The Breast 48 (2019) 82–88

Contents lists available at ScienceDirect

The Breast

journal homepage: www.elsevier.com/brst

Original article

Prognostic factors associated with locoronal relapses, metastatic relapses, and death among women with breast cancer. Population-based cohort study

Freshteh Osmani [a], Ebrahim Hajizadeh [b, *], Aliakbar Rasekhi [b], Mohammad Esmaeil Akbari [c]

[a] Infectious Diseases Research Center, Faculty of Medicine, Birjand University of Medical Sciences, Birjand, Iran
[b] Department of Biostatistics, Faculty of Medical Sciences, Tarbiat Modares University (TMU), Tehran, Iran
[c] Cancer Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran

ARTICLE INFO

Article history:
Received 7 August 2019
Received in revised form
17 September 2019
Accepted 18 September 2019
Available online 18 September 2019

Keywords:
Breast neoplasms
Neoplasm recurrence
Local
Survival analysis
Frailty

ABSTRACT

Background: This study was designed to identify the prognostic factors associated with two types of relapses of breast neoplasms. The aim of this study was to evaluate the association between two possible relapses for the increased incidence of distant metastases observed in patients with local relapses injuries, using multivariate statistical models.
Design: And Setting: A population-based cohort study that was designed as a single center: the cancer research center, Shahid Beheshti University of medical sciences.
Methods: This study was conducted on 1815 patients with breast cancer having age of 22 or more. This study considers the analysis of recurrence and survival by joint modeling of three correlated outcomes: local recurrence, distant recurrence (metastasis) and death. The goals are to find out the effects of treatments on recurrences and death, the effects of relapses on death and the correlation between local and distant recurrences.
Results: According to obtained results of the fitted models, the risk of local and metastatic relapses or death increased for patients with at least one positive lymph node (N+) or for patients with a grade greater than I. Also, the variable HR+ was significantly associated with the hazards of locoronal, metastatic recurrence and the death for both reduced and proposed models ($P < 0.05$).
Conclusions: We concluded that if the association between these outcomes are not taken into account, we may lose important information. Given the small number of recurrent events, these results should be considered with caution.

1. Introduction

In many research settings, the event of interest can be experienced more than once per subject. Such outcomes have been termed as recurrent events. Such data occur often in longitudinal follow-up studies. Examples of recurrent events include repeated hospitalizations, bladder tumor recurrence times among patients in a randomized treatment trial and recurrent heart attacks [1,2]. For recurrent event data, there are various models proposed in the literature of survival analysis, including conditional intensity models [7–9], marginal intensity models, the frailty model approach and marginal means and rates models [10,11]. In many applications, however, there may exist a dependent terminal event such as death that stops the follow-up. For example, patients may experience recurrent hospitalizations which are terminated by death. Such a terminal event is likely to be strongly correlated with recurrent events of interest and should be accounted for in the analysis. For recurrent event data in the presence of a terminal event, the existing methods generally fall into two approaches frailty methods and marginal methods. Frailty models use frailties or random effects to account for the correlation between the recurrent and terminal events. For example, Huang and Wang (2004) provided a shared frailty model with proportional intensity and proportional hazards for recurrent events and the terminal

* Corresponding author. Department of Biostatistics, Faculty of Medical Sciences, Tarbiat Modares University, Jalal Ale Ahmad Highway, Tehran, Iran.
E-mail addresses: dr.osmani68@gmail.com (F. Osmani), f.osmani@modares.ac.ir, hajizadeh@modares.ac.ir, hajitm@yahoo.com (E. Hajizadeh), rasekhi@modares.ac.ir (A. Rasekhi).

https://doi.org/10.1016/j.breast.2019.09.010
0960-9776/

event, respectively [12].Kalbeisch and Schaubel studied a joint semi-parametric model in which a shared gamma frailty is used to account for the correlation between the recurrent event rate and terminal event hazard function [13]. Cook et al., provided various classes of robust methods for modeling the recurrent event mean with a terminating event [14].The impact of two types of recurrences on the survival of patients with breast cancer has been a matter of contention for the recent decades [3,4]. The explanation of prognostic factors and their effect are critical for making progress in the prevention of disease and treatment. The occurrences of local and metastatic recurrences may provide information about the declining of patient's health. These recurrent events and a terminal event can be rather explained by prognostic factors such as biological measurements or characteristics of the patients associated with the tumor size or the environment [15,16]. Various prognostic factors that for which we do not have measurements in the clinical dataset must be added to explain the progression of the disease. A model that can deal with non-observed factors that can explain heterogeneity of data, correlated recurrent event times with a dependent terminal event time is needed. This leads us to the proposed joint frailty model in this article.

