ABSTRACT

Background: The correlation between hospital volume and postoperative outcomes has led to the centralization of complex procedures in several countries. However, the results reported in relation to gastric cancer (GC) are contradictory. This study aimed to analyze GC surgical volumes and 30-day postoperative mortality in Italy and to provide a simulation for modeling centralization of GC resections based on district case volumes.

Methods: A national registry was used to identify all GC resections, record mortality rates, and track the national in-border GC resection health travel. Hospitals were grouped according to caseload. Centralization of all GC procedures performed within the same district was modeled. The outcome measures were a minimal volume of 25 GC resections/year and the 30-day postoperative mortality.

Results: In 2018, 5,873 GC resections were performed in 498 Italian hospitals (mean resections per hospital per year: 11.8); the postoperative mortality rate (5.51%) was tracked from 2016–2018. GC resection health travel ranged from 2% to 50.5%, with a significant (P<0.001) difference between northern and central/southern Italy. The mean mortality rate was 7.7% in hospitals performing one to 3 GC resections per year, compared with 4.7% in those with >17 GC resections/year (P≤0.01). Most Italian districts achieved 25 procedures/year after centralization; however, 66.3% of GC cases in southern Italy vs. 42.2% in central and 52.7% in the northern regions (P<0.001) required reallocation.

Conclusion: Postoperative mortality after GC resection correlated with hospital volume. Despite health travel, most Italian districts can reach a high-volume threshold, but discrepancies in mortality rates are alarming.

Trial Registration: Research Registry Identifier researchregistry6869

Keywords: Stomach neoplasms; Hospitals, high-volume; Quality of health care; Surgical oncology

INTRODUCTION

The correlation between hospital volume and postoperative outcome has been extensively reported in the literature, as well as in relation to different upper gastrointestinal (GI) procedures [1].
This positive volume-outcome association has led to the centralization of several GI procedures in many European countries. For instance, in the UK, the Department of Health recommended centralizing curative surgical services into specialized centers in 2001 [2], whereas the Association of Surgeons in the Netherlands introduced volume standards for complex surgical procedures, including upper GI cancer resections, between 2011 and 2014 [3]. Centralization causes system reorganization, with a decline in the number of hospitals performing GI resections in both countries and an increased number of surgeries per hospital over the years [3,4]. The postoperative results obtained in the UK and Dutch experiences were in favor of the centralized process, although with documented benefits limited to a 30-day mortality in the UK [4] or to postoperative outcomes of elderly patients in the Netherlands [3]. An updated study in this field based on the Dutch Cancer Registry documented the benefits of centralization in terms of improved 2-year overall survival after centralization of non-cardia gastric adenocarcinoma [5]. In contrast, hospital volume has no effect on the surgical and oncological outcomes in gastric cancer (GC) patients treated in East Asia [6].

In Italy, GC is the fifth most common cancer in both men and women with an estimated 14,500 new cases and 8,700 GC-related deaths in 2020. Overall survival is poor, ranging from 31% to 34% in both sexes [7]. A centralized process is yet to be introduced for both GC and other malignancies. Although advocated since 2014, the referral path for cancer patients (including GC) is still ineffective; only 7 of 21 Italian provinces have a cancer referral path in place known as the Regional Oncology Network. Despite this, preliminary data obtained from 2010 to 2015 documented that postoperative mortality decreased in Italian hospitals performing more than 40 GC procedures per year, but official and updated results are still lacking [8].

The primary aim of this report was to explore the relationship between GC volume and 30-day postoperative mortality in Italy while the secondary aim was to provide a simulation for modeling centralization of GC resections based on district case volumes.

MATERIALS AND METHODS

The study was designed in accordance with the SQUIRE guidelines. Data on GC resections performed in Italy were obtained using the latest edition (2019) of the Italian National Healthcare Outcomes Programme (Piano Nazionale Esiti [PNE]) [9] and were registered at Researchregistry.com (Research Registry UIN: researchregistry6869).

