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Case study

Intraoperative serum lactate is not a predictor of survival after glioblastoma surgery

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ABSTRACT

Background: Cancer cells can produce lactate in high concentrations. Two previous studies examined the clinical relevance of serum lactate as a biomarker in patients with brain tumors. Patients with high-grade tumors have higher serum concentrations of lactate than those with low-grade tumors. We hypothesized that serum lactic could be used of biomarker to predictor of survival in patients with glioblastoma (GB).
Methods: This was a retrospective study. Demographic, lactate concentrations and imaging data from 275 adult patients with primary GB was included in the analysis. The progression free survival (PFS) and overall survival (OS) rates were compared in patients who had above and below the median concentrations of lactate. We also investigated the correlation between lactate concentrations and tumor volume. Multivariate analyses were conducted to test the association lactate, tumor volume and demographic variables with PFS and OS.
Results: The median serum concentration of lactate was 2.3 mmol/L. A weak correlation was found between lactate concentrations and tumor volume. Kaplan–Meier curves demonstrated similar survival in patients with higher or lower than 2.3 mmol/L of lactate. The multivariate analysis indicated that the intraoperative levels of lactate were not independently associated with changes in survival. On another hand, a preoperative T1 volume was an independent predictor PFS (HR 95%CI: 1.41, 1.02–1.82, $p = 0.006$) and OS (HR 95%CI: 1.47, 1.11–1.96, $p = 0.006$).
Conclusion: This retrospective study suggests that the serum concentrations of lactate cannot be used as a biomarker to predict survival after GB surgery.

Conclusion: To date, there are no clinically available serum biomarkers to determine prognosis in patients with high-grade gliomas. These tumors may produce high levels of lactic acid. We hypothesized that serum lactic could be used of biomarker to predictor of survival in patients with glioblastoma (GB). In this study, we collected perioperative and survival data from 275 adult patients with primary high-grade gliomas to determine whether intraoperative serum acid lactic concentrations can serve as a marker of prognosis. The median serum concentration of lactate was 2.3 mmol/L. Our analysis indicated the intraoperative levels of lactate were not independently associated with changes in survival. This retrospective study suggests that the serum concentrations of lactate cannot be used as a biomarker to predict survival after GB surgery.

1. Introduction

While normal cells produce lactate during anaerobic metabolism, cancer cells can produce this metabolite during aerobic glycolysis as well (Warburg effect) [1]. Recently, investigators have focused on lactate as a potential biomarker to discriminate between low- and high-grade brain tumors [2,3]. Mariappan

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et al. demonstrated that patients with high-grade primary brain tumors (i.e. glioblastoma, GB) show a higher intraoperative rise in the serum concentration of lactate compared to patients with low-grade tumors [3,4].

Glioblastoma cells are able to alter their metabolism in response to changes in the tumor microenvironment [5]. GB tumor cells can be display angiogenic or invasive properties based on their metabolic requirements [5]. Angiogenic GB cells rely on glycolysis for energy production while invasive cells typically found near blood vessels predominantly use the mitochondrial complex I as a source of energy [5]. Experimental data on angiogenic GB cells suggests that long-periods of hypoxia or treatment with anti-angiogenic agents cause a shift in their metabolism toward an increased rate of glycolysis. This metabolic shift correlates with a transformation from angiogenic GB cells to invasive GB cells [5,6].

Furthermore, using magnetic resonance spectroscopic (MRS), several clinical studies have demonstrated that the preoperative measurement of metabolites such as lactate can be used to predict survival outcomes [7,8]. In a recent study, Nelson et al. demonstrated that patients with higher lactate levels in MRS had poorer survival [9]. In patients with GB the preoperative tumor burden appears to be an independent predictor of survival [10,11]. For instance, elderly patients with tumors <4 cm have a significantly longer survival than those subjects with tumors >4 cm [10]. It has been suggested that larger tumors are more aggressive due to their ability to proliferate at a faster rate [10,11]. Using MRS, it has been demonstrated that rapidly growing brain tumors produce high concentrations of lactate [12–14]. However, to date there are no studies investigating the correlation between tumor volume and serum lactate concentrations.

