

## ORIGINAL INVESTIGATION

## Inadequate emergence after anesthesia for elective cancer surgery: a single-center cohort study



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Received 22 January 2020; accepted 20 June 2021

Available online 3 July 2021

### KEYWORDS

Inadequate emergence;  
Emergence delirium;  
Hypoactive emergence;  
Quality of recovery;  
Cancer surgeries

### Abstract

**Background:** Inadequate emergence after anesthesia (IEA) is a common phenomenon in adult patients undergoing anesthesia. The aim of this study was to evaluate the incidence and determinants of IEA for elective cancer surgery, and to study its influence on the quality of recovery. **Methods:** In this observational, prospective study, 148 patients scheduled for elective cancer surgery were included. IEA was considered for patients having emergence delirium or hypoactive emergence applying The Richmond Agitation and Sedation Scale (RASS) 10 minutes after admission at PACU. Postoperative Quality of Recovery Scale (PQRS) was used at baseline and after surgery at minutes 15 (T15) and 40 (T40), and days 1 (D1) and 3 (D3).

**Results:** Of the 148 patients, 48 (32%) had IEA. Complete recovery at PQRS was less frequent in patients with IEA on physiological domain at T15 and D1, and activities of daily living domain at D3. Patients with IEA recovered more frequently in emotive domain at T15, T40, and D3. Determinants of IEA were age, risk of surgery, congestive heart disease, cerebrovascular disease, ASA physical status, RCRI score, and duration of anesthesia. IEA patients had more frequently postoperative delirium and stayed for longer at PACU and at the hospital.

**Conclusion:** IEA was a common phenomenon after anesthesia for elective curative surgery for cancer. Patients with IEA were older and had more comorbidities and a higher surgical risk. Patients with IEA had a less frequent complete recovery on the PD and in AD domains, and a more frequent complete recovery on the ED.

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## Introduction

The transition from unconsciousness to full wakefulness is normally a smooth and uneventful period. Inadequate emergence is characterized by a disturbance of activity level in the immediate postoperative that includes emergence delirium (ED) and hypoactive emergence (HE).<sup>1,2</sup> Emergence delirium is characterized by agitation, irritability, hypervigilance, and hyperactivity after emergence of anesthesia, without symptomatic fluctuation or lucid intervals. Hypoactive emergence is characterized by lethargy, motor activity depression, and hypovigilance.<sup>3</sup>

Usually, inadequate emergence is not associated with permanent effects and has been described primarily in pediatric populations but may occur in adults.<sup>2,4</sup> The incidence of ED in adults varies from 4.7% to 22.2% depending on the population characteristics and methods used.<sup>4</sup> The incidence of HE in adults varies from 3.2% to 8.6%.<sup>5</sup>

Some risk factors, like endotracheal intubation (ETT), volatile anesthetics, male sex,<sup>1,6–9</sup> preoperative anxiety, and postoperative pain<sup>2,4,5</sup> were associated with this harmful state.

There is a high incidence of cancer in the surgical population, particularly in older patients, with higher life expectancy being associated with a higher risk of cancer development.<sup>10,11</sup> Emergence delirium can have clinical consequences such as increase the risk of inadvertent catheter removal, attempts at self-extubation, hemorrhage, length of stay in the PostAnesthesia Care Unit (PACU), injuries to the patients as well as increased hospital costs.<sup>4,8</sup> These adverse clinical consequences may be more deleterious and important in patients with cancer because of the relatively more fragile population due to chronic disease.

The use of standardized and valid instruments may be helpful with the propose of evaluate quality of postoperative recovery after surgery and anesthesia,<sup>12</sup> enabling us to adequately identify patient-based outcomes that influence the overall recovery process.<sup>13</sup> Korttila<sup>14</sup> described an early phase of recovery after anesthesia, defined as the period before discharge from the postanesthesia care unit and that may be evaluated with the Postoperative Quality Recovery Scale (PQRS), which assesses physiologic and biologic outcomes.<sup>12,14–17</sup>

The aim of this study was to evaluate the determinants of inadequate emergence after surgery for curative neoplastic surgery. We also wanted to evaluate the influence of inadequate emergence in the quality of recovery.

## Methods

This observational and prospective study was approved by the Ethical Committee of Centro Hospitalar São João, Porto, Portugal. Written informed consent was obtained from all participants. All adult patients scheduled for elective cancer surgeries with a curative intent that were admitted to the PACU during the period of June to October 2016 were eligible to the study.

