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Original Research

Quality of surgery and surgical reporting for patients with primary gastrointestinal stromal tumours participating in the EORTC STBSG 62024 adjuvant imatinib study☆

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Abstract ***Background:*** EORTC (European Organisation of Research and Treatment of Cancer) 62024 is a phase III randomised trial evaluating adjuvant imatinib in patients with gastrointestinal stromal tumours (GISTs) and no evidence of residual disease after surgery in 908 patients from 11 countries participated. As surgical treatment aspects (tumour rupture and incomplete resection) contribute to the risk of recurrence, the data of primary surgery were reviewed.
Methods: The surgical record, local pathology report and a surgical questionnaire on details of the operation had to be completed when patients entered the study. Surgeons from 5 countries, covering 8 languages, reviewed the full set of data being available from 793 patients (87.3%).
Results: A known GIST was the reason for surgery in only 58% of the cases, and 12% of the

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Surgical reporting

patients were treated as an emergency. The R0-resection rate was 87%. The extent of resection was local excision in 17%, segmental resection in 59%, full-organ resection in 11% and multivisceral resection in 11%, with lymphadenectomy performed in 24% of the patients. Shelling out of the tumour was performed in 9.7%, and the proportion of tumours removed in parts was higher in the endoscopy/laparoscopy group. The incidence of tumour rupture (representing M1) was 9%. The consistency between preoperative and intraoperative findings was 82%. The postoperative complication rate was 7.3%.

Conclusion: The standardisation of surgery in this study was inferior. Given the review data, 18% of the patients should not have participated in the trial. Quality of surgery and improperly reported intraoperative details might influence the trial results. A detailed surgical questionnaire filled out by the surgeon is mandatory before entering the patient in an adjuvant trial in GIST.

1. Background

Gastrointestinal stromal tumours (GISTs), although rare, have become 'the model' of treating solid cancers with targeted therapy [1]. Surgery is the standard of care in locally confined GIST, and complete resection of the primary tumour is mandatory for the cure of the patients [2]. All trials evaluating adjuvant imatinib irrespective of the duration of treatment are based on the fact that treatment starts after R0 resection of a localised, primary GIST and metastatic disease has not be detected [3–5]. EORTC (European Organisation of Research and Treatment of Cancer) study 62024 was designed to evaluate the efficacy of two years of adjuvant imatinib after complete resection of GIST(5).

The main factors for the prognosis and the risk of dissemination of GIST are size and location of the tumour within the gastrointestinal tract, the mitotic rate of the tumour as well as the presence and type of mutations in *KIT* or *PDGFRα* genes [6, 7]. Furthermore, preoperative and intraoperative tumour rupture plays a crucial role for tumour cell spillage to the abdominal cavity [8]. Today, there are consensus guidelines on how surgery for primary GISTs should be performed, [9] and systematic reviews have been conducted comparing laparoscopic versus open resection for gastric GIST [10, 11]. Hence, the quality of surgery and surgical reporting is crucial for such a type of trial in order to be able to differentiate between adjuvant therapy in case of R0 resection and postoperative therapy in case of incomplete resection or tumour rupture.

2. Purpose of the study

The purpose of the project was to evaluate the quality of surgical procedures in patients who were recruited to the study. We also wanted to analyse the quality of reporting of surgery performed within a multinational trial. Furthermore, it was intended to assess whether the surgery documentation form used in this study was proven helpful and accurate.

3. Materials and methods

EORTC 62024 was an open-label, phase III, randomised adjuvant trial, and patients were randomly assigned to 2 years of imatinib 400 mg daily or no further therapy if their tumour was of intermediate or high risk for recurrence according to the 2002 National Institutes of Health (NIH) Consensus [12]. The primary end-point of the initial study was overall survival, later amended to 'definitive failure to the first tyrosine kinase inhibitor' [5]. Surgery had to be performed from 2 weeks to 3 months before random assignment, and surgical margins had to be either R0 or R1. Intraoperative tumour rupture was coded as R1. No prior radiation therapy or systemic treatment for GIST was allowed. Distant metastases were not permitted as were any peritoneal lesion not contiguous to the primary tumour. Regional positive lymph nodes were permitted, if they had been completely excised. Randomization was stratified by centre, risk category (high versus intermediate), tumour site (gastric versus other), and resection level (R0 versus R1).