Although the PNE program was not intended to provide rankings, ratings, or scores, it was developed as an assessment tool intended to support clinical audits and the organization of control programs. In its latest version, the National Agency for Regional Healthcare Services collected data using the Hospital Information System (Sistema Informativo Ospedaliero [SIO]) and the Tax Register System (Anagrafe Tributaria [AT]). The SIO collects information on all hospital admissions (elective and emergency) recorded in Italy using hospital discharge forms (Scheda di Dimissione Ospedaliera [SDO]), which are based on the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) classification. Data collected using SDO included patient demographics (gender, date/place of birth, and place of residence), admissions (date of admission, identification code of the ward/hospital of admission), discharge (date, main diagnosis, and up to 5 secondary diagnoses; main intervention and up to 5 secondary procedures with relevant dates), and diagnosis related groups. The Italian AT provides citizens a fiscal code, officially known as Codice Fiscale,
which is an alphanumeric code similar to the National Insurance and Social Security Number, currently used in the UK and US, respectively. Furthermore, the AT registry provides secured data on patient deaths. Moreover, the PNE links the SIO and AT registries to create a database of patients treated for a specific procedure and their outcomes.

The PNE registry recorded all patients who underwent GC resections performed in Italy with a primary or secondary diagnosis of malignant gastric tumor (ICD-9-CM 151, 197.8) and a surgical procedure of partial or total gastrectomy (ICD-9-CM 43.5-43.9). PNE was used for the following analyses: GC resection volumes, GC resection health travel (intended as a patient migration from the place of residence to a hospital in another Italian province to undergo surgical resection), and postoperative mortality rates.

Specifically, for volume analyses, patients were tracked if they underwent GC resection between January 1 and November 30, 2018, in any of the Italian provinces with the sole exception of Sicily (excluded from PNE volume data).

For GC health-travel analyses, all GC resections performed in Italy (including Sicily) between January 1 and December 31, 2018, were recorded. For each Italian province, any resident with a GC diagnosis who underwent resection was differentiated if the surgical treatment was performed within the same province or if treated elsewhere in Italy. Notably, healthcare in Italy is provided to all citizens and residents by a mixed public-private system, which is organized by the Ministry of Health and is province-based. Notably, all surgical/medical treatments and hospitalizations provided by public or private hospitals affiliated with this system are free of charge. However, the lack of an official referral to the treatment path allows citizens to freely move from one region or province to another to preferentially choose a hospital.

Finally, for the analysis of mortality rates, the PNE provided triennial data (2016–2018) for all Italian provinces, excluding Sicily, and defined the rate as the number of 30-day postoperative deaths after GC resections per the number of GC resections performed. Patients were excluded from the mortality rate analysis based on the following criteria: they were not residing in Italy, were younger than 18 years or older than 100 years, the hospital stay was less than 2 days, a previous hospital admission for malignant GC (ICD-9-CM 151, V10.04), and/or partial or total gastrectomy (ICD-9-CM 43.5–43.9) was performed in the previous 5 years and up to 6 months prior to the index surgery. Patient-adjusted mortality rates were calculated using the following risk adjustment variables: gender, age, and comorbidities recorded in the index admission for GC resection and in all previous admissions (Supplementary Table 1 and Supplementary Data 1). Data were analyzed after merging hospitals providing GC volumes in 2018 and mortality rates from 2016 to 2018.

Definitions
In Italy, a district is a type of administrative division managed by the local government (provincia). In contrast, a province is an administrative division within the country (regione), whereas a region is a broader area, including several provinces. Northern Italy (Italia settentrionale) is a geographical region consisting of 8 administrative provinces: Aosta Valley, Piedmont, Liguria, Lombardy, Emilia-Romagna, Veneto, Friuli-Venezia Giulia, and Trentino-Alto Adige/Südtirol. Central Italy (Italia centrale) encompasses Lazio, Marche, Tuscany, and Umbria. Southern Italy (Sud Italia or Italia meridionale) includes Abruzzo, Apulia, Basilicata, Calabria, Campania, Molise, Sicily, and Sardinia.
Centralization modeling and outcome measures

All hospitals and institutions were classified based on their locations according to the district, province, and region. The modeling analysis was performed based on the assumption of centralizing all GC procedures performed in various hospitals within the same district, as shown in Fig. 1. The first outcome measure was a minimal volume of 25 GC resections per year, as set by the Italian Ministry of Health and the Italian National Institute of Health, in accordance with the Italian Societies of Medical and Surgical Oncology to define high-volume institutions for GC treatment. To achieve this outcome, the number of patients in need of reallocation (the number of patients treated in institutions performing less than 25 resections per year, which would require treatment elsewhere) was calculated (Fig. 1). The second measured outcome was the 30-day postoperative mortality rate, which was set as less than or equal to the national average, as documented by PNE data (benchmark criteria).

