CANCER OF THE GALL BLADDER AND EXTRA-HEPATIC BILIARY TREE **MEDICAL APPENDIX**

DEFINITIONS

1. **Cancer of the gall bladder**, although the fifth most common gastrointestinal cancer, is a rare malignancy with an annual incidence of about 3/100,000 patients. It occurs most often in the elderly and has a poor prognosis.

2. About 90% are adenocarcinomas and 2% are of squamous cell type. Adeno-squamous lesions may also occur. Other subtypes include small cell, carcinoid and undifferentiated carcinomas, none exceeding 1% of the total. Sarcoma, malignant melanoma (both primary and secondary) and primary lymphoma (including MAL Tomas) have also been described. In recent years, carcinoma in situ has been recognised.

3. **Cancer of the biliary tree (cholangiocarcinoma)** also occurs mostly in the elderly. Its incidence, which is about half that of gallbladder cancer, is increasing. The tumour is commonly adenocarcinoma but both squamous carcinomas and adeno-squamous variants are seen.

4. Other very rare malignancies include carcinoid tumour, melanoma (primary and secondary), lymphoma and rhabdomyosarcoma, which is the commonest malignancy of the extrahepatic bile ducts in children.

CLINICAL MANIFESTATIONS

Gallbladder

5. The median age at diagnosis is 73, with a female to male incidence ratio of approximately 3:1.

6. The most frequent mode of presentation in gallbladder cancer is with abdominal pain, nausea and vomiting, weight loss, jaundice, anorexia, abdominal distension and pruritus. A changed pattern of symptoms in chronic cholecystitis is an important clue.

7. If the tumour obstructs the cystic duct the patient may present with acute cholecystitis or a mucocoele. Half the cases present with obstructive jaundice and a palpable mass in the right hypochondrium.

8. At presentation most gall bladder cancers already occupy the entire gall bladder. They then spread via the lymphatics with blood-borne metastases in lung and bone occurring late in the disease.

9. Common findings on radiography or ultrasonography include thickening of, or a mass in the gall bladder, and cholelithiasis. Many gall bladder cancers are unsuspected and are found incidentally at surgery for cholelithiasis.

Biliary tree

10. The median age at diagnosis is 69 with a slight male predominance.

11. Cancer of the biliary tree usually presents with jaundice due to cholestasis but sometimes with cholangitis and biliary pain. Pain is usual in periampullary cancers. Particularly with proximal tumours jaundice may be absent. Other symptoms may include anorexia, weight loss and pruritus.

12. Malignant tumours of the biliary tree extend locally. Lymphatic and vascular spread is less common.

General notes on cancer aetiology

13. Clinical cancer is the end result of a multistage process involving initiating and promoting agents. If the carcinogen is an initiating agent, eg asbestos – rather than a substance influencing a later stage nearer clinical manifestation, eg cigarette smoking – cancer incidence in the population may continue to rise, albeit more slowly, for a considerable time after exposure to the carcinogen has ceased.

Risk factors in the individual case of all cancers

14. The main factors that determine whether a particular individual develops cancer relate to constitution and exposure to environmental factors.

Genetics

15. The close connection between certain chromosomal abnormalities associated with recognised clinical syndromes and subsequent tumour development, eg polyposis coli and cancer of the large bowel and xeroderma pigmentosum and skin tumours, confirms that an individual's genetic make-up has an affect on his susceptibility to cancer.

16. Many studies have looked at cancer rate in the families of individuals with the disease. There appears to be no material tendency for cancer in general to cluster in families and no genes have been identified that increase the risk of cancer in all tissues. However, all common cancers do cluster in families to some extent – the risk of a sibling of a patient developing a tumour at the same site is twice normal. This might be due to genetic susceptibility but could equally well reflect lifestyle, eg diet or hygiene or a common legacy of infections in early life.

Environmental factors

17. Our knowledge of the environmental causes of cancer relies on animal laboratory investigation and human epidemiology, with the 2 approaches complementing each other. Since there are features common to most cancers, there are factors which can cause cancer at all or many sites. Present evidence confirms the importance of life-style factors in cancer causation.

Tobacco smoke

18. Cigarette smoking is thought to cause 30% of all cancer deaths and has been conclusively linked to cancer of the lung, upper respiratory tract, oesophagus, bladder, stomach, liver, kidney and chronic myeloid leukaemia. It may also cause cancer of the colon and the rectum. Relevant factors include number of cigarettes smoked, tar content, age at smoking onset and duration of habit.

