between ^{31}P NMR spectroscopy and tissue O_2 tension measurements in murine fibrosarcoma. *Radiat Res* 1989, **120**, 477–493.
29. Kallinowksi F, Zander R, Hoeckel M, Vaupel P. Tumor tissue oxygenation as evaluated by computerized pO_2 histography. *Int J Radiat Oncol Biol Phys* 1990, **19**, 953–961.
30. Roszinski S, Wiedemann G, Jiang SZ, Baretton G, Wagner T, Weiss C. Effects of hyperthermia and/or hyperglycemia on pH and pO_2 in well oxygenated xenotransplanted human sarcoma. *Int J Radiat Oncol Biol Phys* 1991, **20**, 1273–1280.
31. Dorie MJ, Kallman RF. Reoxygenation in the RIF-1 tumor. *Int J Radiat Oncol Biol Phys* 1984, **10**, 687–693.
32. Rofstad EK. Hypoxia and reoxygenation in human melanoma xenografts. *Int J Radiat Oncol Biol Phys* 1989, **17**, 81–89.
33. Moulder JE, Rockwell SC. Hypoxic fractions of solid tumors: experimental techniques, methods of analysis, and a survey of existing data. *Int J Radiat Oncol Biol Phys* 1984, **10**, 695–712.
34. Li SJ, Wehrle JP, Rajan SS, Steen RG, Glickson JD, Hilton J. Response of radiation-induced fibrosarcoma-1 in mice to cyclophosphamide monitored by *in vivo* ^{31}P nuclear magnetic resonance spectroscopy. *Cancer Res* 1988, **48**, 4736–4742.
35. Schiffer LM, Braunschweiger PG. Preliminary observations on the correlation of proliferative phenomena with *in vivo* ^{31}P NMR spectroscopy after tumor chemotherapy. *Ann NY Acad Sci* 1986, **400**, 270–277.
36. Deschner EE, Gray LH. Influence of oxygen tension on X-ray induced chromosomal damage in Ehrlich ascites tumor cells irradiated *in vitro* and *in vivo*. *Radiat Res* 1959, **11**, 115–146.
37. Drewinko B, Patchen M, Yang LY, Barlogie B. Differential killing efficacy of twenty antitumor drugs on proliferating and nonproliferating human tumor cells. *Cancer Res* 1981, **41**, 2328–2333.
38. Gupta V, Costanzi JJ. Role of hypoxia in anticancer drug-induced cytotoxicity for Ehrlich ascites cells. *Cancer Res* 1987, **47**, 2407–2412.
39. Yamauchi T, Riffin TA, Yang P, Sikic BI. Differential protective effects of varying degrees of hypoxia on the cytotoxicities of etoposide and bleomycin. *Cancer Chemother Pharmacol* 1987, **19**, 282–286.
40. Mulcahy RT. Effect of oxygen on misonidazole chemosensitization and cytotoxicity. *Cancer Res* 1984, **44**, 4409–4413.
41. Taylor YC, Rauth AM. Oxygen tension, cellular respiration, and redox state as variables influencing the cytotoxicity of the radiosensitizer misonidazole. *Radiat Res* 1982, **91**, 104–123.
42. Jähde E, Rajewsky MF. Protection of cultured malignant cells from anthracycline cytotoxicity by low extracellular pH: a possible mechanism for primary chemoresistance. *Blut* 1986, **51**, 255.
43. Jähde E, Glüsenkamp KH, Rajewsky MF. Protection of cultured malignant cells from mitoxantrone cytotoxicity at low extracellular pH: a possible mechanism for chemoresistance *in vivo*. *Eur J Cancer* 1990, **26**, 101–106.
44. Siemann DW, Chapman M, Beikirch A. Effects of oxygenation and pH on tumor cell response to alkylating chemotherapy. *Int J Radiat Oncol Biol Phys* 1991, **20**, 287–298.
45. DeVita VT. The influence of information on drug resistance on protocol design. *Annals Oncol* 1991, **2**, 93–106.
46. Brown JM, Koong A. Therapeutic advantage of hypoxic cells in tumors: a theoretical study. *J Natl Cancer Inst* 1991, **83**, 178–185.