Statistical analysis

Continuous variables were analyzed where data represent mean ± standard deviation (SD) and compared using a t-test, whereas categorical variables were reported using frequencies with percentages and analyzed using the $\chi^2$ test. The interquartile ranges (IQRs) were calculated to compare hospital volumes. Volumes were calculated in each district, and patients were pooled into 3 subgroups (southern Italy/Sardinia, northern Italy, and central Italy) to calculate the odds of being reallocated to another hospital; the differences among Italian regions were analyzed. Mortality rates were recorded as obtained from the PNE registry, and weighted means were calculated to assess mortality rates following centralization ($W_j = 1/n \times \sum_i w_i X_{j_i} = 1/n \times w_i$). PNE data were exported using Excel to create a database for computation of analysis and statistics were obtained using MedCalc for Windows, version 10.2.0.0. A P-value of <0.05 was considered statistically significant.

Fig. 1. (A) Modeling centralization in an Italian district: the Umbrian districts were used to illustrate the centralized method. Although the number of hospitals in each district is actual, the number of beds representing GC procedures is illustrative. In this model, GC procedures performed in different hospitals were centralized in a single institution per district. (B) GC resections performed in hospitals providing less than 25 resections per year (red beds) to be reallocated for centralization. (C) Two hospitals (one in each district) have been centralized for GC resections.

GC = gastric cancer.
**RESULTS**

In 2018, the PNE registry included 5,873 GC resections performed in 498 Italian hospitals (mean number of GC resections per hospital per year: 11.8, range 1–127, **Table 1**). Sixty institutions performed ≥25 GC resections per year with a mean number of resections per hospital of 42.0±19.5. Between 2016 and 2018, 17,561 resections were performed in 589 hospitals, with a crude mortality rate of 5.51% as reported by the PNE, and a mean hospital mortality rate of 7.2%.

**Fig. 2** illustrates the variation in health travel for GC resection in the Italian provinces, ranging from 2% in Lombardy to 50.5% in Calabria. Overall, 56.5% of residents in northern Italy underwent GC resections within the same province, compared to 24.5% in central Italy and 18.9% in southern Italy (including Sardinia and Sicily) (P<0.0001).

Merged analyses (GC volumes in 2018 and mortality rates from 2016–2018) included 5,838 GC resections performed in 493 hospitals. Institutions were categorized according to volume as follows: IQR1, 1–3 GC resections per year; IQR2, 4–7 GC resections per year; IQR3, 8–16 GC resections per year; and IQR4, 17–127 resections per year. As summarized in **Table 2**, 249 hospitals in the first 2 quartiles performed resections, representing 50.5% of institutions; however, the hospitals ranking in the top quartile performed 3,620 procedures, which is approximately 62.0% of all resections. In addition, the mean mortality rate was 7.7% in first quartile-ranked institutions compared with 4.7% in top-volume institutions (P≤0.01) (**Table 2**).

**Modeling centralization in Italian districts**

**Fig. 3** shows Italian districts reaching the minimum volume of 25 GC resections per year. As documented, most Italian districts can achieve enough resections using a centralized model. However, approximately 54.6% of patients would need to be reallocated to another institution, and this percentage was significantly (P<0.0001) higher in southern Italy than that in the central and northern regions (66.3% vs. 49.2% and 52.7%, respectively, **Table 3**).