In many published trials, adjuvant chemotherapy was associated with decreased local and distant recurrence rates and also with an increased recurrence-free survival rate, but not an increased overall survival rate. Montagna et al. showed that after a locoronal relapse, there is a high risk of experiencing a metastatic event [5]. O'Shaughnessy showed a strong link between a metastatic relapse and death [6].

In this article, we consider two different types of recurrent events which could be associated. Moreover, death is considered as a dependent terminating event for the relapses, it is necessary to analyze these recurrent events jointly with the terminal event to make valid inferences.

A joint frailty hazard model is developed for joint-modeling of three correlated time-to-event outcomes: (1) local recurrence, (2) distant recurrence, and (3) overall survival. The term frailty is introduced to model population heterogeneity. The dependence is modeled by conditioning on a shared frailty that is included in the three hazard functions. Independent variables can be included in the model as covariates. This study aimed to investigate the applicability and performance of a joint frailty model, comparing it with three reduced models with using a breast cancer data set.

2. Methods

2.1. Study population

This rstry-based retrospective cohort study was conducted at the Shahid Beheshti Breast Cancer Research Center, using medical records. Eligibility criteria required subjects to be female, patients with a definite diagnosis of breast cancer who were followed up at Shohada Tajrish Hospital for at least 6 months after surgery. Outcome information was sought from the patient's clinicians or their General Practitioner. The follow-up period was 18 years after initial surgery from January 1998 until February 2016. However, there was no way to identify patients with recurrence after 18 years unless they visited this hospital for treatment. In order to avoid the possibility of not receiving information of patient recurrence or death of any cause, we contact them so that we can accurately update our records. In this follow-up period, we identified 2235 recurrent breast cancer that were separated based on the type of recurrence.

Data collected included: age at diagnosis how their breast cancer was discovered, tumor size, grade, lymph node involvement (node: N+ or N−), the positive status of hormone receptors (HR + or HR−), their surgery, HER2, tumor histopathology, adjuvant treatment(s) received and their outcome at last follow up were considered. Tumor histology was classed as invasive ductal cancer (IDC), invasive lobular cancer (ILC), special (mixedhistologies, medullary, colloid, tubular and adenoid cystic carcinomas) and other (micropapillary. A micrometastasis in a lymph node was classed as a positive node, but isolated tumor cells was classed as a negative node. The physician collected data available in the patient's medical record, and results of parameters systematically evaluated for the management of the patient's disease. HER2 or human epidermal growth factor receptor-2 is a protein and if its rate is abnormally raised at the surface of the tumoral cells, then the tumor is classified HER2+. The positive HER2 status was tested in the centralized laboratory based on ISH result (FISH, CISH or SISH) described according to the IHC result. A tumor was considered HR + if more than 10% of tumor cells were positive by immune histochemical analysis. Data were entered by the investigators in electronic forms and transferred to the centralized database. Exit criteria in this study were including incomplete information for each patient that these observations were made due to a defect in medical records and patient pathology reports. Also, patients who have been followed up for up to five months and variables that overlap with the results of the research were removed, then four hundred and twenty patients were excluded. Finally, a total of 1815 patients were included in the study. Patients from the time of breast-conserving surgery were considered at risk of recurrence or death.

The primary endpoint was to describe clinical and tumor characteristics of patients with metastatic or locally advanced breast cancer, and progression-free for at least 3 years after initiation of 1st-line therapy with trastuzumab. Analysis of potential prognostic factors of long survival and tolerance of types of treatments; presence or not of metastases and local relapse. The dominant recurrent site was categorized as follows: soft tissue dominant disease (local recurrence to the skin, chest wall, lymph nodes, or breast); bone dominant disease (bone metastases with or without soft tissue involvement); and visceral dominant disease (metastases to organs with or without bone or soft tissue involvement).

We shall first describe the raw data, then, we will examine the further information which can be obtained by using a mathematical model.

2.2. Classification of groups

Tumors were classified by immunohistochemical staining (IHC) according to St. Gallen subtypes as follows: luminal A (ER+ and/or PR+, HER2 and Ki67% < 30%), luminal B HER2(ER+ and/or PR+, HER2and Ki67% ≥ 30%), luminal B HER2+(ER+ and/or PR + andHER2+), HER2-neu non-luminal (ER/PR and HER2+) and basal-like (ER/PR and HER2). ER/PR status was determined by IHC. Tumors were considered ER+ and PR + if>1% staining. Tumors were considered HER2+if they scored 3 + by IHC. In cases of a HER2score of 2+, tumors were considered HER2+ if FISH or SISH showed HER2 gene amplification. Tumors with 2 + scores, where FISH/SISH wasn't undertaken were excluded.

