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Achieving long term survival in oesophagectomy patients aged over 75

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HIGHLIGHTS

- Long term survival is achievable in patients over 75 undergoing oesophagectomy.
- The only factors that significantly affect long term survival are tumour stage and resection margins.
- Peri-operative mortality in patients aged over 75 can be reduced by using an enhanced recovery after surgery programme.

ARTICLE INFO

ABSTRACT

Aims: Surgical resection is often the only curative treatment for oesophageal cancer. The aim of this retrospective cohort study was to analyse outcomes following oesophageal resection in patients aged 75 years and older and the impact of an Enhanced Recovery after Surgery (ERAS) program in this cohort.
Methods: Patients aged over 75 years undergoing oesophagectomy between 2003 and 2013 were identified from a single centre using an electronic database. Data on pre-operative comorbidity, tumour stage and length of hospital stay (LOS) were collected. Complications were classified according to the Clavien-Dindo system. Thirty day, 1- and 5-year mortality rates were calculated.
Results: 147 patients were identified with a median age of 78.5 (IQR 76.7–80.9). 33% (n = 44) had a grade 3 complication or higher. Median LOS in hospital was 16 days (IQR 13.0–22.0). Thirty-day mortality was 3.4%, 1-year and 5-year survival was 65% and 21% respectively. 45% of patients were enrolled into an Enhanced Recovery After Surgery program and they demonstrated a significantly reduced length of stay from 18 to 14 days (p = 0.005) and 30-day mortality from 6.2% to 0% (p = 0.04) compared to the time period before the program.
Conclusion: Long-term survival is achievable in patients aged over 75 years.

1. Introduction

Half of all patients with oesophageal cancer are aged over 75 [1–4]. Of the 15–20% of patients with resectable disease, the 5 year survival rates are approximately 25% [5,6]. Surgical resection is associated with a 30-day morbidity and mortality of 32% and 2% respectively [7]. The outcomes of surgical resection in elderly patients such as those aged 75 years and over are presumed to be worse as a result of a poorer physiological reserve and more co-morbidity. Indeed, increasing age is associated with a lower resection rate for oesophageal cancer [8]. However, studies demonstrate no difference in survival for patients aged 75 years and over in comparison to patients aged under 75 years [5]. In addition, there have been many improvements in peri-operative care, particularly since the introduction of an Enhanced Recovery After Surgery (ERAS) programs. The effect of this is unclear on the outcomes of patients aged 75 years and over undergoing oesophageal resection.

The Nottingham Oesophagogastric Cancer Unit (NOGU) is a regional centre for major cancer resections covering a population of 4.5 million patients, performing 180 cancer resections a year [7,9]. [centre name] have demonstrated significant improvements in outcomes in younger patient cohorts since the introduction of ERAS programs [10]. The aim of this study to analyse the outcomes of those aged over 75 undergoing oesophagectomy for oesophageal

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cancer and the effect on outcomes of the introduction of ERAS.

2. Materials and methods

This is a single centre retrospective observational study using data generated from an electronic database. The unit policy is all patients undergo a clinical review in the outpatients and multi-disciplinary team discussion prior to surgery. All patients undergoing surgery have a pre-operative assessment including clinical examination, blood tests and an electrocardiogram. Further tests such as pulmonary function, blood gas sampling were performed as clinically indicated at the discretion of the clinician. Routine follow up comprised of 3 monthly reviews for the first two years then six monthly thereafter up to a period of 5 years post operatively. These data and outcomes are all recorded electronically in the NOGU database.

2.1. Inclusion and exclusion criteria

Any patient aged over 75 at time of operation undergoing an oesophago-gastric resection for oesophageal malignancy between the dates of January 2003 and August 2013 were included. Any patient who did not undergo resection with curative intent was excluded.

2.2. Outcome measures

The outcomes of interest were post-operative morbidity and mortality plus length of stay in hospital. After discharge, all patients had an outpatient review every 3 months for the first two years and 6 monthly thereafter, up to a period of 5 years. Survival data was calculated based on follow up until August 2013, to give one and five year survival rates.