When the EORTC 62024 study was developed in 2003, a surgery report form reporting the surgical procedure and its circumstances developed by the surgical steering committee (P.H., S.B., A.G. and Dr. Vicente Artigas, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain, see supplements) had to be completed at baseline. The items referred to the surgeon who performed the operation included whether the reason for surgery was for a known GIST, completion surgery or for an emergency. The exact location of the tumour was asked for as well as the surgical access (open, laparoscopic or endoscopic), the R-status and whether the resection specimen was retrieved in one part or several parts, and also whether the abdominal cavity had been explored was a further item. It had to be answered whether there was intraoperative or preoperative tumour rupture, whether lymphadenectomy was performed, and a classification of the type of surgery (local excision, limited resection, typical organ resection, multivisceral resection or shelling out) was required. Finally, consistency of preoperative imaging

versus intraoperative findings had to be judged, and postoperative complications and whether those led to reoperation or not had to be reported. The surgeon who originally operated the patient should have filled out the form, and a copy of the original operation report/endoscopic procedure plus the pathology report had to be submitted. However, it was not mandatory that the documents accompanied the surgery form at baseline because of time constraints. The study was closed for patient entry in October 2008.

Later, a group of surgeons experienced in GIST and covering all languages (P.H., S.B., E.S., F.v.C. and AG) reviewed the source data, i.e. original surgical reports as well as the pathology reports on the surgical specimen. The findings were documented on a refined case record form (appendix 2) and compared with the data documented at baseline on the surgery form.

3.1. Statistical analysis

We compared surgical form data reported by the sites with the data obtained at re-review of the original data using descriptive statistics only.

4. Results

For 907 out of the 908 patients (97%) who had been randomised into the study, the surgical questionnaire had been filled out. A copy of the original surgery and pathology reports had been submitted in 697 patients and was available for review (76.8% of all patients randomised, see Table 1). The surgical questionnaire (F2 form, supplement) had been filled out in 91% by data managers of the medical oncologists in median 43 days postoperatively based on letter of discharge.

4.1. Reason for surgery

A preoperatively known GIST was the reason in only 514 (57%) of the patients, and another 19 (2.1%) patients underwent completion surgery for prior incomplete tumour removal. Another tumour than GIST was the indication for surgery in 234 (26%) patients. One hundred twenty-three (14%) patients had their GIST removed during an emergency surgery procedure. In 17 (1.9%) patients, there were other reasons for surgery such as hernia repair, suspected ovarian cyst/mass or for biliary tree reconstruction. For one patient, the reason for surgery was missing.

The type of surgery performed was open laparotomy in the overwhelming majority of the cases (n = 806, 88.8%), a laparoscopic tumour approach in 95 cases (10.5%) and endoscopic removal in 5 cases (0.6%). At review, it turned out that 9 procedures had been documented wrongly: six laparoscopic and one endoscopic procedure had been done by open surgery, whereas two open surgeries in reality had been performed laparoscopically. However, open laparotomy had followed prior endoscopic or laparoscopic attempts of tumour removal in 109 cases (15.6%, 109/697).

4.2. Location of the primary tumour

There was a 97.2% concordance in documenting the site of the primary tumour for the major locations: stomach, n = 503 (55.4%); small bowel, n = 289 (31.8%); duodenum, n = 40 (4.4%); colorectum, 28 (3.1%) and oesophagus, n = 7 (0.8), see Table 2. However, in 52 patients (5.7%), the primary tumour was described to be in the abdominal cavity (n = 31), extraintestinal (n = 11) or retroperitoneum (n = 10). The review could clarify 16 cases; however, there remained at least 34 patients (3.7%) who might have been operated for metastatic disease. In addition, 30 of 91 patients undergoing laparoscopic resection did not have a full exploration of the abdominal cavity as requested per protocol, a fact that happened in only 2 of 781 patients with open laparotomy.