2.3. Joint frailty model for disease recurrences and survival

For a breast cancer patient i (i = 1, 2,•, n), denote the numbers of local and distant recurrences by n_i and $n_i^{'}$, respectively, which it will be zero if there is no relapse for the patient. We consider here three time to event responses for patient i denoted by $(\{T_{1ij}\}_{j=1}^{n_i}, \{T_{2ij'}\}_{j'=1}^{n_i^{'}}, T_{3i})$, where T_{1ij} is the time from surgical resection of the tumor to the jth local relapse for the ith patient, $T_{2ij'}$ is the time from surgical resection of the tumor to the jth distant relapse, and T_{3i} is survival

time, which is defined as the time from surgical resection of the tumor to death or last follow-up. The hazard functions for the triple failure times are [19]:

$$\begin{array}{l} \text{Local} \\ \text{Metastasis} \\ \text{Death} \end{array} \begin{cases} h_{1i}\left(t_{1ij'}\right) = h_2\left(t_{1ij'}\right)\exp\left(\beta_1^T Z_i^{(L)} + \theta_{1i}\right) \\ h_{2i}\left(t_{2ij'}\right) = h_2\left(t_{1ij'}\right)\exp\left(\beta_2^T Z_i^{(D)} + \theta_{2i}\right) \\ h_{3i}\left(t_{3i}\right) = h_3\left(t_{3i}\right)\exp\left(\beta_3^T Z_i^{(S)} + \alpha_1\theta_{1i} + \alpha_2\theta_{2i}\right) \end{cases}$$

where $h_1(t), h_2(t), h_3(t)$ are unknown baseline hazards for local recurrence, distant recurrence, and survival, respectively; $Z^{(L)}$, $Z^{(D)}$ and $Z^{(S)}$ are vectors of covariates associated with local recurrence, distant recurrence, and survival, respectively, and $\beta_1^T, \beta_2^T, \beta_3^T$ are corresponding regression parameter vectors. The effects θ_{1i} and θ_{2i} act on local recurrence time T_1 and distant recurrence time T_2, respectively. Thus, it is not presumed that patient effect is the same for both local and distant recurrences; α_1, α_2 are regression parameters on θ_{1i}, θ_{2i}, respectively [17]. It implies that there is a positive correlation between local (distant) recurrence and survival if $\alpha_1 > 0$ ($\alpha_2 > 0$). The P coefficient represents the correlation between θ_{1i} (local recurrences) and θ_{2i} (distant recurrences). Thus, $P > 0$ implies that there is a positive correlation between local and distant relapses.

We proposed here joint frailty models with parametric Weibull functions that directly use the maximum likelihood estimation method for estimating parameters.

2.4. Application to breast cancer patients

Duration of follow up was from the date of the patient's (first) surgery to the date of their last follow up. Maximum follow up was from January 1998 to February 2016. Subject, tumor and treatment factors were examined to identify factors associated with an increased risk of two types of recurrence and death.

We consider here two different types of recurrent events which could be associated. Moreover, death is considered as a dependent terminating event for the recurrences, it is necessary to analyze these recurrent events jointly with the terminal event to make valid inferences. The use of the proposed joint frailty model is justified with such data. The coefficients α1 and α2 indicate the sign of the association whether a type of recurrent event, locoronal or/and metastatic recurrences and death are significantly negatively or positively associated. The variances of the random effects (ui, vi) measure also the association between the two types of recurrent events and death and also whether there are inter relapse dependencies. With such a method, we are able to assess the association between local and distant recurrences of BC and death, and secondly the interrelapse dependency. The analysis was performed using R software (version 10.3.2).

3. Results

3.1. Data

Patient's age in this study was between 22 and 84 years with mean and standard deviation 47.84,11.75 respectively. 12.9% of patients had stage I of a disease, (49.1%) Stage II, (35.4%) Stage III and

Table 1
Frequency distribution of characteristics in patients with breast cancer.