Diet

19. There is good evidence that some common cancers would be less common if diet were modified. Animal fat consumption, particularly red meat, high salt intake and ingestion of very hot beverages and food have all been linked to specific cancers. Similarly what is not in the diet may be important. Low consumption of vegetables and fruit in the presence of high calorie intake is associated with several different tumour types, eg childhood obesity and cancer of the breast and prostate, adult obesity and endometrial cancer. Consumption of alcohol (particularly along with cigarettes) increases the risk of cancer of the upper respiratory and digestive tracts. There is evidence that as little as 2 drinks a day may contribute to breast, colon and rectal cancer. In total, diet is considered to account for 30% of all cancer mortality in developed countries, alcohol for a further 3% and salt for 1%.

Radiation

20. Radiation is difficult to avoid and, in total, radiation of all types causes 2% of all cancer deaths. Most of these deaths result from natural sources, particularly sunlight, UVB.

- **UVB radiation** causes 90% of all skin cancers, including basal cell cancers, malignant melanoma and squamous cell carcinoma.

- **Electromagnetic radiation** as a cause of cancer has been the subject of several recent studies. The results are confusing and inconsistent and reported associations may not be causal. It is of 2 main types:

    i. **Extremely low frequency fields**, eg power lines and household appliances. Basic science confirms that these radiations are of too low frequency to initiate cancer-causing genetic mutation as they are of insufficient energy to ionise molecules.

    ii. **Radiofrequency electromagnetic radiation**, eg cellular telephones, microwaves and living creatures. Although more energetic than i. (above), they are still unable to cause molecular ionisation.

21. In conclusion, at this date there is no good scientific evidence that electromagnetic radiation causes cancer. Any possible association remains hypothesis.

- **Ionising radiation**

22. Ionising radiation can penetrate animal tissues and damage DNA and theoretically has the power to produce cancer in most tissues. The actual risk due to exposure to ionising radiation may, however, be different. It is often overestimated and not evidence-based. Amongst Japanese residents of Hiroshima and Nagasaki who survived more than a year after detonation, only 1% has died of tumours.

23. Studies of humans exposed to high dosage of ionising radiation, eg the Japanese atomic bomb survivors or individuals medically irradiated for tumours, have shown an increased incidence of cancer due to that exposure. There is, however, no firm evidence from human low-dose epidemiological studies, which unequivocally demonstrates an increase in cancer incidence. This may be due to the very large size of study population, which would be needed to demonstrate an increased incidence.

24. For radiation purposes it is, therefore, accepted that there is no threshold level below which no carcinogenic effect is produced and the risk of a cancer developing is extrapolated on a dose-proportional basis from high to low doses and dose rates.

25. All humans are constantly exposed to ionising radiation from both the natural environment and man-made products. The natural sources include cosmic radiation from space, radiation from the ground, and from inhaled and ingested materials. Air travel and mining both increase exposure to background radiation. Radiation originating in the body comes mainly from potassium, while lungs are exposed through radon in inhaled air. Man-made radiation comes from medical uses, past atomic tests, man-made products and radioactive waste.

26. Natural radiation differs depending on location. In the UK the average annual dose is less than 2,000 microsieverts. There is, however, a considerable range; it may rise to 8,000 microsieverts in some areas and to 100,000 in some homes. The UK average annual dose from man-made sources in total is less than 300 microsieverts and, again, there may be variation.

27. From 1952 to 1958 the UK carried out 21 atmospheric nuclear tests in the Pacific Ocean. The locations were chosen because of their isolation and low natural radiation level. On average the Christmas Island annual background radiation is less than 700 microsieverts.

Radiation dose

28. The effects of ionising radiation depend on the exposure size of the accumulated dose. A discussion of radiation dose is written separately.

Therapeutic drugs

29. About 20 agents, not all of which are in current use, are known to cause cancer. Potential carcinogens may still be used if the hazard is judged to be less than the chance of saving a life, eg certain cancer drugs. Close scrutiny is kept on drug hazards and the position of oestrogens in hormone replacement therapy (HRT), known to cause endometrial cancer, and of the oral contraceptive pills, which have been associated with carcinoma of the cervix, breast and hepatoma, is closely monitored. Together, prescribed drugs are held responsible for less than 1% of all fatal cancers.

Occupation

30. Historically, study of occupational exposures has identified many important carcinogens. Material or process modification and, latterly, health and safety statute have removed many potential hazards in the developed world. However, the long latent period of cancer means that a considerable time will be required for the effects of industrial carcinogens to be eliminated and, equally, that new hazards may remain unsuspected for a long time. At present overall, occupation is considered responsible for 2-3% of all fatal Cancers in developed countries. Particularly important occupational carcinogens are asbestos dust exposure, exposure to combustion products of fossil fuels and ionising radiation.

Pollution

31. Investigation of the relation between environmental pollution – air, soil and water – and cancer is difficult because of the widespread nature of pollution and similar risk to people over a wide geographical area. It is generally accepted that in the UK at the beginning of the last century, air pollution via combustion may have contributed to a few percent of lung cancers. Over the last 30 years with increasing statute on pollution reduction this has become much less common. Advances in chemical analysis have allowed recent interest in pollution of soil and water as possible cancer risks.