Exclusion criteria were patient refusal, the incapacity of providing informed consent, age under 18 years, foreign nationality, known psychiatric or neurological disease, and a score of < 25 in the mini-mental state examination (MMSE).<sup>18</sup>

All patients were interviewed either in the night before surgery or on the day of surgery, at least three hours before surgery in the surgical ward. A small interview was conducted to obtain consent, perform the MMSE test, and collect the medical history.

Clinical risk factors (history of ischemic heart disease, history of compensated or prior heart failure, history of cerebrovascular disease, diabetes mellitus, and renal insufficiency) and surgical risk were evaluated according to the Cardiac Risk Stratification for Noncardiac Surgical Procedures of the 2007 guidelines on Perioperative Cardiovascular Evaluation and Care for Noncardiac Surgery of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines.<sup>19</sup>

The patients' characteristics were age, gender, benzodiazepine administration before surgery, chronic benzodiazepines use, Statins use, American Society of Anesthesiologists physical status (ASA-PS), Revised Cardiac Risk Index (RCRI), type of anesthesia, postoperative nausea and vomiting, length of stay (LOS) in the PACU, and in the hospital.

Vulnerability was evaluated using the Clinical Frailty Scale, with frailty being defined as a score  $\geq$  of 4 on this scale.<sup>20</sup>

We considered a disability score greater than or equal to 25% to indicate disability, based on the WHODAS questionnaire.<sup>21</sup>

Inadequate emergence of anesthesia (IEA) was considered for patients having emergence delirium or hypoactive emergence. The Richmond Agitation and Sedation Scale (RASS) applied 10 minutes after admission at the PACU was used to identify these two types of IEA: ED, considered for patients with a RASS score higher than +1 and HE for patients with a RASS lower than -2.

The RASS is a 10-point scale with four levels of anxiety/agitation, one level to denote a calm and alert state patient, and 5 levels of sedation.<sup>22</sup>

Quality of Recovery was evaluated using the Postoperative Quality of Recovery Scale (PQRS) Portuguese version before (T0) and after surgery at minute 15 (T15) and 40 (T40), at day 1 (D1,) and day 3 (D3) evaluating recovery in five domains: physiological (PD), nociceptive (ND), emotive (ED), cognition (CD), and activities of daily living (AD). Recovery was defined as the return to baseline values or better for all questions within each domain; this was done for all the 5 domains together and for each individually. Satisfaction with anesthesia was assessed on this scale with a five-point rating question included in PQRS.

For delirium screening, at PACU the nursing delirium screening scale (Nu-DESC)<sup>23</sup> was used, and patients with a Nu-DESC score of 2 or more points were considered to have postoperative delirium. Patients were tested for delirium by the research team at the time they were formally declared to be 'ready for discharge' to the regular ward by the physician in charge of the recovery room.

Respiratory complications recorded were considered according to Murphy et al.<sup>24</sup>: upper airway obstruction requiring an intervention, mild-moderate hypoxemia, severe hypoxemia, signs of respiratory distress or impending ventilatory failure, symptoms of respiratory or upper airway muscle weakness, reintubation, and clinical evidence or suspicion of pulmonary aspiration.

Residual neuromuscular block (RNMB) was defined as TOF < 0.9 and it was quantified at admission to the PACU using acceleromyography of the adductor pollicis muscle (TOF-Watch®).

## Statistical analysis

Descriptive analysis of variables was used to summarize data. Ordinal and continuous data found not to follow a normal distribution, based on the Kolmogorov-Smirnov test for normality of the underlying population, are presented as median and interquartile range. Normally-distributed data are presented as mean and standard deviation (SD).

A univariate analysis was performed to identify determinants for inadequate recovery (emergence delirium and hypoactive recovery), using the Mann-Whitney *U* test to compare continuous variables and Chi-square or Fisher's exact test to compare proportions between two groups of subjects. Differences were considered statistically significant when  $p$  was < 0.05.

Data was analyzed using SPSS software for Windows Version 23.0 (SPSS Inc., Chicago, IL, USA).

## Results

From the 154 patients consecutively admitted in the PACU during the study period, a total of 148 patients were studied. Six patients were excluded: 2 patients were incapable of providing informed consent, 1 patient refused to participate, and 3 had a neurological or psychiatric disease. Forty-eight (32%) patients had IEA: 12 patients (8%) screened positive for ED, and 36 patients (24%) for HE.