2.3. Explanatory variables

Patient's age and co-morbid status were recorded. All patients underwent a clinical review and were discussed at the MDT prior to surgery. The results were electronically documented, a patient was considered to have a disease if it was recorded as present in the electronic notes. Co-morbidities were classified by system according to their ICD-10 (International Classification of Diseases version 10) codes for analysis [11].

Disease variables included the histological TNM stage, the use of neo-adjuvant therapy and surgical approach. Details of post-operative complications were recorded in the electronic notes and graded according to the Clavien-Dindo classification system [12]. Complications were classified according to their organ of origin. Respiratory complications included post-operative pneumonia, lower respiratory tract infection, pulmonary oedema or pulmonary embolus. Cardiac complications included any post-operative arrhythmia or myocardial infarction. Specific complications of interest such as anastomotic leak were recorded individually.

In August 2009 an ERAS program was used routinely for all patients. This consisted of early mobilization with daily physiotherapy goals, optimizing analgesia with epidural or paravertebral catheters rather than opioid analgesia and early oral feeding day 5 post-operatively (Table 1).

2.4. Statistical analysis

All statistical analysis was performed using SPSS version 23 with a p value of <0.05 considered significant. Categorical variables were analysed using a Chi-Squared test. A Mann-Whitney U-test was used for continuous, non-parametric data.

Survival analysis was performed using the Kaplan-Meier estimates. Univariate analysis was undertaken for each variable using the log rank test in order to identify which variables had a significant effect on survival.

3. Results

The initial database search returned 175 patients, 28 were excluded leaving 147 patients for further analysis (Table 2).

3.1. Patient demographics

The median age was 78.5 (IQR 76.7–80.9) (Fig. 1). 72% of patients had at least one significant co-morbidity, the most common being hypertension and cardiac disease followed by endocrine disorders. Only 21% received neo-adjuvant chemotherapy prior to surgery (Table 3).

3.2. Operative variables

Resection rates increased throughout the decade; 74% (n = 97) of the resections took place in the second half of the study period. Histology showed the majority of patients had advanced disease with a high rate of circumferential margin involvement (Table 4).

3.3. Post-operative recovery and complications

The median length of stay in hospital was 16 days (IQR of 13.0–22.0). The majority of patients experienced a post-operative complication, this was usually cardio-respiratory in origin (47%,

Table 1
Enhanced recovery after surgery pathway for oesophagectomy patients [10].

Post-operative day	
Day 0	Extubate as soon as possible if on ventilator
	Analgesia: epidural or paravertebral ± patient controlled analgesia
Day 1	Leave critical care
	Physiotherapy goal: chest physio and sit out of bed
Day 2	Physiotherapy goal: chest physio, sit out of bed, walk 10 m
Day 3	Chest drain changed to valved bag
	Physiotherapy: chest physio, sit out of bed, walk the length of the ward ×2
Day 4	Physiotherapy: sit out of bed, walk the length of the ward ×3
Day 5	Commence oral intake if no clinical evidence of leak.
	Remove nasogastric tube, chest drain, epidural/paravertebral and central line. Start oral analgesia.
	Physiotherapy: walk freely on ward, shower
Day 6	Physiotherapy: shower, walk independently, climb stairs
Day 7	Full mobilization and activities of daily living. Discharge.

Table 2
Reasons for exclusion.

Reason for exclusion	n
Non-operatively managed	2
No oesophageal resection	10
Open close	10
Not malignant pathology	1
Incomplete data	5

n = 62). 8% of patients had an anastamotic leak (Table 4).

After the introduction of the ERAS program, the median length of stay in hospital was significantly reduced from 18 to 14 days in this cohort (Mann Whitney U, p = 0.005) [10]. Its introduction improved 30-day survival without an increase complication rate (Chi-squared, p = 0.04 and p = 0.532 respectively).

3.4. Survival

At time of data collection the median length of follow up was 50.2 months (IQR 26.80—78.3), during this time 95 of the 147 patients had died. Median survival was 19.4 months (IQR 7.9—53.0), one and five year survival rates were 65% and 21% respectively (Fig. 2).

Five (3.4%) patients died within 30-days. Three of these patients died from post-operative pneumonia, one from a pulmonary embolus and one from clostridium difficile colitis. 30-day mortality fell from 6.2% to 0% (p = 0.04) after the introduction of the ERAS programme.