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Survival Trends for Neuroblastoma Patients in Finland: Negative Reflections on Screening

Risto Sankila and Matti Hakama

Based on 257 neuroblastoma patients in the age group 0–14 years and reported to the Finnish Cancer Registry, the 5-year cumulative survival rates have improved from 15% in the 1950s to 57% in 1980–1986. The potential benefit of screening for neuroblastoma was assessed on the basis of these nationwide survival trends. It is likely that any decrease in the overall neuroblastoma mortality due to screening would be small, because the survival rates of the Finnish neuroblastoma patients are already, even without screening, similar to those in Japan, which has a nationwide public health policy to screen for neuroblastoma.
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INTRODUCTION

NEUROBLASTOMA IS the third most common tumour among children after leukaemias and brain tumours [1]. Screening for neuroblastoma is technically possible by detecting the excess amounts of catecholamine metabolites in urine excreted by most of the tumours [2]. The purpose of this study is to estimate the survival rates of neuroblastoma patients in Finland without any screening. The rates and trends are available at the population-based, nationwide Finnish Cancer Registry which has been functioning since 1953. By comparing the Finnish rates to those reported in Japan, where a nationwide policy for screening for neuroblastoma has been established, we assess the likely benefit of introducing a screening programme for neuroblastoma.

PATIENTS AND METHODS

The population-based, nationwide Finnish Cancer Registry has been functioning since 1953. All hospitals, physicians and pathological laboratories are required to notify the Registry of all cancer cases that come to their attention. The Registry also receives information on all death certificates in which a cancer diagnosis is mentioned.

Between 1953 and 1986 altogether 259 histologically verified neuroblastomas and ganglioneuroblastomas in the age group of 0–14 years were reported to the Finnish Cancer Registry. 2 of

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Table 1. 5-year cumulative survival rates (%) of neuroblastoma patients in Finland by period and age at diagnosis (numbers of patients and 95% CI for age group 0–14 years in parenthesis).

Period	Age (years)				
	0	1–2	3–5	6–14	0–14
1953–1959	29 (7)	20 (15)	0 (9)	11 (9)	15 (4–26, 40)
1960–1969	53 (19)	19 (21)	5 (20)	18 (11)	24 (14–34, 71)
1970–1979	63 (27)	41 (22)	14 (21)	27 (11)	40 (29–50, 81)
1980–1986	88 (25)	32 (24)	35 (11)	40 (5)	57 (45–69, 65)
1953–1986	65 (78)	30 (82)	13 (61)	22 (36)	36 (30–42, 257)

these patients were incidentally diagnosed at autopsy, and were excluded from the study. Thus, cumulative observed survival rates were calculated for 257 patients using life-table method. The patients were followed up from the date of diagnosis until death or emigration or the common closing date 31 December 1990 using data from the National Population Registry. No patient was lost from the follow-up.

RESULTS

The overall 5-year cumulative survival rate for the 257 patients was 36% (95% confidence interval 30–42%, Table 1). The survival rates improved from 15% (95% CI 4–26%) in 1953–1959 to 57% (95% CI 45–69%) in 1980–1986 (Table 1). Patients under 1 year of age at diagnosis had the highest survival rates: 29% (95% CI 0–63%) in 1953–1959 and 88% (95% CI 75–100%) in 1980–1986. The survival rates were U-shaped by age (Table 1).

Of the 60 patients (diagnosed in 1953–1980, allowing for a minimum follow-up of 10 years) who survived for at least 5 years, only 3 died later. Thus, the 5-year survival rates approximate the ultimate cure rate of the patients.

DISCUSSION

The prognosis of neuroblastoma patients is very good if the diagnosis is made in the first year of life (up to 75–100% survive depending on stage) or if the tumour is localised or of a special type of non-localised disease, i.e. stage 4S by the International Neuroblastoma Staging System [3, 4]. The prognosis of patients older than 1 year with non-localised tumours (stage 4) has been poor (less than 20% survive) [3, 5].

There seems to be a trend towards increasing survival rates. In Denmark the 2-year survival rate was 0% in 1943–1949 compared with 32% in 1970–1980 [6]. In our study the 5-year overall survival rates were 15% in 1953–1959 and 57% in 1980–1986. These improvements are most probably due to advances in clinical diagnosis and treatment. The 57% 5-year survival rate in our series in 1980–1986 is similar to the 55% survival rate reported in the U.S.A. in 1980–1985 [3], but somewhat higher than the corresponding 43% rate in the U.K. in 1983–1985 [7] or 50% in a large clinical series in Germany in 1979–1985 [5]. It is worth noticing that the Finnish series is unselected, nationwide, and with complete follow-up, thus producing reliable estimates of the survival rates.