As presented in Table 1, patients with IEA were older (median 69 vs. 64 years;  $p = 0.017$ ) and had more frequently a high-risk surgery (65% vs. 28%;  $p < 0.001$ ). Patients with IEA had more frequently disability (33% vs. 16%,  $p = 0.016$ ). Regarding the perioperative scores, patients with IEA had higher ASA-PS (48% vs. 28% with ASA-PS III/IV;  $p = 0.017$ ) and a higher RCRI score (17% vs. 9% higher than 2,  $p = 0.001$ ). They also had more frequently congestive heart disease (25% vs. 5%;  $p = 0.001$ ) and cerebrovascular disease (8% vs. 0%;  $p = 0.003$ ). The median duration of anesthesia was longer in IEA patients (180 vs. 128 minutes;  $p < 0.001$ ). IEA patients had a higher incidence of postoperative delirium (27% vs. 10%;  $p = 0.007$ ), had a longer median length of PACU stay (196 vs. 125 minutes;  $p < 0.001$ ) and a longer median length of hospital stay (7 vs. 6 days;  $p < 0.001$ ). Patients with IEA had more frequently medication use of Statins (54% vs. 28%,  $p = 0.002$ ) and Beta-Blockers (31% vs. 16%,  $p = 0.035$ ).

IEA patients had similar rates of ischemic heart disease, diabetes with insulin therapy, renal insufficiency, frailty, and rate of benzodiazepines chronic medication. Postoperatively, IEA patients have similar rates of PONV, RNMB, respiratory events, and they had similar rates of satisfaction with anesthesia.

Table 2 presents the comparison of recovery in every domain at each time point using the PQRS. Patients with IEA presented with a complete recovery at PQRS less frequently on PD at T15 (4% vs. 16%;  $p = 0.030$ ) and at D1 (53% vs. 83%;  $p < 0.001$ ), complete recovery was more frequent in ED at T15 (48% vs. 27%;  $p < 0.001$ ), T40 (55% vs. 23%;

$p < 0.001$ ) and D3 (61% vs. 30%;  $p < 0.001$ ). Patients with IEA presented more frequently an incomplete recovery at Activities of Daily Living domain measured at D3 (32% vs. 53%,  $p = 0.019$ ).

## Discussion

The major findings of this study were: 1) IEA was a common phenomenon in adult patients undergoing anesthesia for elective curative surgery for cancer; 2) patients with IEA were significantly older and had more comorbidities, were submitted to a high-risk surgery more frequently, and had higher ASA-PS and RCRI scores; 3) patients with IEA had more frequently postoperative delirium, and a higher LOS at the PACU and the hospital; and 5) patients with IEA had a less frequent complete recovery on both physiologic and activities of daily living domains, and a more frequent complete recovery on the emotional domain.

IEA is a common phenomenon in adult patients undergoing anesthesia for elective cancer surgery. Subdividing inadequate emergence, the incidence of ED was 8% and the incidence of HP was 24%, showing a higher incidence of HE, as was shown in the study of Xara et al. However, this finding is the opposite of the one in the study by Kim et al.<sup>25</sup>

We must understand our results taken into account the population set of particular patients submitted to elective curative cancer surgery, what may explain results concerning age, the presence of comorbidities, postoperative delirium, and LOS in PACU and hospital.

Age may play a considerable role in the etiology of IEA, and according to Viswanath et al.<sup>26</sup> patients over the age of 64 have a higher incidence of ED. As in a previous study by Radtke et al.,<sup>1</sup> in our study patients with IEA were older.

The risk of surgery influenced the development of IEA, and the major surgical risk was associated with the appearance of IEA in these patients, as Xara et al. have previously found.<sup>5</sup> In that study, besides age and surgical risk, ASA physical status score, RCRI score, and comorbidities were also part of preoperative determinants.

Patients with longer duration of anesthesia had a higher incidence of IEA. The duration of the anesthesia is empirically related to the duration of the surgery and is easy to understand that longer anesthesia may imply more drugs and eventually a higher magnitude of surgery.

Although described by others,<sup>8,9,25</sup> the choice of anesthesia type was not a determinant factor for IEA. This may be explained because of the considered adult population for whom pure inhalational anesthesia was not an option, and considering the fact that total intravenous anesthesia and balanced general anesthesia was included in the same group of general anesthesia.