4.3. Surgical technique for the primary tumour

Lymphadenectomy was performed in 198 patients (21.8%), and it turned out that 16.8% of the patients had undergone regional/radical lymphadenectomy. There was a discordance of reporting in 8.6% of reviewed

Table 1
Countries participating in the trial, number of recruited patients, and availability of source data for review.

Countries	Nr. of patients randomised in the study	Nr. of patients with detailed review of surgery records, local pathology report and surgery questionnaire
France	266	258 (97%)
Belgium	14	10 (71.4%)
Great Britain	84	49 (58.3%)
Australia/ New Zealand/ Singapore	81	53 (65.4%)
Germany	126	120 (95.2%)
Poland	60	60 (100%)
The Netherlands	63	60 (95.2%)
Italy	127	64 (50.4%)
Spain	80	23 (28.7%)
Denmark	7	0
Total	**908**	**697 (76.8%)**

Table 2
Consistency about the resection level and margins (R0/R1) between initial documentation and surgical review.

Local site	Panel surgeon review		
	R0 (N = 575)	R1 (N = 120)	R2 (N = 2)
	N (%)	N (%)	N (%)
R0	531 (92.3)	13 (10.8)	0 (0.0)
R1	42 (7.3)	104 (86.7)	0 (0.0)
R2	2 (0.3)	2 (1.7)	2 (100.0)
Unknown	0 (0.0)	1 (0.8)	0 (0.0)

cases. The extent of surgery to remove the primary tumour needed to be classified as 'local excision' (endoscopically or open wedge resection), 'limited resection' (small bowel or duodenal segment, partial resection of the stomach), 'typical organ resection' (total gastrectomy, low anterior resection or abdominoperineal excision), 'multivisceral resection' (including adjacent organs) or 'other' (with verbal specification). Table 2 depicts the proportion of patients in the respective groups. The majority of patients underwent a limited resection; however, the rate of multivisceral resections added to more than 10%.

4.4. Results of surgery

At baseline, the resection level was reported to be R0 in 763 cases (84%) (see Table 3). Of these, 578 cases could be reviewed, and in 533 cases (92.2%), R0-resection status was confirmed. However, 43 cases of the R0 group were reclassified as R1 (7.4%) and another two cases as R2 resection. In the 117 cases initially classified R1, in 103 cases (88.0%) this was confirmed after review. However, 11 cases were classified now as R0 (9.4%), and another 2 cases were moved to R2 resections. There was a discordance of reporting in 8.5% of reviewed cases.

Regarding the quality of the surgical procedures, a shelling-out procedure had initially been documented in 74 cases (8.1%). Of these, only 44 cases of 58 reviewed were confirmed; however, another 12 cases were found where this fact had been missed before. There were a few (n = 35) patients overall who got their tumour removed in parts instead of monobloc. The highest proportion was found after endoscopic procedures (3/5 cases), whereas during open laparotomy, this happened only in 3.2% of the procedures, most often as a result of tumour rupture.

4.5. Incidence of tumour rupture

There was a different number of tumour ruptures in the comparison of baseline data versus source data review (see Table 4). At baseline, 73 patients (8.3%) had been reported with tumour rupture, 34 of them with preoperative and 39 patients with intraoperative rupture. After review, there were 22 more cases with preoperative or intraoperative tumour fragmentation, but 8 cases could be attributed to the 'no rupture' group summing up to an overall discordance rate of 5.6%. Most often, intraluminal bleeding of the primary tumour had been misunderstood as tumour rupture. In the review group of 697 cases, the proportion of patients with tumour rupture adds to 13.9%.

Table 3
Extent of surgery and type of surgical approach in baseline (submission) and review data.

	Nr Obs (%)	After review, Nr Obs (%)
Extent of surgery		
Local excision	253 (27.9)	260 (37.3)
Limited excision	452 (49.8)	297 (42.6)
Typical organ resection	83 (9.1)	58 (8.3)
Multivisceral resection	104 (11.5)	78 (11.2)
Other	14 (1.5)	3 (0.4)
Missing	2 (0.2)	1 (0.1)
Type of surgery		
Open laparotomy	806 (88.8)	635 (91.1)
Laparoscopy	95 (10.5)	58 (8.3)
Endoscopy	5 (0.6)	4 (0.6)
Total/total reviewed	**908**	**697**

4.6. Postoperative complications

It was reported at baseline that 838 patients (92.3%) had undergone tumour resection without perioperative complications, and in 19 patients (2.1%), reoperation was required. After review, the rates were almost identical with 92.7% of the procedures without complications and a reoperation rate of 2.6% (18/697 cases).