Long-term survival did not vary by, age (p = 0.65, age groups 75—80, 80—85, over 85), sex (p = 0.15), number of co-morbidities

(p = 0.42), whether the patient had received neo-adjuvant chemotherapy (Fig. 3, p = 0.34) or operative approach (p = 0.32). The introduction of an ERAS protocol had no effect on long-term survival (Fig. 4, p = 0.57). The only factors that significantly reduced survival were a more advanced histological stage (p < 0.005) and having an R1 resection (p < 0.005).

4. Discussion

Long-term survival after oesophagectomy is achievable in patients aged over 75 years and comparable with patients of any age [7,13]. The majority (72%) of these patients have multiple co-morbidities and advanced disease. However, neither age nor co-morbid status had an effect on long-term survival; the only influential factor was disease stage. The ERAS program has significantly reduced post-operative length of stay. Despite this, the 30-day mortality was double of that recorded by the National Oesophago-Gastric Cancer Audit (3.4% vs. 1.7%) [7].

The ERAS program, implemented in 2009, has previously been shown to improve outcomes for younger patients undergoing oesophageal resections [10]. There is a lack of effectiveness data on the benefit of ERAS programs in older patients undergoing oesophageal resection. Most studies have concentrated on younger patient cohorts. This may in part, be due to concerns of older patients not being able to tolerate ERAS programs and these patients may experience an increased rate of major complications as a result [14,15]. However, ERAS programs have successfully been used in older patients undergoing colorectal resections reducing recovery times and complication rates [16,17].

Mortality and length of stay significantly reduced after the introduction of the ERAS programme in the unit. However, the data
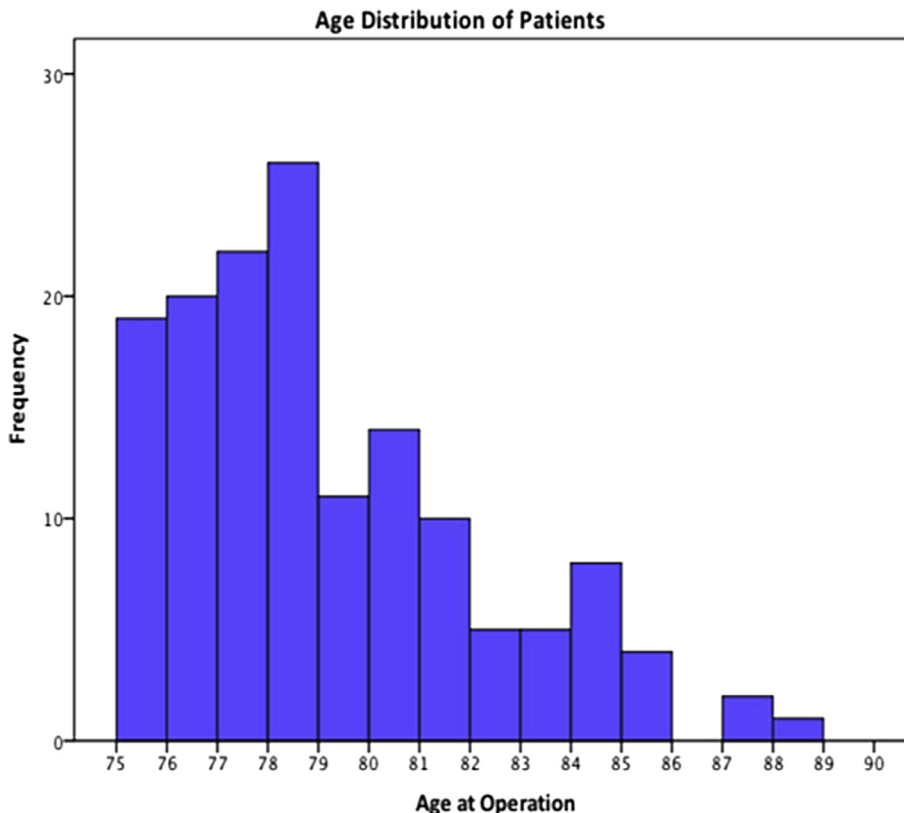

Fig. 1. Age distribution of patients.

Table 3
Patient demographics.