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**Table 1. Number of GC resections performed in Italy**

| Variables | Value |
|-----------|-------|
| No. of GC resections in 2018 (498 hospitals) | 5,873 |
| Mean No. of resections | 11.8±263.3 |
| Median No. of resections | 7.0 |
| Range | 1.0–127.0 |
| GC resections in 2018 in hospitals with ≥25 resections per year (60 hospitals) | 2,518 |
| Mean No. of resections | 42.0±19.5 |
| Median No. of resections | 37.5 |
| Range | 25.0–127.0 |
| Mortality after GC resections 2016–2018 (589 hospitals) | 17,561 |
| Mortality % | 5.51 |
| Mean mortality % | 7.2±12.5 |
| Median mortality % | 3.3 |
| Range | 0.0–100.0 |
| ADJ mortality after GC resections 2016–2018 (92 hospitals) | 4.8±2.6 |
| Mean ADJ mortality % | 4.5 |
| Median ADJ mortality % | 0.0–12.9 |

Values are presented as number (%) or mean ± standard deviation. GC = gastric cancer; ADJ = adjusted.
Gastric Cancer and Hospital Volume

Fig. 2. Italian map documenting in-border health travels for GC resections; for each province, the rate of patients traveling elsewhere to receive surgical treatment has been illustrated analyzing Piano Nazionale Esiti data. GC = gastric cancer.

Table 2. Volume of resections, number of hospitals, and mortality rates

| Variables                        | IQR1  | IQR2  | IQR3  | IQR4  | P-value       |
|---------------------------------|-------|-------|-------|-------|---------------|
| GC resections per year to define IQR | 1–3   | 4–7   | 8–16  | 17–127|               |
| No. of hospitals                | 149   | 100   | 128   | 116   |               |
| No. of GC resections (2018)     | 254   | 551   | 1,413 | 3,620 |               |
| Mortality % (2016–2018; mean ± SD) | 7.7±12.5 | 8.1±8.0 | 6.5±6.9 | 4.7±4.3 | IQR1 vs. IQR4: P<0.010  
IQR2 vs. IQR4: P<0.001 
IQR3 vs. IQR4: P<0.010 |

GC = gastric cancer; IQR = interquartile range; SD = standard deviation.

Fig. 3. Modeling centralization: green areas showing Italian districts achieving 25 gastric cancer resections per year; analysis based on Piano Nazionale Esiti data.
The distribution of mortality rates before centralization and weighted mean mortality rates in districts reaching a minimum of 25 GC resections per year are shown in Fig. 4, which highlights how the centralized model reduces data dispersion. Indeed, before centralization, SD for mortality ranged between 12.5 and 4.3 (IQR1–IQR4) but was reduced to 3.07 upon centralization.

Table 3. Redistribution of patients and gastric cancer resections after centralization

| Variables                             | GC resections performed in low volume institutions (<25 GC resections per year) to be redistributed | GC resections performed in high volume institutions (≥25 GC resections per year) |
|---------------------------------------|--------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------|
| North                                 | 1,508 (52.7)                                                                                     | 1,354 (47.3)                                                                    |
| Central Italy                         | 700 (49.2)                                                                                        | 722 (50.8)                                                                       |
| South and Sardinia                    | 752 (66.3)                                                                                        | 382 (33.7)                                                                       |
| Total                                 | 2,960 (54.6)                                                                                      | 2,458 (45.4)                                                                    |

Values are presented as number (%). South and Sardinia vs. North: OR, 1.76; 95% CI, 1.531–2.040; P<0.001. South and Sardinia vs. Central Italy: OR, 2.03; 95% CI, 1.728–2.385; P<0.001. GC = gastric cancer; OR = odds ratio; CI = confidence interval.

Fig. 4. Volume of gastric cancer resections (analysis based on Piano Nazionale Esiti data) (A) Mortality rate according to interquartile range before centralization, (B) Weighted mean mortality rate after centralization.
Fig. 5. Weighted mean mortality rates after centralization (analysis based on Piano Nazionale Esiti data) (A) Weighted mean mortality in all Italian districts. (B) Blue areas showing Italian districts achieving 25 gastric cancer resections per year with a mortality rate ≤5.51%. Grey dots denote unavailable adjusted mortality rate district hospitals; blue dots denote districts where at least one hospital had an adjusted mortality rate ≤4.8%; red dots denote districts where all hospitals had an adjusted mortality rate >4.8%.