Variable	Modalities	n(%)
Family history	No	1089(60)
	First degree	276(15.2)
	Second-degree	368(16.7)
	Missing	145(8.1)
Surgery	BCS	1071(59)
	Mastectomy	653(36)
	Missing	91(5)
Tumor Stage	I	236(12.9)
	II	889(49.1)
	III	642(35.4)
	IIII	47(2.6)
Grade	I	196(10.8)
	II	926(51)
	III	604(33.3)
	Missing	87 (4.8)
Chemotherapy	Yes	1751(96.5)
	No	64(3.5)
The number of involved lymph nodes	0	601(33.1)
	1–3	635(35)
	3–10	397(21.9)
	>10	143(7.9)
	Missing	38(2.1)
Hormone therapy	Without hormone therapy	10(2.9)
	Tamoxifen	1511(83.3)
	Letrozole	138(7.6)
	Other hormonal treatments	101(5.6)
	Missing	11(0.6)
HR status	HR+	1026(57.2)
	HR-	766 (41)
	Missing	23(1.8)
HER2	Negative	1325(73)
	Positive	272(15)
	Missing	218(12)
IHC result	3+	962(50.9)
	2+	217(14.1)
	Missing	635(35)

only 2.6% of patients were in stage IV of disease (the most dangerous stage of the disease). Frequency distribution of variables in this study is presented in Table 1. The median follow-up period created with the inverse Kaplan-Meier method was 30.57 months with a range of 6–187 months. A total of 1161 (64.1%) patients did not have a recurrence, of which 474 (19.7%) died. A total of 273 (25.5%) patients experienced a metastatic recurrence, 177 (16.5%) had one locoronal recurrences, and 10 (<1%) had two locoronal recurrences. In fact, 129 (12.1%) patients had a metastatic recurrence before dying, whereas 9 (<1%) patients had a locoronal recurrence before death. Moreover, 78 (7.3%) patients had a locoronal recurrence, then a metastatic recurrence and then died. During the follow-up, 332 (31.0%) patients had died, and the remaining patients were alive (censored) at the end of the follow-up. We assumed this censoring was independent of any type of recurrences or death. Most patients, followed over a long time, died after a distant metastasis. Their number is almost 14 times bigger than the number of patients died after a locoronal recurrence. This implies that distant metastasis is a fatal event. We applied the proposed model to analyze the different relapses and survival among these patients.

3.2. Results with joint and reduced models

The results are provided in Table 2. According to all the fitted models, the proposed and the reduced models, the risk of local, metastatic relapses, or death increased for patients with at least one positive lymph node (N+) or for patients with a grade greater than I. For all models fitted, the risk of death was not significantly different for patients younger than 40 years versus those older than 55 years, but it was significantly lower for individuals aged between 40 and 60 years compared to those older than 55 years. The risk of metastatic or locoronal relapses increased for individuals younger than 40 years compared to those older than 55 years. Tumor size (>20 mm) has a significant effect on the risks of these three events. The reduced model did not detect the effect of tumor size for the risk of local recurrences. The risk of locoronal and metastatic recurrences was higher for HER2+ patients, but no association was found with

Table 2
Analysis with multivariate frailty and reduced models of the locoronal and metastatic recurrences and death for breast cancer patients.