Patient demographics	Overall	Pre-ERAS	Post-ERAS
n	147	81	66
Median age [IQR]	78.5 [76.7—80.9]	78.8 [IQR 74.8—82.8]	78.5 [IQR 73.5—83.5]
Gender [M:F]	112:35	23:58	54:12
Co-morbidities (%)			
HTN	43 [39%]	19 [32%]	24 [49%]
Cardiac	32 [29%]	17 [28%]	15 [31%]
Endocrine	23 [21%]	12 [20%]	13 [27%]
Pulmonary	13 [12%]	6 [10%]	7 [14%]
Vascular	9 [8%]	4 [7%]	5 [10%]
Neurological	8 [7%]	5 [8%]	3 [6%]
Renal	3 [3%]	1 [2%]	2 [4%]
Hepatic	0 [0%]	0 [0%]	0 [0%]
Incomplete data	38	21	17
Number of co-morbidities			
0	29 [27%]	20 [33%]	9 [18%]
1	50 [46%]	28 [47%]	22 [45%]
2	22 [20%]	11 [18%]	11 [22%]
3	5 [5%]	1 [2%]	4 [8%]
Neo-adjuvant chemotherapy	31 [21%]	12 [15%]	19 [29%]
Disease stage			
Tis	4	3	1
1	18	10	5
2a	36	16	20
2b	19	13	6
3	69	38	31
Surgical approach			
Left thoracotomy	73	40	33
Two-stage Ivor-Lewis	60	34	27
Three stage KcKeown	10	6	4
Transhiatal	3	1	2
Two-stage Ivor-Lewis with colonic interposition	1	0	1

Table 4
Post-operative length of stay and complications.

Post operative recovery	
Median length of stay [IQR]	16 days [13—22]
Median length of stay before ERAS	18 days [14—23]
Median length of stay after ERAS	14 days [9—21]
Post-operative complications	66 [49%]
Respiratory	32 [24%]
Cardiac	30 [22%]
Acute kidney injury	3 [2%]
Anastamotic leak	10 [8%]
Pleural effusion	10 [7%]
Post-operative bleeding	4 [3%]
Wound infection	3 [2%]
Chylothorax	3 [2%]
Pneumothorax	2 [1%]
Tracheo-oesophageal fistula	1 [1%]
Clavien-Dindo complication grade	
0	50 [34%]
1	1 [1%]
2	39 [26%]
3a	20 [14%]
3b	7 [5%]
4a	4 [3%]
4b	1 [1%]
5	12 [8%]
Not recorded	13
Resection rates	
R1	55 [37%]
R0	92 [63%]
Circumferential involvement	53
Distal involvement	1
Proximal involvement	1

measures such as length of hospital stay, are known to be multi-factorial in origin. Length of stay is also influenced by the social circumstances of patients and the availability of services should support after discharge be needed as well as post-operative recovery.

The retrospective nature of this study has limitations e.g. the American Society of Anesthesiologists physical status classification system grade and World Health Organisation performance status were intermittently recorded and would have provided important information on risk factors within this group. In addition, data was only available for those managed operatively, thus preventing comparison to those who were deemed unsuitable.

Despite the achievable long-term survival demonstrated here in patients aged over 75, the multi-disciplinary team will consider age as well as the presence of multiple co-morbidities as risk factors for operative morbidity and mortality. Patient selection is key to good outcomes in this cohort, pre-operative scoring systems to predict peri-operative outcomes for older cohorts have been developed [5,18,19]. For example, the Steyerberg score was developed specifically for patients aged over 65 undergoing oesophageal resection [18,19]. However, it does not assess physiological reserve. Whilst not utilised in this study, cardio-pulmonary exercise testing, grip strength, nutritional and WHO performance status may better assess a patient's physiological status and hence suitability for surgery [20,21]. A geriatrician led, pre-operative assessment clinic has since been introduced in NOGU that utilises the quantitative tests outlined above, the outcomes of this clinic will be the subject of future research.