32. Another complicating factor in accurately attributing risk of cancer to individual external agents is **interaction**. Some carcinogenic agents act together to produce effects much greater than the sum of the separate individual effects, eg smoking and asbestos in relation to cancer of the lung: smoking, alcohol in relation to carcinoma of the oesophagus, and aflatoxin and hepatitis B infection in cancer of the liver.

AETIOLOGY of GALLBLADDER and BILIARY TREE CANCERS

33. Although it is usual to consider cancer of the gall bladder and extrahepatic biliary tree together, there is considerable evidence that the 2 conditions are of different aetiology:

Gallbladder

34. There is undoubtedly a **genetic** factor. In Europe the rate is very high in Germany and surrounding central countries, low in Mediterranean countries and low and declining in Britain and Ireland. In the USA this cancer is more common in Caucasians than in African Americans. In Native Americans the incidence is 6 times higher. As mentioned above, there is a marked female preponderance.

35. A number of other well-documented associations with cancer of the gall bladder have been described. Gallstones are found in 75% of those with gallbladder cancer but in a large post-mortem series cancer was found in only 3% of those with gallstones. This throws strong doubt on the validity of a long accepted causal relationship while suggesting that the 2 conditions may share similar risk factors including female gender and obesity. There has been sharp decrease, over a period of 20 years, in the incidence of gallbladder cancer in the USA. This is associated with an increase in the rate of cholecystectomy for gallstones but also with a decrease in the consumption of saturated fat which could be the more important factor.

36. Chronic cholecystitis, which is not always due to gallstones, is found in 40-50% of cases and is a risk factor. Calcification of the gallbladder ("porcelain" gallbladder) is associated with cancer in over 20% of cases.

37. There is a higher incidence of gall bladder cancer in chronic typhoid carriers. Other risk factors include obesity, congenital abnormalities of the bile ducts, ulcerative colitis, and primary sclerosing cholangitis (PSC).

38. Cancer of the gall bladder has been correlated with external exposure to ionising radiation.

Bile ducts

39. In most cases of cancer of the bile ducts, the cause is unknown. Unlike gallbladder cancer, its incidence is slightly higher in men than in women and it is associated with cholelithiasis in only about 30% of cases.

40. Known risk factors include biliary stasis and infection, ulcerative colitis, infestation with *chlonorchis* and *opisthorchis* liver flukes endemic in areas of Asia, exposure to Thoratrast (a radioactive diagnostic agent), the presence of choledochal cysts, congenital abnormalities of the bile ducts and PSC.

41. Biliary cancer has not been linked with exposure to external ionising radiation.

CONCLUSION

42. Cancers of the gall bladder and biliary tree are malignant tumours. Their cause is unknown, but constitutional and environmental factors play a part in their aetiology.

43. There is no evidence that these cancers are caused by climatic extremes, trauma, physical or mental stress or lowered resistance arising from hardship or other diseases. Their progress is independent of external factors other than medical treatment.

REFERENCES

Bismuth H and Aldridge M C. In: (Eds) Peckham et al. Oxford Textbook of Oncology. 1996. Oxford University Press. p1221-37.

Boice J D. Studies of Atomic Bomb Survivors. JAMA 1990;264:622-623.

Chapman R W and Angus P. In: (Eds) Bircher et al. Oxford Textbook of Clinical Hepatology. 2nd Ed. 1999. Oxford. Oxford University Press. p1686.

Darby, S C, Kendall G M, Fell T P et al. A summary of mortality and incidence of cancer in men from the United Kingdom who participated in the United Kingdom's atmospheric nuclear weapon tests and experimental programmes. BMJ 1990;296:332-338.

Doll R. Epidemiology of Human Neoplasia. In: Eds McGee J O'D, Isaacson P G and Wright N A. Oxford Textbook of Pathology. 1992. Oxford. Oxford University Press. p679-694.

Doll R and Peto R. Epidemiology of Cancer. In: Eds Weatherall D J, Ledingham J G G and Warrell D A. Oxford Textbook of Medicine. 3rd Ed. 1996. Oxford. Oxford University Press. p204.

Harnden D G, Lorenzen J, Pusztai L and McGee J O'D. Carcinogenesis. In: (Eds) McGee J O'D, Isaacson P G and Wright N A. Oxford Textbook of Pathology. 1992. Oxford. Oxford University Press. p633-678.

Kelly P. Tumours of the gall bladder and biliary tree. In: (Eds). McGee J O'D, Isaacson P G and Wright N A. Oxford Textbook of Pathology 1992. Oxford. Oxford University Press p1413-1416.