Variables	Modalities	Proposed (piecewise constant)		Reduced	
		HR	(95% CI)	HR	(95% CI)
For local relapses					
Age (ref: >55 years)	**≤40 years**	2.86	(1.76–4.64)	2.59	(1.77–3.93)
	>40 years and ≤55 years	1.32	(0.94–1.86)	1.46	(1.07–1.99)
Grade (ref: I)	**II**	1.63	(1.15–2.30)	1.81	(1.21–2.69)
	III	2.05	(1.33–3.17)	1.84	(1.18–2.92)
The number of involved lymph nodes (ref: 0)	**1–3**	2.45	(1.49–4.03)	1.41	(1.04–1.91)
	3–10	4.18	(3.67–7.32)	2.96	(1.55–4.09)
	>10	7.61	(4.07–12.73)	5.83	(3.52–9.06)
Tumor size (ref: <20 mm)	**≥20 mm**	1.61	(1.15–2.25)	1.34	(0.98–1.86)
HER2+(ref: No)	**Yes**	1.83	(1.18–2.82)	1.59	(1.09–2.34)
Type of surgery (ref: BCS)	**mastectomy**	0.63	(0.12–1.89)	0.93	(0.15–0.99)
Radiotherapy(RT) **(ref: No Radiotherapy)**	**Radiotherapy**	0.58	(0.14–0.97)	0.81	(0.37–2.43)
Use of trastuzumab **(ref: No use)**	**Use of trastuzumab**	0.34	(0.14–0.93)	0.76	(0.25–1.39)
Chemotherapy **(ref: No Chemotherapy)**	**Chemotherapy**	0.89	(0.47–1.25)	1.28	(0.93–2.41)
hormone therapy **(ref: No hormone therapy)**	**hormone therapy**	0.76	(1.48–2.41)	1.16	(0.87–1.55)
For metastatic relapses					
Age (ref: >55 years)	**≤40 years**	2.81	(1.31–6.03)	1.85	(1.29–2.67)
	>40 years and ≤55 years	0.80	(0.49–1.29)	1.09	(0.84–1.42)
Grade (ref: I)	**II**	2.79	(1.53–5.09)	1.63	(1.16–2.31)
	III	4.56	(2.26–9.20)	1.89	(1.29–2.78)
The number of involved lymph nodes(ref: 0)	**1–3**	3.47	(2.15–5.59)	1.99	(1.53–2.59)
	3–10	5.68	(2.97–8.12)	3.26	(2.05–5.74)
	>10	9.41	(5.42–14.83)	7.23	(4.02–10.27)
Tumor size (ref: <20 mm)	**≥20 mm**	3.95	(2.37–6.60)	1.55	(1.11–2.15)
HER2+(ref: No)	**Yes**	2.19	(1.10–4.34)	1.76	(1.36–2.28)
Type of surgery (ref: BCS)	**mastectomy**	1.84	(0.74–3.27)	2.41	(1.34–5.06)
Use of trastuzumab **(ref: No use)**	**Use of trastuzumab**	0.94	(0.68–1.30)	0.96	(0.65–1.41)
Chemotherapy **(ref: No Chemotherapy)**	**Chemotherapy**	1.17	(0.93–1.47)	1.07	(0.75–1.53)
Radiotherapy(RT) **(ref: No Radiotherapy)**	**Radiotherapy**	0.81	(0.57–1.15)	0.72	(0.25–1.93)
hormone therapy **(ref: No hormone therapy)**	**hormone therapy**	0.47	(0.22–1.31)	1.51	(1.20–1.90)
For death					
Age (ref: >55 years)	**≤40 years**	1.22	(0.39–3.80)	0.94	(0.64–1.38)
	>40 years and ≤55 years	0.29	(0.14–0.59)	0.66	(0.51–0.84)
Grade (ref: I)	**II**	4.59	(1.79–11.74)	1.70	(1.24–2.31)
	III	14.78	(4.76–45.90)	2.36	(1.67–3.33)
The number of involved lymph nodes(ref: 0)	**1–3**	4.33	(2.06–9.08)	1.74	(1.37–2.19)
	3–10	4.28	(1.57–7.16)	5.26	(3.75–8.79)
	>10	12.71	(6.92–19.13)	8.23	(4.02–13.67)
Tumor size (ref: <20 mm)	**≥20 mm**	5.92	(2.53–13.86)	1.61	(1.27–2.04)
HER2+(ref: No)	**Yes**	2.10	(0.75–5.85)	1.33	(0.97–1.83)
Type of surgery (ref: BCS)	**mastectomy**	1.27	(1.03–2.84)	2.71	(1.16–4.31)
Use of trastuzumab **(ref: No use)**	**Use of trastuzumab**	3.58	(1.92–6.23)	2.58	(0.77–5.31)
Chemotherapy **(ref: No Chemotherapy)**	**Chemotherapy**	2.82	(1.73–5.02)	1.96	(0.47–3.64)
hormone therapy **(ref: No hormone therapy)**	**hormone therapy**	1.87	(0.23–3.07)	2.06	(0.97–5.14)
$\theta = \text{var}(u_i)$ (SE)		1.10	(0.11)		
$\eta = \text{var}(v_i)$ (SE)		7.39	(0.63)		
$\alpha 1$ (SE)		−0.25	(1.45)		
$\alpha 2$ (SE)		1.66	(0.59)		
ρ (SE)		0.99	(0.01)		

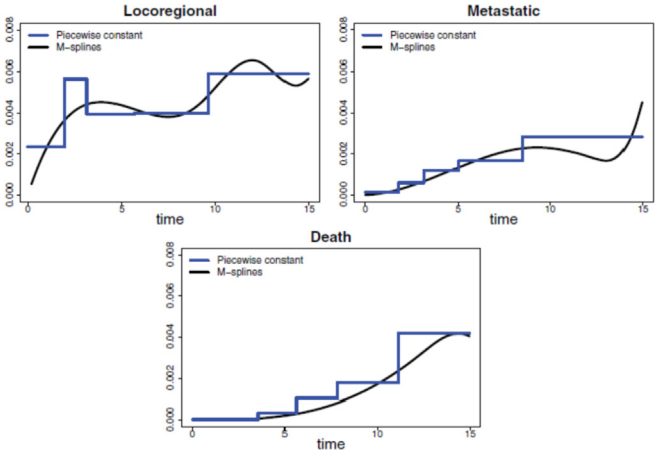


Fig. 1. Baseline hazard functions for locoronal, metastatic, and death processes after a breast cancer obtained by fitting proposed multivariate frailty models.