was collected over a decade and many improvements in peri-operative care have occurred that may confound the improvements demonstrated from the implementation of ERAS. Outcome
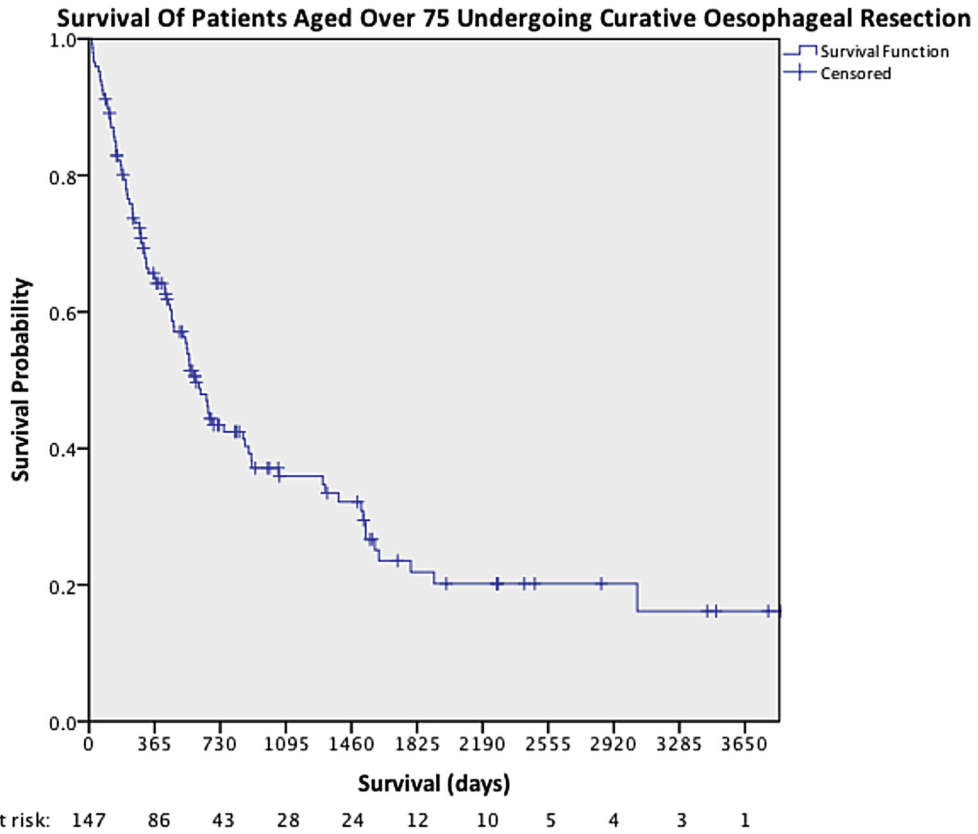
5. Conclusion

Long-term survival is achievable in an elderly population. Curative resection should not be denied on the basis of age.

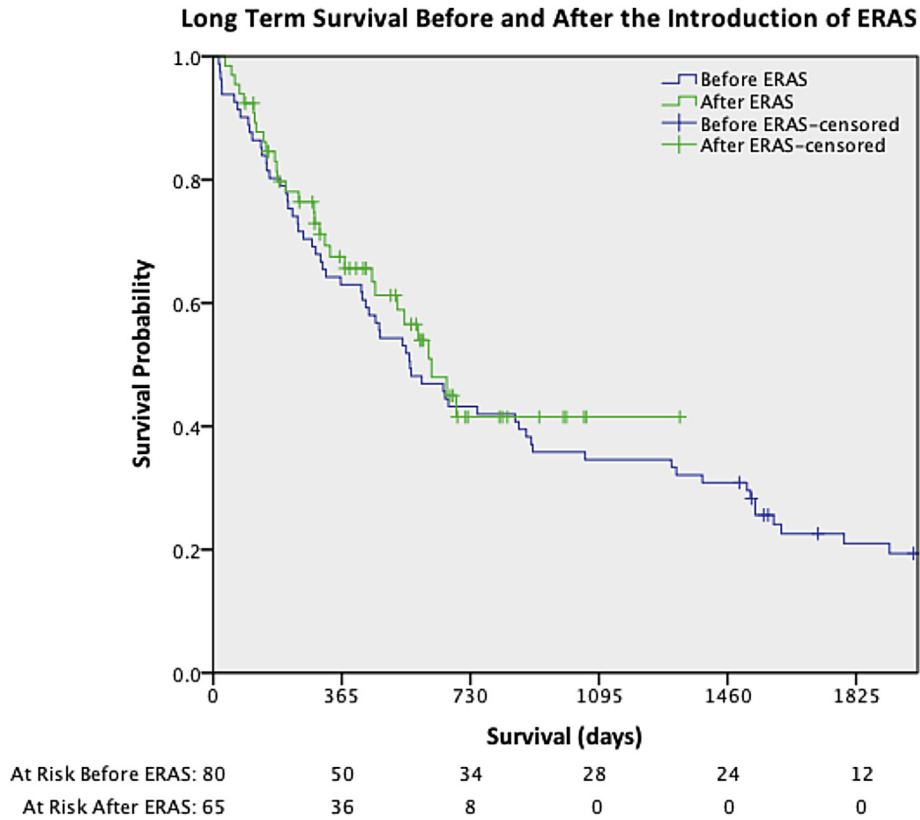**Fig. 2.** Survival of patients aged over 75 undergroing curative oesophageal resection.

