staging.

CONSENT

The study is a retrospective analysis of a laboratory investigative procedure. No personal data of any patient is being presented. An informed consent of all patients was obtained prior to performing the investigative procedure.

ETHICAL APPROVAL

It is not applicable.

REFERENCES

1. Dhir V, Mohandas KM. Epidemiology of digestive tract cancers in India IV- Gall bladder and pancreas. *Indian J Gastroenterol* 1999; 18:24-8.
2. Shukla HS, Sirohi B, Behari A, Sharma A, Majumdar J, Ganguly M et al. Indian Council of Medical Research Consensus document for the management of gall bladder cancer. *J Med Paediatr Oncol* 2015; 36(2):79-84.
3. Kapoor VK. Is gall bladder cancer a bad cancer per se? *World J Gastrointest Surg* 2015; (7):107-109.
4. Piehler JM, Crichlow RW. Primary carcinoma of the gallbladder. *Surg Gynecol Obstet* 1978; 147:929-42.
5. Pandey M, Pathak AK, Gautam A, Aryya NC, Shukla VK. Carcinoma of the gallbladder: a retrospective review of 99 cases. *Digest Dis and Sci* 2001; 46:1145-51.
6. Kapoor VK, Pradeep R, Haribhakti SP, Sikora SS, Kaushik SP. Early carcinoma of the gall bladder: An elusive disease. *J Surg Oncol* 1996; 62:284-87.
7. Kocjan G in Gray W, Kocjan G eds. *Diagnostic Cytopathology*. 3rd Edition; 2014. Churchill Livingstone: P 319-332.
8. Gupta S, Kori C, Kumar V, Misra S, Akhtar N. Epidemiological Study of Gallbladder Cancer Patients from North Indian Gangetic Planes- a High-Volume Centre's Experience. *J Gastrointest Canc* 2016; 47:27–35.
9. Kapoor VK, Mc Michael AJ. Gallbladder cancer: an 'Indian' disease. *Natl Med J Ind* 2003; 16:209-13.

- 250 10. Sikora SS, Kapoor R, Pradeep R, Kapoor VK, Saxena R, Kaushik SP. Palliative surgical
251 treatment of malignant obstructive jaundice. *Eur J Surg Oncol* 1994; 20:580-4.
- 252 11. Indian Council of Medical Research. National Cancer Registry Programme. Biennial Report
253 1988–89, an epidemiological study. New Delhi. Indian Council of Medical Research. 1992: Pg14 -
254 15.
- 255 12. Yadav R, Jain D, Mathur SR, Sharma A, Iyer VK. Gallbladder carcinoma: An attempt of WHO
256 histological classification on fine needle aspiration material. *Cyto Journal* 2013; 10:12-20.
- 257 13. Shukla VK, Chauhan VS, Mishra RN, Basu S. Lifestyle, reproductive factors and risk of
258 gallbladder cancer. *Singapore Med J* 2008; 49(11):912-915.
- 259 14. Lambe M, Trichopoulos D, Hsieh CC, Ekblom A, Adami HO, Pavia M. Parity and cancers of the
260 gall bladder and the extrahepatic bile ducts. *Int J Cancer* 1993; 54:941–4.
- 261 15. Moerman CJ, Berns MPH, Bueno de Mesquita HB, Runia S. Reproductive history and cancer of
262 the biliary tract in women. *Int J Cancer* 1994; 57:146–53.
- 263 16. Barbhuiya MA, Singh TD, Poojary SS, Gupta S, Kakkar M, Shrivastav BR, et al. Gallbladder
264 cancer incidence in Gwalior district of India: Five-year trend based on the registry of a regional
265 cancer center. *Indian J Cancer* 2015; 52:430-7.
- 266 17. Deka N, Goswami G, Hazarika M, Bharti A. Evaluation of Gall Bladder Carcinoma by
267 Ultrasonography and its comparison: A study of 50 cases. *J Evol Med Dental Sc* 2014; 3(51):
268 11943 – 11953.
- 269 18. Hamdani NH, Qadri SK, Aggarwalla R, Bhartiya VK, Chaudhuri S, Sanjay Debakshi S et al.
270 Clinicopathological Study of Gall Bladder Carcinoma with Special Reference to Gallstones: Our 8-
271 year Experience from Eastern India. *Asian Pacific J Cancer Prev* 2012; 13(11):5613-5617.
- 272 19. Sikarwar JS, Singh R, Ahirwar V, Bhujade H, Muchhoria S. Assessment and comparison of
273 gallbladder mass by sonography and histopathology. *J of Evolution of Med and Dent Sci.* 2014;
274 3(9):2076 - 2086.
- 275 20. Prakash AT, Sharma LK, Pandit PN. Primary carcinoma of the gallbladder. *Br J Surg* 1975;
276 62:33–6.
- 277 21. Kalita D, Pant L, Singh S, Jain G, Kudesia M, Gupta K, Kaur C. Impact of Routine
278 Histopathological Examination of Gall Bladder Specimens on Early Detection of Malignancy - A
279 Study of 4,115 cholecystectomy specimens. *Asian Pacific J Cancer Prev* 2013; 14 (5):3315-3318.
- 280 22. Jain K, Sreenivas V, Velpandian T, Kapil U, Garg PK. Risk factors for gallbladder cancer: A
281 casecontrol study. *Int. J. Cancer* 2013; 132:1660–1666.
- 282 23. Carty NJ, Johnson CD. Carcinoma of the gall bladder: A survey of cases in Wessex 1982–1989. *J*
283 *Royal Coll Surg Edinb* 1991; 36:238–41.
- 284 24. Carriaga MT, Henson DE. Liver, gallbladder, extrahepatic bile ducts, and pancreas. *Cancer* 1995;
285 75 (Suppl 1):171–90.
- 286 25. Bergdahl L. Gallbladder carcinoma first diagnosed at microscopic examination of gall bladders
287 removed for presumed benign disease. *Ann Surg* 1980;191:19–22.
- 288 26. Zatonski WA, La Vecchia C, Przewozniak K, Maisonneuve P, Lowenfels AB, Boyle P. Risk factors
289 for gall bladder cancer: A Polish case–control study. *Int J Cancer* 1992; 51:707–11.
- 290 27. D'Amico D, Bassi N, D' Erminio A, Brigo L, Boccagni P. Current situation in the treatment of
291 gallbladder cancer: Considerations on the utility of an extended resection. *Hepatogastroenterology* 1991; 38:16–21.
- 292 28. Albores-Saavedra J, Kloppel G, Adsay NV, et al. Carcinoma of the Gallbladder and Extrahepatic
293 Bile Ducts, 4th edn. WHO Press: Geneva, 2010.
- 294 29. Swerdlow AJ, Marmot MG, Grulich AE, Head J. Cancer mortality in Indian and British ethnic
295 immigrants from the Indian subcontinent of England and Wales. *Br J Cancer* 1995; 72:1312–19.
- 296 30. Grulich AE, McCredie M, Coates M. Cancer incidence in Asian migrants to New South Wales,
297 Australia. *Br J Cancer* 1995; 71:400–8.
- 298 31.
- 299