Screening methods based on the detection of excess amounts of catecholamine metabolites have been developed to improve the prognosis of patients by earlier diagnosis [2]. In Japan a nationwide screening programme for children at the age of 6 months has been established [8]. The effectiveness of the Japanese screening programme has been evaluated by process indicators like sensitivity and specificity of the test, by numbers of neuroblastomas detected, by stage shift, by age shift, and most convincingly, by improved survival rates [9–11]. However, these indicators are subject to different biases. An attempt to evaluate the trends in neuroblastoma mortality—the final proof of efficacy—was made only recently concluding that a further study is still necessary [12].

In a Japanese study the 5-year survival rate of neuroblastoma patients diagnosed in 1981–1989 increased to 67% during the screening period [11]. This very high survival rate was regarded as evidence for the effectiveness of screening for neuroblastoma. Such a figure should be compared with concurrent, not historical, controls to remove the bias due to long-term trends in survival which are not related to screening. Second, the overdiagnosis of screen-detected cases that are histologically malignant but biologically benign will cause a bias in the survival rates of screen-detected cases.

The overall 5-year survival rate of 57% in Finland, with a population not subjected to screening in 1980–1986, is relatively close to the 67% reported in Japan with a population subjected to a screening programme for neuroblastoma (and possible overdiagnosis) in 1981–1989 [11]. Thus, a screening programme in Finland would probably not result in a substantial reduction in the residual neuroblastoma mortality, but the benefits would be outweighed by adverse effects, such as false-positive and negative test results, and unnecessary clinical follow-up and invasive diagnostic procedures. The survival trends in Finland lend further support to the conclusions that screening for neuroblastoma cannot at present be recommended as a public health policy [13–15].

1. Finnish Cancer Registry. Cancer incidence in Finland 1984. Cancer Society of Finland. Publication No. 41. Helsinki, 1989, 26–31.
2. Woods WG, Tuchman M. Neuroblastoma: the case for screening infants in North America. *Pediatrics* 1987, **79**, 869–873.
3. Crist WM, Kun LE. Common solid tumors in childhood. *N Engl J Med* 1991, **324**, 461–471.
4. Brodeur GM, Seeger RC, Barret A, *et al.* International criteria for diagnosis, staging, and response to treatment in patients with neuroblastoma. *J Clin Oncol* 1988, **6**, 1874–1881.
5. Berthold F, Burdach S, Kremens B, *et al.* The role of chemotherapy in the treatment of children with neuroblastoma stage IV: the GPO (German Pediatric Oncology Society) experience. *Klin Padiatr* 1990, **202**, 262–269.
6. Carlsen NLT, Christensen IJ, Schroeder H. Prognostic factors in neuroblastoma treated in Denmark from 1943 to 1980. *Cancer* 1986, **58**, 2726–2735.
7. Stiller CA, Bunch KJ. Trends in survival for childhood cancer in Britain diagnosed 1971–85. *Br J Cancer* 1990, **62**, 806–816.
8. Takeda T. History and current status of neuroblastoma screening in Japan. *Med Pediatr Oncol* 1989, **17**, 361–363.
9. Nishi M, Miyake H, Takeda T, *et al.* Effects of the mass screening of neuroblastoma in Sapporo City. *Cancer* 1987, **60**, 433–436.
10. Takeda T, Hatae Y, Nakadate H, *et al.* Japanese experience of screening. *Med Pediatr Oncol* 1989, **17**, 368–372.
11. Naito H, Sasaki M, Yamashiro K, *et al.* Improvement in prognosis of neuroblastoma through mass population screening. *J Pediatr Surg* 1990, **25**, 245–248.
12. Hanawa Y, Sawada T, Tsunoda A. Decrease in childhood neuroblastoma death in Japan. *Med Pediatr Oncol* 1990, **18**, 472–475.
13. Miller AB, Chamberlain J, Day NE, Hakama M, Prorok PC. Report on a workshop on the UICC project on evaluation of screening for cancer. *Int J Cancer* 1990, **46**, 761–769.
14. Expert group on neuroblastoma screening. Report to the Health Services Research Comittee. London, 1991 (mimiographed).
15. Murphy SB, Cohn SL, Craft AW, *et al.* Do children benefit from mass screening for neuroblastoma? *Lancet* 1991, **337**, 344–346.