In contrast with other studies, we could not find an association with a chronic use of benzodiazepines, as well as premedication with benzodiazepines.<sup>1,27</sup>

Beta-blockers and statins use were more frequently used by IEA patients, what may be an indirect marker for comorbidities, particularly of the cardiovascular type. In our study, IEA patients had more comorbidities as demonstrated by a higher ASA-PS and RCRI, making them more susceptible to postoperative complications. Similarly, patients that develop postoperative delirium also have an association

**Table 1** Patient baseline characteristics (n = 148).

Variable	Normal recovery	Inadequate emergence	p
Age, n (%)	64 (52.3–72.8)	69 (58–78.8)	0.017 <sup>b</sup>
< 65	52 (52)	19 (40)	
≥ 65 (years)	48 (48)	29 (60)	0.157 <sup>a</sup>
Men, n (%)	44 (44)	21 (43.8)	0.977 <sup>a</sup>
Women, n (%)	56 (56)	27 (56.3)	
ASA, n (%)			0.017 <sup>a</sup>
I/II	72 (72)	25 (71)	
III/IV	28 (28)	23 (48)	
High-risk surgery, n (%)	28 (28)	31 (65)	< 0.001 <sup>a</sup>
Ischemic heart disease, n (%)	12 (12)	9 (19)	0.271 <sup>a</sup>
Congestive heart disease, n (%)	5 (5)	12 (25)	< 0.001 <sup>c</sup>
Diabetes with insulin therapy, n (%)	5 (5)	3 (6)	0.753 <sup>c</sup>
Renal insufficiency, n (%)	4 (4)	4 (8)	0.275 <sup>c</sup>
Cerebrovascular disease, n (%)	0 (0)	4 (8)	0.003 <sup>c</sup>
RCRI, n (%)			0,001 <sup>a</sup>
≤ 2	97 (97)	40 (83)	
> 2	3(3)	8 (17)	
Chronic BB medication, n (%)	16 (16)	15 (31)	0.035 <sup>a</sup>
Chronic BZD medication, n (%)	17 (17)	10 (21)	0.572 <sup>a</sup>
BZD premedication, n (%)	22 (22)	9 (20)	0.695 <sup>a</sup>
Type of anesthesia, n (%)			0.077 <sup>a</sup>
GB	66 (66)	36 (75)	
LR	11 (11)	0 (0)	
CB	21 (21)	12 (25)	
AS	2 (2)	0 (0)	
Statins, n (%)	28 (28)	26 (54)	0.002 <sup>a</sup>
PONV, n (%)	16 (16)	8 (17)	0.918 <sup>a</sup>
RNMB, n (%)	9 (12)	9 (23)	0.132 <sup>a</sup>
Respiratory events, n (%)	24 (24)	12 (25)	0.894 <sup>a</sup>
Satisfaction, n (%)	80 (80)	33 (69)	0.132 <sup>a</sup>
Frail, n (%)	26 (26)	19 (40)	0.093 <sup>a</sup>
Disability, n (%)	16 (16)	16 (33)	0.016 <sup>a</sup>
Anesthesia duration, median (IQR)	128 (93-180)	180 (140-248)	< 0.001 <sup>b</sup>
Postop delirium, n (%)	10 (10)	13 (27)	0.007 <sup>a</sup>
PACU LOS (min), median (IQR)	125 (85–181.5)	196 (120–1000)	< 0.001 <sup>b</sup>
Hospital LOS (days), median (IQR)	6 (2.0–8.0)	7 (5.3–11.5)	< 0.001 <sup>b</sup>

ASA, American Society of Anesthesiologists; RCRI, Revised Cardiac Risk Index; BB, beta blockers; BZD, benzodiazepine; GB, general anesthesia; LR, Regional anesthesia; CB, combined anesthesia; AS, sedation and analgesia; PONV, postoperative Nausea and Vomiting; RNMB, residual neuromuscular block; Postop, postoperative; PACU, Postanesthesia Care Unit; LOS, Length Of Stay; IQR, Interquartil range.

<sup>a</sup> Pearson  $\chi^2$ .

<sup>b</sup> Mann-Whitney U test.

<sup>c</sup> Fisher's exact test.

with comorbidities,<sup>28</sup> making it possible that these cognitive alterations have a common pathway that may explain this cerebral transient failure. As found by others,<sup>5,27</sup> IEA patients had a higher incidence of postoperative delirium. Card et al.<sup>27</sup> had the same results and concluded that for patients undergoing general anesthesia, delirium beginning in the immediate postoperative period may be a common fact and may represent cerebral dysfunction present immediately upon arrival to the PACU. There may be a relation between IEA, postoperative delirium, and a longer stay at the PACU.<sup>8</sup> In fact, in our study, patients with IEA presented a higher LOS in the PACU and the hospital reflecting an impor-

tant burden in hospital consumption of resources in these patients.