Fig. 3. Long term survival before and after the introduction of ERAS.
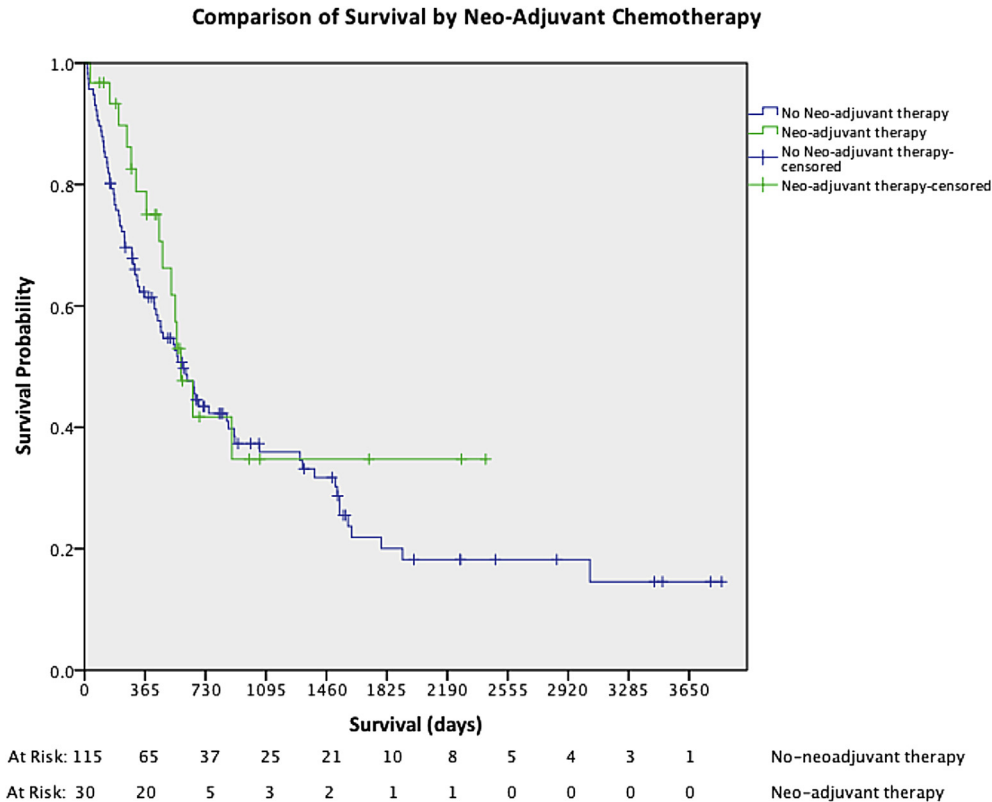
Fig. 4. Comparison of survival by neo-adjuvant chemotherapy.

Although minimized through careful patient selection and the use of enhanced recovery protocols, resection comes with significant peri-operative risks and patients with their respective careers and families need to be counselled thoroughly.

Ethical approval

Retrospective observational study, registered with trust audit department and deemed not to require ethical approval as per local guidelines.

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Author contribution

B Oakley – study design, data analysis/interpretation, writing.
C Lamb – study design, data analysis/interpretation, writing.
R Vohra – paper writing and review.
J Catton – study design, data interpretation, review.

Conflict of interest

No conflict of interests declared.

Registration of research studies

Researchregistry892.

Guarantor

James Catton.

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