Based on these previous findings, we conducted a retrospective study to test the association between the serum lactate concentrations, preoperative tumor volumes and survival of patients with primary GBs. We hypothesized that the intraoperative serum concentrations of lactate correlate with preoperative tumor volumes and could be used as an independent predictor of progression-free (PFS) or overall survival (OS) after resection for primary GBs.

2. Material and methods

We conducted a retrospective study that included patients with GBs who underwent surgery between January 2006 and July 2015 at The University of Texas M.D. Anderson Cancer Center. The study was approved by our institutional review board (IRB# PA12-0447). The study included patients who were 18 years or older, had surgery for primary, supratentorial GB and had received adjuvant temozolomide and radiation. Those patients who underwent craniotomy for other non-glial, recurrent or infratentorial GBs or who had missing intraoperative serum lactate measurements were excluded from the analysis. Our database contains prospectively collected demographic, tumor related, perioperative and survival data. The following variables were retrieved from the database and included in the statistical analysis: patient age, gender, body mass index (BMI), American Society of Anesthesiology (ASA) physical status, preoperative T1-weighted magnetic resonance imaging (MRI) calculated volume, preoperative T2-weighted MRI fluid-attenuated inversion-recovery (FLAIR) calculated volume, isocitrate dehydrogenase-1 (IDH-1) mutation status, intraoperative serum lactate concentrations, and survival data. Intraoperative serum lactate concentrations were collected from arterial blood gasses typically obtained after induction of general anesthesia and before skin incision or dura opening. The first available intraoperative lactate concentration measured was used for statistical analysis.

2.1. Statistical analysis

PFS and OS were the primary endpoints of this study. PFS was defined as the time between the surgery date and the date of first evidence of progression (imaging) or the date of death (whichever occurred first). Patients were censored at the last known date if neither recurrence nor death occurred. OS was defined as the time from the date of surgery to the date of death or last follow-up. Patients were censored at the last follow-up if death did not occur [15].

Summary statistics included mean, standard deviation, median, and range. Frequency counts and percentages were calculated for categorical variables. Fisher's exact test or Chi-square test was used to evaluate the association between two categorical variables. Wilcoxon rank sum test was used to evaluate the difference in a continuous variable between patient groups. Correlations between the serum lactate concentrations and tumor dimensions were evaluated by Spearman correlation coefficient. A P value <0.05 was considered significant.

The Kaplan–Meier method was used for time-to-event analysis including PFS and OS. We estimated the median time to event in months with 95% confidence interval. To evaluate the difference in time-to-event endpoints between patient groups we used the log-rank test. We performed univariate Cox proportional hazards models to evaluate the effects of continuous variables on time-to-event outcomes. To determine the association between important covariates and survival, multivariable Cox proportional hazards models were created after including important covariates that are known to be associated with a significant impact on PFS or OS. A P value <0.05 was considered significant. Statistical software SAS 9.1.3 (SAS, Cary, NC) and S-Plus 8.0 (TIBCO Software Inc., Palo Alto, CA) were used for the analyses.

3. Results

Two hundred seventy-five patients met study criteria for inclusion. The median [interquartile] age and BMI of the patient population were 58 [49–66] and 27.18 [23.99–30.27], respectively. Sixty-two percent of the patients were male (n = 170) and 84% had an ASA physical of 3 or higher (Table 1). Our database contained data on IDH-1/2 mutation status in 96 patients. Only 18 patients (19%) had IDH-1 mutated tumors. The median serum lactate concentration was 2.3 mmol/L. Serum lactate levels measured ≤2 mmol/L in 42% of patients (n = 118), between 2 and 3 mmol/L in 27% of patients (n = 75), and >3 mmol/L in 29% of patients (n = 79).

Table 1
Patients characteristics (N = 275).

Variable	Category	Median [25–75%]
Age, years		58 [49–66]
Gender, n (%)	Male	175 (68%)
	Female	105 (32%)
Body Mass index		27.18 [23.99–30.27]
ASA physical	1–2	43 (15.64)
Status, n (%)	3–4	232 (84.36)
Preoperative T1 volume		26.27 [13.32–45.35]
Preoperative T2 FLAIR		73.69 [39.49–111.75]
Intraoperative lactate (mmo/L)		2.3 [1.6–3.3]
Progression status	No	31 (11.27)
	Yes	229 (83.28)
	Unknown	15 (5.45)
Alive status	Alive	76 (27.64)
	Dead	199 (72.36)