Table 4. GC volume changes according to centralization and benchmark criteria

| Variables | A. GC resections (no centralization; 498 hospitals) | B. GC resections (no centralization: just hospitals with ≥25 resections per year; 60 hospitals) | C. GC resections (after centralizations; 69 districts) | D. GC resections (after centralization: just hospitals with ADJ% mortality ≤4.8%; 36 districts) | P-value |
|-----------|---------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|---------|
| Mean ± SD | 11.8±263.3                                        | 42.0±19.5                                        | 79.0±96.0                                        | 103.6±122.4                                      | <0.001* |
| Median    | 7.0                                               | 37.5                                            | 49.0                                            | 65.0                                             |         |
| Range     | 1.0–127.0                                         | 25.0–127.0                                      | 25.0–592.0                                      | 28.0–592.0                                       |         |

GC = gastric cancer; SD = standard deviation.
*Mean GC volumes A vs. B; A vs. C; A vs. D: P<0.001.

Fig. 5 reveals weighted mean mortality rates after centralization across the country. In addition, further analysis was provided to show the districts with a 30-day postoperative weighted mean mortality rate ≤5.51%, which could mostly be achieved in northern Italian districts (Fig. 5). Districts with at least one hospital providing an adjusted mortality rate ≤4.8% have also been recorded. Finally, the change in GC volume with and without centralization is tabulated in Table 4. Indeed, modeling centralization based on district criteria selected 69 Italian districts, which would have performed a mean number of 79 GC resections per year in 2018. However, the 36 districts with a weighted mean mortality rate ≤5.51% would have performed a mean number of 103 resections per year (GC mean volume before centralization vs. centralization and vs. centralization + benchmark criteria, P<0.0001).

DISCUSSION

In this study, we provided a model for centralizing GC resections by pooling patients undergoing surgery in different Italian hospitals within the same district to achieve a minimal volume of at least 25 GC resections per year (threshold for high volume, according to the current Italian standards). As shown, this outcome is feasible and reachable. Thus,
even if a greater percentage of Italian hospitals currently perform 4–16 resections per year, it
would not be difficult to incorporate a centralized model within the districts. Here, we
also evaluated the effects on postoperative mortality rates by modeling centralization.
Unfortunately, the results highlight discrepancies with respect to several Italian regions.

Since the first report in 1979 [10], a growing number of studies have reported a significant
reduction in postoperative mortality when surgery is performed in high-volume centers
[11]. Similarly, in the Lazio province, the top-volume institution (Fondazione Policlinico
Università Agostino Gemelli IRCCS) has a reported raw mortality rate of 2.15% following
GC resection compared to a mean of 5.72% in the same province [12].

This trend has been consistently described in GI cancer surgery, particularly in pancreatic
cancer and esophageal neoplasm treatment [13,14]. Despite this, many studies have
considered volume as a proxy for other variables [15]. These include measurable and non-
measurable factors such as case-mix (complexity of operation and comorbidities), availability
of facilities for perioperative management (such as intensive care units), postoperative
complications (such as interventional radiology), and multidisciplinary treatment, including
tumor boards. All these factors should be considered for postoperative mortality, particularly
regarding “failure to rescue” events [16,17].

Quality improvement requires a complex model and several indicators. Avedis Donabedian, the
father of modern health management, proposed a framework to evaluate patient care based
on structure, process, and outcome indicators [18]. Specifically, structural indicators relate to
resources and the setting in which the treatment takes place, whereas process indicators refer
to the actual treatment given to the patient, and outcome indicators reflect the outcome of this
treatment. A recent review focusing on GC care, identified “volume” as a structure indicator
that could be further categorized if referred to the hospital or the surgeon. In both cases, this
indicator was used in studies analyzing GC to measure postoperative mortality, morbidity, and
overall survival with contradictory results; however, a high volume was not associated with a
poor outcome in any of the reviewed studies [18]. One of the major drawbacks in this field is the
difficulty in defining the threshold that should be considered as high volume, although most
studies set the cutoff at 20 GC procedures per year [19]. Accordingly, the threshold set at 25 GC
resections in the current study agrees with the literature.

