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Role of age and tumour stage in the temporal pattern of 'cure' from stomach cancer: A population-based study in Osaka, Japan

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ABSTRACT

Objectives: To evaluate progress in stomach cancer care in Japan since 1975. *Design*: Population-based study of data extracted from the Osaka Cancer Registry. *Setting*: Population-based cancer registry in the area of Osaka Prefecture. *Participants*: All 66,032 cases diagnosed with a stomach cancer in Osaka Prefecture, Japan between 1975 and 2000 and registered in the Osaka Cancer Registry. *Main outcome measures*: 'Cure' fraction and median survival time for 'uncured' patients were estimated with multivariable mixture 'cure' model. The role played by age and stage at diagnosis on the changes in 'cure' parameters between 1975 and 2000 was evaluated. Missing stage was handled by multiple imputation approach. *Results*: More than 50% of the patients diagnosed with a stomach cancer in 1996–2000 were estimated 'cured' from their cancer, corresponding to a 20% increase since 1975–1980. Median survival time for 'uncured' patients however remained unchanged at about 8 months. 'Cure' fraction was over 85% for localised tumours and 30% for regional tumours, but stayed as low as 2.5% for distant metastatic cancers. Improvement was underestimated by about 10% because of ageing of cancer patients. Changes in stage distribution explained up to 40% of the increase in 'cure' fraction among men and up to 13% in women. Overdiagnosis was unlikely to play any role in these patterns. *Conclusions*: 'Cure' fraction from stomach cancer dramatically increased in Osaka, Japan since 1975, partly because of earlier stage at diagnosis, but mostly due to improvement in treatment of stomach cancer patients. This study, based on a leading country in term of stomach cancer management, provides insightful results for other countries in which 'cure' fraction is usually much lower.

1. Introduction

Stomach cancer has been the leading incident site in Japan for the last half century [1]. Stomach cancer screening started in Japan in the early 1960s, followed later by successive improvements in surgical treatment. As a result, five-year relative survival from stomach cancer has dramatically increased in Japan, doubling in Osaka since the 1970s [2].

'Cure' fraction models [3–7] enable us to estimate proportion of patients 'cured', defined as the proportion of cancer patients which life expectancy goes back to that of general population. Population 'cure' is a statistical concept defined at population level rather than an individual, clinical concept. Five-year survival, traditionally used as an indicator of recovering from cancer, is however affected by lead-time bias, which occurs typically with earlier diagnosis not associated with improved prognosis. By contrast, 'cure' fraction is not influenced by lead-time bias and represents then a useful indicator for evaluating long-term trends in cancer care using population-based data. 'Cure' models can also estimate the median survival of 'uncured', or 'fatal', patients.

'Cure' fraction has been estimated for stomach cancer in low-incidence areas such as Europe and the US [8,9], but none, to our knowledge, in an area with high incidence of stomach cancer such as Japan.

We aim to monitor trends in 'cure' fraction and median survival time for 'uncured' patients for stomach cancer in Osaka, Japan, in order to evaluate cancer care in long-term period. 'Cure' fraction model was applied on population-based Osaka cancer registry data. Missing information for tumour stage was handled by multiple imputation [10].

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2. Patients and methods

2.1. Data sources

We analysed 66,032 patients diagnosed with a first, primary malignant tumour of the stomach (ICD-10 code, C16) in Osaka between 1975 and 2000. The vital status of the patients is not centralised and automatic, and is therefore assessed only at five and ten years after diagnosis. The minimum potential follow-up was ten years patients, except for those diagnosed in 1996–2000 with a follow-up limited at five years. The Osaka Cancer Registry (OCR), one of the largest population-based cancer registries in the world, was established in 1962, allowing evaluation of long-term trends in cancer survival. Tumour stage was defined according to UICC TNM classification: localised tumour as T1–T2/N0/M0, regional metastases as T1–T2/N1–N2–N3/M0 or T3–T4/N0/M0, and distant metastasis as M1, regardless T and N.

2.2. Statistical methods

Statistical 'cure' is defined when the cancer patients group has the same mortality as general population with similar general characteristics (sex, age, etc.). In other words, the cancer population does not express any excess mortality when compared to the general population or the relative survival curve reaches a plateau [4,7].