4.7. Consistency of preoperative versus intraoperative findings

Table 5 depicts the comparison of preoperative imaging assessment of the tumour with the intraoperative findings. A significant proportion of the patients did not undergo imaging beyond ultrasound, particularly those who underwent emergency surgery. Despite this, 89% of the preoperative assessment was consistent with the intraoperative situs. In total, 72 patients (10.3%) of the reviewed cohort intraoperatively showed more tumour than expected.

5. Discussion

In trials with adjuvant treatment after complete removal of a primary tumour, two aspects are crucial: first, the quality of the surgical procedure providing the basis for the study and evaluation of tumour situation and, second, adequate reporting of the intraoperative findings and procedures performed. There are details of surgical

Table 4
Incidence of tumour rupture: concordance between reporting at baseline versus after source data evaluation.

Panel surgeon review	Local site		
	No (N = 614)	Preoperative (N = 39)	Intraoperative (N = 44)
	N (%)	N (%)	N (%)
No	587 (95.6)	5 (12.8)	3 (6.8)
Yes, preoperative	7 (1.1)	33 (84.6)	3 (6.8)
Yes, intraoperative	15 (2.4)	1 (2.6)	38 (86.4)
Missing	5 (0.8)	0 (0.0)	0 (0.0)

Table 5
Comparison of consistency of preoperative imaging with intraoperative findings of tumour spread.

	Intra-operative judgement consistent with preop imaging findings			
	Yes (N = 582)	More tumour than expected (N = 62	Less tumour than expected (N = 5)	Not attributable (N = 48)
	N (%)	N (%)	N (%)	N (%)
Intraoperative judgement consistent with preop imaging findings – review				
Yes	528 (90.7)	21 (33.9)	3 (60.0)	12 (25.0)
No, more tumour than expected	31 (5.3)	36 (58.1)	0 (0.0)	5 (10.4)
No, less tumour than expected	1 (0.2)	0 (0.0)	1 (20.0)	1 (2.1)
Not attributable	22 (3.8)	5 (8.1)	1 (20.0)	30 (62.5)

treatment of primary GISTs that contribute to the risk of recurrence: intraoperative tumour rupture [8,13], incomplete resection [14], or inadequate assessment of the peritoneal cavity resulting in less extensive staging and undetected intra-abdominal tumour spread. Problems might be aggravated when surgery is performed as an emergency [15] or if a GIST is not at all expected to be the underlying problem and the surgeon is from a different discipline with less experience in oncologic procedures. In GISTs, this is more likely to happen than in gastrointestinal (GI) epithelial cancers. In 2003 when the trial was launched, GIST was not a fully understood disease and surgery particularly lacked standardisation and guidelines [16].

Technical surgical failures in handling the primary tumour included intraoperative tumour rupture at review (n = 54) that was more often the case than preoperatively in 43 cases. Intraoperative rupture indicates inadequate handling of the often-frail, soft and easily bleeding primary tumours. The same holds true for removal of the primary GIST in pieces instead of a monobloc resection, found in another 35 cases. Taken together, almost 10% of the patients had undergone inadequate surgery and were put at an increased risk of recurrence. When assessing single items of reporting, the complete assessment of the abdominal cavity during surgery showed the lowest correct answer rates. This happened most often after emergency surgery. It might turn out that, like in colorectal cancer [15], also in GIST, performing primary tumour removal as an emergency procedure is an adverse prognostic factor to be taken into consideration for adjuvant treatment.