Data obtained from the Dutch CRITICS trial documented higher surgical quality (measured
as the lowest Maruyama index) in hospitals with higher volumes; however, contrary to our
findings, no significant correlation between postoperative mortality and hospital volume
was found [20]. Nevertheless, when comparing clinical data, treatment characteristics,
postoperative mortality, and short-term survival before and after centralization in the
Netherlands, the 30-day postoperative mortality rate dropped from 6.5% to 4.1% and
decreased from 10.6% to 7.2% after 90 days, and the 2-year overall survival rate increased
from 55.4% to 58.5% [5].

In another US study, hospitals were ranked according to volume, with a threshold of more
than 17 GC procedures in the highest quintile and less than 4 procedures in the lowest
quintile. A significant difference was documented in perioperative mortality rates (5.7% vs.
8.9%, respectively) and 5-year overall survival rates (30.0% vs. 26.7%, respectively) [21],
which is consistent with our results.
However, it could prove difficult to compare the results obtained in Europe and the US with those reported in Eastern countries as “low-volume” institutions often have higher volumes than many of the “high-volume” Western hospitals. For instance, when comparing high- vs. low-volume settings, Korean institutions defined a university hospital with approximately 80 GC resections per year in the latter category [6].

This investigation has several limitations. For instance, the results were derived from administrative data, although PNE is a reliable source of data for analysis. In this regard, the registry excluded patients with a hospital stay shorter than 2 days, and this could have limited the mortality rate analysis by excluding very early deaths due to severe postoperative complications. Furthermore, the centralization criteria were arbitrary, defined based on geographic proximity, and not based on available resources and facilities. Indeed, given the results of health travel for GC resection, surgeries performed in Italian districts did not mirror the catchment area. As a result, the model produced districts (such as Rome or Milan) with more than 500 GC resections per year. However, rather than focusing on the extremities of the model, the primary aim of this study was to demonstrate that most districts could achieve a sufficient volume when using a centralized process. Nevertheless, the disparity in the mortality rates was alarming and should promote patient outcome as the true treatment objective. To this extent, perioperative mortality should be one of the many indicators, along with histology (such as nodal harvest and radical resection), multidisciplinary treatment (such as rate of patients undergoing neoadjuvant/adjuvant therapy, multidisciplinary team discussion, and nutritional support), patient-reported outcomes, and, importantly, patient survival. Another limitation is that the main results presented were unadjusted mortality rates and may suffer from patient comorbidities, as highlighted by the US data and experience in this field [22]. However, weighted mean mortalities were calculated to weigh each hospital volume by sample size. Thus, a larger series would make a greater contribution to the mean effect size (mortality rate).

The barriers to the centralized process deserve further annotation: in Mediterranean countries with NHS, such as Spain, a mixed process of centralized treatments and decentralized services has been developed with acknowledged results for rectal cancer procedures [23,24].

In other settings, such as California, where a different health system is in place, 67.1% of patients who underwent gastrectomy were treated at hospitals nearest to their home [25]. Understanding national in-border health tourism in Italy could prove difficult as patients intentionally travel to receive specific healthcare services despite the availability of a free NHS in their province. The indirect costs derived from these travels are currently not documented and, as such, are difficult to measure.

Notably, the current study considered a homogeneous category of surgery, since all GC procedures excluded esophageal cancers; thus, for gastric resection, it was case-mix adjusted. Unfortunately, patient-adjusted mortality rates were available only for a marginal number of hospitals, and it was not possible to provide a breakthrough in this outcome.

Finally, according to the present results, the 30-day postoperative mortality after GC resection also correlated with hospital volume in Italy. Despite medical tourism particularly affecting southern regions, most Italian districts could reach a minimal threshold of 25 GC resections per year. However, volume should not be considered as the sole criterion, since
the results obtained regarding postoperative mortality highlighted an alarming discrepancy between the northern and southern Italian regions, implicating that national health governance measures are required to address this situation.

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SUPPLEMENTARY MATERIALS

Supplementary Table 1
ICD-9 codes
Click here to view

Supplementary Data 1
Additional risk factors
Click here to view

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