Majno P, Azoulay D & Bismuth H. In: (Eds) Bircher et al. Oxford Textbook of Clinical Hepatology. 2nd Ed. 1999. Oxford. Oxford University Press. p1542.

Rosai J. In: Rosai J (Ed). Ackerman's Surgical Pathology. 8th Ed. 1996. St Louis. Mosby. p943-962.

Rosvold E. In: (Eds) Raghavan D et al. Textbook of Uncommon Cancers. 2nd Ed. 1999. Chichester. John Wiley & Sons. p420-422.

Royle et al. In: (Eds) Peckham et al. Oxford Textbook of Oncology. 1996. Oxford University Press. p215-216.

Schimizu Y, Schull W J and Kato H. Cancer risk among Atomic Bomb Survivors: the RERF Life Span Study. JAMA 1990;264:601-604.

Sherlock S & Dooley J. Diseases of the Liver and Biliary System. 10th Ed. 1997. Oxford. Blackwell. p641-645.

Summerfield J A. In: (Eds) Weatherall D J, Ledingham J G G and Warrell D A. Oxford Textbook of Medicine. 3rd Ed. 1996. Oxford. Oxford University Press. p2045-53.

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Annex A

Radiation dose

1. The first definition of a unit of radiation dose was made in 1928 by the International Congress of Radiology. The roentgen (R) was defined as that quantity of radiation which produces in 1 cm of air one unit of charge of either sign, thus defining a unit of exposure. Units of **absorbed dose**, the actual energy absorbed in the tissue being irradiated are now used. The radiation absorbed dose or **rad** is now cited in SI (Systeme Internationale) units – joules per kg – of absorbing material. The fundamental unit, 1 joule/kg, is 1 gray (1 Gy), equivalent to 100 rads (R).

2. Different radiation types have greater or lesser effect per unit dose, so they are all expressed relative to the effects of X-rays, ie. a unit equivalent dose is used. To calculate the roentgen equivalent in man (**rem**), the absorbed radiation dose is multiplied by a radiation weighting factor, dependent on type and energy of the radiation. The current SI unit of equivalent dose is the **Sievert**. For X-rays and gamma rays the equivalent dose in sieverts and the absorbed radiation dose in grays are the same. The relationship between the different dose units is:-

   1 gray (Gy) = 1 joule/kg = 100 rads (R) = 100 rems (r) = 1 sievert (Sv) = 1,000 millisieverts (mSv) = 1,000,000 microsieverts (microSv). Typical doses of radiation include:

   Chest X-ray – 0.02 mSv
   Brain scan – 7 mSv
   Bone scan – 4 mSv
   Average annual UK dose from cosmic rays – 0.26 mSv
   Average annual UK dose from gamma rays – 0.35 mSv
   Average annual UK dose from natural background radiation – 2.2 mSv

3. **Effects of total body irradiation**

Equivalent dose (Sv)	**Effect**
Sub lethal to man 0.0001 (0.1 mSv)	Around 2 weeks' natural background radiation, no detectable effect
0.001 (1 mSv)	Around 6 months' natural background radiation, no detectable effect
0.01 (10 mSv)	No detectable effect
0.1 (100 mSv)	Minimal decrease in peripheral lymphocyte count, no clinical effect
1 (1000 mSv)	Mild acute radiation sickness in some individuals (nausea, possible vomiting), no acute deaths, early decrease in peripheral lymphocyte count, decrease in all WBC and platelets at 2-3 weeks, increase in late risk of leukaemia, solid tumours

Equivalent dose (Sv)	Effect
Lethal to man 10 (10,000 mSv)	Severe acute radiation sickness, severe vomiting, diarrhoea, death within 30 days of all exposed individuals. Severe depression of blood cell and platelet production, damage to gastrointestinal mucosa.
100 (100,000 mSv)	Immediate severe vomiting, disorientation, coma, death within hours
1000 (1,000,000 mSv)	Death of some micro-organisms, some insects within hours
10,000 (10,000,000 mSv)	Death of most bacteria, some viruses
100,000 (100,000,000 mSv)	Death of all living organisms, denaturation of proteins

Radiation dose limits

4. Since the days of Marie Curie it has been appreciated that ionising radiation exposure may be hazardous to health. Radiation dose limits were first recommended for ionising radiation exposure in 1928. The statutory limit on the amount of radiation to which the general public may be exposed in excess of natural background radiation and excluding medical exposure is set, from 1 January 2000, at 1 mSv per annum.

5. The most important source of man-made exposure is medical investigation which accounts for 90% of man-made exposure. Average natural background radiation is raised to 2.6 mSv by all man-made exposure. UK estimated exposure, excluding medical investigation, is 0.04 mSv. Other statutory limits include occupational dose limits. From 1 January 2000, these are 20 mSv per annum for classified workers and 6 mSv per annum for unclassified workers.

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