Mixture parametric 'cure' fraction model [7,8,11,12] was employed with *strsmix* command for the statistical package Stata [6]. Such mixture models model the survival function of the group of the 'uncured' patients ($S_u(t)$) on top of the fraction of 'cured' patients. In the mixture cure fraction model, the all-cause survival can be written as the product of the expected survival, $S^*(t)$ and the disease-related survival functions

$$S(t) = S^*(t)(\pi + (1-\pi)S_u(t))$$

where π is the 'cure' fraction. The expected (or background) mortality was provided by complete (i.e. by single year of age), smoothed national life tables by sex and calendar year [13].

'Cure' fraction was estimated from the logit link and the survival function of the 'uncured' patients ($S_u(t)$), by a Weibull distribution. The survival function can therefore be written as:

$$S(t) = S^*(t)\exp(-\lambda t^{\gamma})$$

or equivalently on the hazard scale:

$$h(t) = h^*(t) + \lambda\gamma t^{\gamma-1}$$

with the Weibull parameters of scale (λ) and shape (γ). The 'cure' fraction is estimated using:

$$\pi = \text{invlogit}(\alpha + \beta' X)$$

when we used logistic link function with modelling covariates X. 'Cure' models were applied separately by sex, and included as covariables calendar period of diagnosis (1975–80, 1981–85, 1986–90, 1991–95, 1996–2000), age at diagnosis (15–39, 40–59, 60–74, 75–99) and tumour stage at diagnosis (localised, regional, distant). The 'cure' fraction and both Weibull parameters were allowed to vary by calendar period, age and stage.

Such multivariable models enabled us to predict 'cure' parameters for patients diagnosed in 1996–2000, whose maximum potential follow-up was five years. We examined the characteristics of patients with missing stage before multiple imputation, then we assumed the mechanism of missingness as Missing At Random. The 'cure' models were applied on the ten completed data sets containing the imputed values of stage for cases with missing information (11.4%). The imputation model was a multinomial logistic regression including follow-up time, vital status, period of diagnosis, age at diagnosis, and interactions between follow-up time and the other factors. Rubin's rules were applied to estimate the 'cure' fraction, median survival time for 'uncured' and their respective standard errors from the ten completed data sets [10].

The effects of age and stage at diagnosis on the time trends in 'cure' fraction and median survival time of 'uncured' patients were determined by the percentage change in the model parameters for period, age and stage at diagnosis estimated by successive multivariable 'cure' models. Given the full model including period, age and stage, the effect of, say, stage on the temporal trends is the

Table 1
Characteristics of stomach cancer patients in Osaka (Japan), 1975–2000.

	Period of diagnosis										Total	
	1975–80		1981–85		1986–90		1991–95		1996–2000		*N*	%
	N	%	*N*	%	*N*	%	*N*	%	*N*	%		
Total	11,811	100.0	12,387	100.0	13,595	100.0	14,035	100.0	14,204	100.0	66,032	100.0
Sex												
Men	7300	61.8	7915	63.9	8850	65.1	9368	66.7	9737	68.6	43,170	65.4
Women	4511	38.2	4472	36.1	4745	34.9	4667	33.3	4467	31.4	22,862	34.6
Age												
15–39	1066	9.0	878	7.1	682	5.0	397	2.8	309	2.2	3332	5.0
40–59	4012	34.0	4428	35.7	5122	37.7	4899	34.9	4268	30.0	22,729	34.4
60–74	5003	42.4	4943	39.9	5284	38.9	5855	41.7	6484	45.6	27,569	41.8
75–99	1730	14.6	2138	17.3	2507	18.4	2884	20.5	3143	22.1	12,402	18.8
Stage (before imputation)												
Localised	2552	27.2	3691	33.7	5169	41.5	5688	45.4	6219	47.4	23,319	39.9
Regional	4823	51.4	4932	45.0	4715	37.9	4444	35.4	4305	32.8	23,219	39.7
Distant	2014	21.5	2341	21.4	2573	20.7	2410	19.2	2601	19.8	11,939	20.4
Missing[a]	2422	(20.5)	1423	(11.5)	1138	(8.4)	1493	(10.6)	1079	(7.6)	7555	(11.4)
Stage (after imputation)												
Localised	3206	27.1	4056	32.7	5520	40.6	6279	44.7	6631	46.7	25,692	38.9
Regional	6055	51.3	5580	45.0	5168	38.0	4985	35.5	4687	33.0	26,474	40.1
Distant	2551	21.6	2751	22.2	2908	21.4	2771	19.7	2887	20.3	13,867	21.0

[a] Frequencies of stage before imputation are shown for the cases without missing stage information; on top of that is shown between brackets the proportion of missing stage.