the risk of death. The proposed models showed that the risk of locoronal, metastatic relapses, or death increased for patients with tumors greater than 20 mm in the reduced models, we observed only a significant effect of tumor size for the risk of metastatic recurrences and death; but it was not significant for the risk of local relapses. Also, baseline hazard functions for locoronal, metastatic, and death processes after a breast cancer obtained by fitting proposed multivariate frailty models are shown in Fig. 1. According to the obtained results, we observed an underestimation in the regression coefficient in the reduced models, particularly for the death hazard function. For the proposed models, the parameters η and $\alpha 2$ are both high and significantly different from zero, this means that there was a positive and strong association between the risk of metastatic relapses and death. The parameter θ was significantly different from zero too, but the parameter $\alpha 1$ was not. This means that there were interrelapses association and no dependency between the risk of death and the risk of locoronal relapses.

4. Discussion

In this paper, we presented a joint frailty model with two correlated random effects to model two types of recurrent events simultaneously with a dependent terminal event (death). The proposed model was able to indicate the dependency among the two types of recurrent events for right-censored data, but it can also handle the association between recurrent and terminal events too. We can express that the approach works well for practical situations in this study and was better than using three distinct reduced models (shared frailty models for the recurrent events and a cox model for a terminal event). This approach accounts for dependencies among outcomes, inter-relapse dependencies, and unobserved heterogeneity in data. As observed in the context of shared frailty models, the latent frailties can arrange anything that improves the fit of the model. The variable HR+ was significantly associated with the risk of locoronal and metastatic recurrences, and death for all fitted models ($P < 0.05$). The time-varying effect of this variable has also been noticed in Dignam et al. [18] The correlation coefficient ρ was significantly high and different from zero, indicating a strong association between the risk of locoronal relapses and the risk of metastatic relapses. The dependencies obtained here confirmed what we found in Refs. [5,6,20].

One key advantage of this proposed approach is that different covariate effects can be assessed by the two parts of recurrence hazard functions or death hazard function; these covariates can be time-dependent or independent. In addition, they also provide information on whether one or both types of recurrences can be used as substitute endpoints for overall survival [21,22]. We noticed that locoronal relapses and death are related events. We did the same joint analysis with distant metastasis and death and we conclude that these two events are also associated. We may conclude that if we omit to consider the distant metastasis events in the analysis, we can conclude that locoronal relapses and death are highly associated, which is not totally true. Again, this shows the value of the proposed model which can deal with the whole data information and provide direct dependencies between events [23,24]. Convergence of the model could be hard to obtain in data with few events. However, convergence could be reached when the number of parameters to estimate decrease [26,27]. This study gives estimates of incidence and mortality rates in epidemiology, which are meaningful for clinicians. We also use the maximum likelihood estimation method. In several articles such as Huang and Liu, the estimation method used is a type of the expectation-maximization (EM) algorithm which does not provide a direct variance estimator of random effects [25,28]. According to few numbers of recurrent events observed in this work, several multi-state models could be investigated. Moreover, to use the same information as in our method, the number of severities which should be modeled to consider all potential states would be high and may lead to computational issues. Many other applications could be adapted to the proposed multivariate model, for instance when we want to study simultaneously three types of competing causes of failure (e.g. competing risk of death) or when we want to study the evolution of a patient's state over time, after an admission in an intensive care unit (ICU), to study infections, discharge of alive patients or death in ICU. In analyses of the natural history of cancer, there is great interest in a dynamic prediction of death, that is, in the computation of the predictive distribution of death at a certain moment in time, given the history of events (local or distant relapses) and covariates until that moment. These predictions and a measure of their accuracy are in progress, they may provide valuable insight for future research.

5. Conclusions

In conclusion, in this large population-based sample of breast cancer women, we found positive associations between multiple recurrences and death. In other words, we concluded that proposed models have properly converged. In addition, in our application, few repeated occurrence of both types, local and distant recurrences were seen. Hence, the frailties reflect more linkage between locoronal recurrences and death or between metastasis and death, than a within-patient dependence. On the other hand, these results should be considered with caution, given the small number of recurrent events.

Ethical statement

The current study was checked and approved by the Ethics Committee of the Tarbiat Modares University of Medical Sciences (IR.TMU.REC.1396.632). Also, we have read and complied with the policy of the journal on ethical consent, as stated in the Guide to Authors.