The occurrence of hypoactive emergence has been viewed as an indicator of respiratory complications to occur with RNMB, but we could not confirm that association. Contrary to the findings in Xara et al.,<sup>5</sup> we could not find that IEA patients had more frequent RNMB and respiratory complications.

In our study, PQRS was able to find a less frequent complete recovery on the physiologic domain and a more frequent complete recovery on the emotional domain in patients with IEA. The physiologic domain refers to the

**Table 2** Comparison of recovery in every domain at each time point using the PQRS.

Variable	Normal recovery	Inadequate emergence	p
<b>PQRS – Physiological Domain</b>			
15 min	16/100 (16)	2/48 (4)	0.030 <sup>a</sup>
40 min	31/99 (31)	9/47 (19)	0.124 <sup>a</sup>
Day 1	80/96 (83)	25/47 (53)	< 0.001 <sup>a</sup>
<b>PQRS – Nociceptive Domain</b>			
15 min	74/100 (74)	39/48 (81)	0.331 <sup>a</sup>
40 min	69/99 (70)	35/47 (75)	0.552 <sup>a</sup>
Day 1	67/97 (69)	38/46 (83)	0.087 <sup>a</sup>
Day 3	71/97 (73)	33/93 (77)	0.658 <sup>b</sup>
<b>PQRS – Emotive Domain</b>			
15 min	27/100 (27)	23/48 (48)	0.012 <sup>a</sup>
40 min	23/99 (23.2)	26/47 (55)	< 0.001 <sup>a</sup>
Day 1	34/97 (35.1)	22/96 (48)	0.144 <sup>a</sup>
Day 3	29/96 (30.2)	27/44 (61)	< 0.001 <sup>a</sup>
<b>PQRS – Cognitive Domain</b>			
15 min	7/100 (7)	4/48 (8)	0.504 <sup>a</sup>
40 min	16/100 (16)	7/46 (15)	0.904 <sup>a</sup>
Day 1	15/98 (15)	12/45 (27)	0.107 <sup>a</sup>
Day 3	22/96 (23)	7/44 (16)	0.342 <sup>a</sup>
<b>PQRS – Activities of Daily Living Domain</b>			
40 min	21/99 (22)	6/47 (13)	0.219 <sup>a</sup>
Day 1	33/96 (34)	14/47 (30)	0.583 <sup>a</sup>
Day 3	51/96 (53)	14/44 (32)	0.019 <sup>a</sup>

PQRS, Postoperative Quality of Recovery Scale.

<sup>a</sup> Pearson  $\chi^2$ .

<sup>b</sup> Mann–Whitney U test.

measurement of systolic blood pressure, heart rate, temperature, respiratory rate, oxygen saturation, airway control, level of agitation, level of consciousness, and activity on command relate to the emergence and airway safety. Patients with IEA have a delay in recovery of the physiological domain, and they need more time to recover in this domain. The emotional domain refers to the assessment of feelings of anxiety and depression at the time of measurement, using a faces scale. Patients who had IEA had more attention from nurses and anesthesiologists in the PACU, so although the emotional domain may be altered when the patient emerges, the efforts of health professionals in PACU may allow them to recover quickly in this domain.

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Patients with IEA had a less frequent complete recovery of the activities of daily living domain measured at D3, what may be considered as the indirect consequence of more comorbidities less prone to fully recover after surgery.

There were no differences at other PQRS domains, namely cognitive and nociceptive, what may be explained by the fact that IEA was an immediate postoperative occurrence.

This study has some limitations. Because it was an observational study, no power calculation was established and therefore, our results are to be understood as explorative, and are not confirmative. The sample size may be considered too small, impairing the capacity of the study to find differences. Surgery for cancer includes a great variety of surgeries having different magnitude and severity, also resulting in a heterogeneous sample. We did not evaluate

postoperative pain that could have important implications on our results.

## Conclusions

IEA was a common phenomenon in adult patients undergoing anesthesia for elective curative surgery for cancer. Patients with IEA were older and had more comorbidities, and a higher surgical risk. Patients with IEA had more frequently postoperative delirium, and a higher length of stay at the PACU and at the hospital. Patients with IEA had a less frequent complete recovery on the PQRS physiologic domain and in the activities of daily living domain, but they had a more frequent complete recovery on the emotional domain.

## Conflicts of interest

The authors declare no conflicts of interest.

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