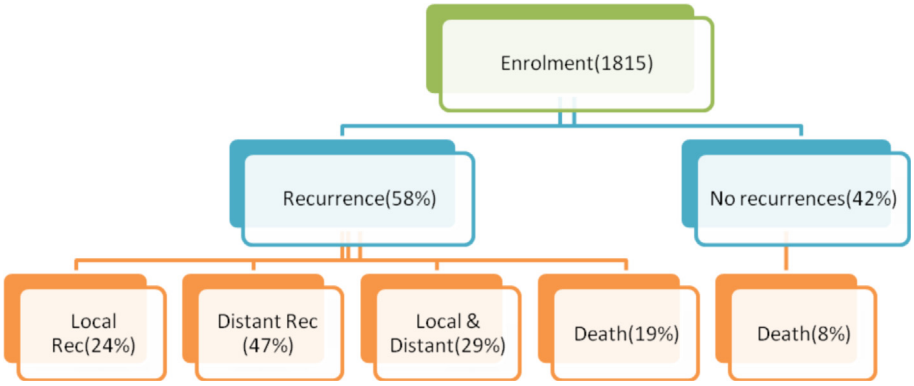
Conflicts of interest

None declared.

Acknowledgments

We would like to thank Cancer Research Center for their wholehearted cooperation for data gathering.

Appendix1. Diagram of the study design



References

[1] Cook RJ, Lawless J. The statistical analysis of recurrent events. New York: Springer Science & Business Media; 2007, ISBN 978-0-387-69809-0. https://doi.org/10.1007/978-0-387-69810-6. eBook.
[2] Osmani F, Hajizadeh E, Mansouri P. Use of smoothing methods for estimating the coefficients of time dependent rate models in survival analysis and its application in psoriasis disease. IRJE Iran J Epidemiol 2016;15(3):36–46. Available from: http://irje.tums.ac.ir/article-1-5537-en.html. 2018=(Ago 21).
[3] Liu L, Huang X. Joint analysis of correlated repeated measures and recurrent events processes in the presence of death, with application to a study on acquired immune deficiency syndrome. J R Stat Soc: Ser C Appl Stat 2009;58(1):65–81. https://doi.org/10.1111/j.1467-9876.2008.00641.x.
[4] Cancer Genome Atlas Network. Comprehensive molecular portraits of human breast tumors. Nature 2012;490(7418):61–70. https://doi.org/10.1038/nature11412. PMID: 23000897.
[5] Montagna E, Bagnardi V, Rotmensz N, et al. Breast cancer subtypes and outcome after local and ronal relapse. Ann Oncol 2012;23(2):324–31. https://doi.org/10.1093/annonc/mdr129. PMID: 21525402.
[6] O'Shaughnessy J. Extending survival with chemotherapy in metastatic breast cancer. The Oncologist 2005;3(10Supplement):20–9. https://doi.org/10.1634/theoncologist.10-90003-20. PMID: 16368868.
[7] Prentice RL, Williams BJ, Peterson AV. On the regression analysis of multivariate failure time data. Biometrika 1981;68(2):373–9. https://doi.org/10.1093/biomet/68.2.373.
[8] Andersen PK, Gill RD. Cox's regression model for counting processes: a large sample study. Ann Stat 1982;10(4):1100–20. Available from: https://www.jstor.org/stable/2240714?seq=1#page_scan_tab_contents. 2018-(Ago 17).
[9] Zeng D, Lin DY. Efficient estimation of semiparametric transformation models for counting processes. Biometrika 2006;93(3):627–40. https://doi.org/10.1093/biomet/93.3.627.
[10] Wei LJ, Lin DY, Weissfeld L. Regression analysis of multivariate incomplete failure time data by modeling marginal distributions. J Am Stat Assoc 1989;84(408):1065–73. https://doi.org/10.1080/01621459.1989.10478873.
[11] Lee EW, Wei LJ, Amato DA, Leurgans S. Cox-type regression analysis for large numbers of small groups of correlated failure time observations. In: Klein JP, Goel PK, editors. Survival analysis: state of the Art.Nato science (series E: applied sciences). Netherlands: Springer; 1992, ISBN 978-94-015-7983-4. p. 237–47. https://doi.org/10.1007/978-94-015-7983-4_14.
[12] Huang CY, Wang MC. Joint modeling and estimation for recurrent event processes and failure time data. J Am Stat Assoc 2004;99(468):1153–65. PMID: 24068850.
[13] Ye Y, Kalbfleisch JD, Schaubel DE. Semiparametric analysis of correlated recurrent and terminal events. Biometrics 2007;63(1):78–87. https://doi.org/10.1111/j.1541-0420.2006.00677.x. PMID: 17447932.
[14] Cook RJ, Lawless JF, Lakhal-Chaieb L, Lee KA. Robust estimation of mean functions and treatment effects for recurrent events under event-dependent censoring and termination: application to skeletal complications in cancer metastatic to bone. J Am Stat Assoc 2009;104(485):60–75. https://doi.org/10.1198/jasa.2009.0004.
[15] Park HS, Kim S, Kim K, et al. Pattern of distant recurrence according to the molecular subtypes in Korean women with breast cancer. World J Surg Oncol 2012;10(1):4. https://doi.org/10.1186/1477-7819-10-4. PMID: 22226178.
[16] Koscielny S, Tubiana M. The link between local recurrence and distant metastases in human breast cancer. Int J Radiat Oncol Biol Phys 1999;43(1):11–24. https://doi.org/10.1016/S0360-3016(98)00424-6. PMID: 9989510.
[17] Mazroui Y, Mathoulin-Pélissier S, MacGrogan G, Brouste V, Rondeau V. Multivariate frailty models for two types of recurrent events with a dependent terminal event: application to breast cancer data. Biom J 2013 Nov;55(6):866–84. https://doi.org/10.3322/caac.20134. PMID: 21969133.
[18] Wu X, Baig A, Kasymjanova G, et al. Pattern of local recurrence and distant metastasis in breast cancer by molecular subtype. Cureus 2016;8(12):e924. https://doi.org/10.7759/cureus.924. PMID: 28090417.
[19] Dignam JJ, Dukic V, Anderson SJ, et al. Hazard of recurrence and adjuvant treatment effects over time in lymph node-negative breast cancer. Breast Canc Res Treat 2009;116(3):595–602. https://doi.org/10.1007/s10549-008-0200-5. PMID: 18830816.
[20] Monteiro-Grillo I, Marques-Vidal P, Jorge M. Psychosocial effect of mastectomy versus conservative surgery in patients with early breast cancer. Clin Transl Oncol 2005;7(11):499–503. PMID: 16373061.
[21] Rondeau V, Mazroui Y, Gonzalez JR. frailtypack: an R package for the analysis of correlated survival data with frailty models using penalized likelihood estimation or parametrical estimation. J Stat Softw 2012;47(4):1–28. https://doi.org/10.18637/jss.v047.i04.
[22] Burzykowski T, Molenberghs G, Buyse M, Geys H, Renard D. Validation of surrogate end points in multiple randomized clinical trials with failure time end points. J R Stat Soc: Ser C Appl Stat 2001;50(4):405–22. https://doi.org/10.1111/1467-9876.00244.
[23] Wapnir IL, Anderson SJ, Mamounas EP, Geyer Jr CE, Jeong JH, Tan-Chiu E, Fisher B, Wolmark N. Prognosis after ipsilateral breast tumor recurrence and locoronal recurrences in five National Surgical Adjuvant Breast and Bowel Project node-positive adjuvant breast cancer trials. J Clin Oncol 2006;24(13):2028–37. https://doi.org/10.1200/JCO.2005.04.3273. PMID: 16648502.
[24] Schmoor C, Sauerbrei W, Bastert G, Schumacher M. Role of isolated locoronal recurrence of breast cancer: results of four prospective studies. J Clin Oncol 2000;18(8):1696–708. https://doi.org/10.1200/JCO.2000.18.8.1696. PMID: 10764430.
[25] Tanis E, van de Velde CJ, Bartelink H, et al. Locoronal recurrence after breast-

conserving therapy remains an independent prognostic factor even after an event free interval of 10 years in early stage breast cancer. Eur J Cancer 2012;48(12):1751–6. https://doi.org/10.1016/j.ejca.2012.02.051.

[26] Osmani F, Hajizadeh E, Mansoori P. Estimation of seasonal effect on the psoriasis recurrence using time dependent coefficient rates model for recurrent events. J Dermatol Cosmetic 2015;6(1):23–30. Available from: http://jdc.tums.ac.ir/browse.php?a_id=5108&sid=1&slc_lang=en. 2018-(Ago 17).

[27] Mansouri P, Hajizadeh E, Osmani F. Analysis of risk factors for psoriasis recurrence using proportional rates model. J Skin Stem Cell 2014;1(3):e25808. https://doi.org/10.17795/jssc25808.

[28] Osmani F, Hajizadeh E, Rasekhi A. Association between multiple recurrent events with multivariate modeling: a retrospective cohort study. J. Res. Health Sci. 2018 Dec 29;18(4). Available from: http://journals.umsha.ac.ir/index.php/JRHS/article/view/4378.