The high rate of lymphadenectomies represents the missing knowledge about the biology of the disease during study recruitment. Today, local tumour resection with disease-free resection margins without lymphadenectomy is the treatment of choice for primary non-metastatic tumours [17]. Not so long before, a radical lymphadenectomy to treat primary GIST was advocated [18]. Requirements for margins of clearance in GIST had not yet been established, and thus, techniques and attitudes of surgery for GI carcinomas often were used. On the other hand, the high rate of multivisceral resection points at the fact that neoadjuvant therapy was not yet established as a recommended treatment [19].

At study entry, the presence of distant metastases was not permitted, including any peritoneal lesion not contiguous to the primary tumour. Thus, there are sources of error in the 62024 patient cohort, i.e. patients who should potentially not have entered the trial: patients with abdominal disease not attributed to a primary tumour site (n = 34), those with an incompletely examined abdominal cavity (n = 30), those with preoperative or intraoperative tumour rupture (n = 97), and those with R2 resection (n = 2) sum up to 163 patients (18%). These numbers are evenly distributed over both study arms.

However, it can be stated that the overall quality of surgery is comparable to other trials reported. In a comparative report of laparoscopic versus open resection in GIST, the postoperative morbidity was 6.3% and 19% in both groups, respectively [20]; thus the complication rate of 7.7% in the 62024 study was at an acceptable stage. Regarding R1 resections, in the US adjuvant study, this concerned 6.5% in the treatment and 9.5% in the placebo group [3], whereas in the SSG XVIII trial, the R1 status concerned 15% in the 1-year therapy arm and 19% in the 3 year's arm [4]. Data on the type of surgery or extent of resection are missing in the other randomised adjuvant studies. Interestingly, in a very recent analysis of 1000 patients treated for GIST, the subgroup of 122 patients treated for primary tumours outside the reporting centre had an R0-resection rate of 47.8% only [21]. Patients with metastatic disease who underwent resection of the primary tumour at the expert centre had a 90.5% R0-resection rate with 7.1% resulting in an R1 and 2.4% in an R2 state, indicating that even today there is a wide variability of surgical quality [21].

Of the three large adjuvant trials conducted [3–5], EORTC 62024 was the only study with a detailed surgical reporting system installed. The surgical questionnaire should preferably be completed by the surgeon who originally operated the patient, and a copy of the original operation report/endoscopic procedure record plus pathology report had to be submitted. The study

looked for adjuvant treatment that is typically handled by medical oncologists. Against intentions, 91% of the data on the surgery form were transferred from the letter of discharge after surgery by the data manager or the study nurse of the medical oncologist.

It turned out that the major cause of error had been the correct interpretation of terms such as 'the tumour was fragmented during operation' or 'tumour tissue very tender during laparoscopy examination it ruptured' to attribute them to tumour rupture as these details are typically not reported in the patient's letter of discharge. On the other hand, terms such 'other like tumour bleeding/upper GI bleeding' were inadequately classified as tumour rupture. The reporting on lymphatic nodal assessment is a less important aspect in adult patients with GIST, and pathologists typically do not assess lymph nodes in GIST once the diagnosis has been made. Thus, it is not striking that besides the correct bringing-in-line of anteceding procedures such as endoscopy or laparoscopy, the assessment of the abdominal cavity during surgery showed the lowest correct answer rates. Technical surgical failures during removal of the primary tumour were more often detected at review (n = 54) than documented before (n = 43). This referred most often to intraoperative tumour rupture indicating an inadequate handling of the often-frail, soft and easily bleeding resection specimens. This analysis is underway. A clearly defined description of procedures and the use of standardised definitions should improve the quality of trial design, conduct, and reporting [22].

Surgeons are not perfect in reporting their procedures and fail to adequately capture important data. The reporting bias in surgical studies was described recently [23], with surgery still the discipline of major impact in cancer healing but less impact in trial conduction [24]. Even in the better-controlled area of breast cancer surgery, only 41% of operative records analysed had data on intraoperative margins during breast conservation surgery [25]. When analysing the GAstric cancer Surgery Trials Reported Outcomes Standardisation (GASTROS) study, the conclusion was that 'it is necessary to standardise the reporting in future trials examining therapeutic surgical interventions for gastric cancer' to enhance the evidence base for clinical practice [26].

Pathology reports allow controlling surgery by margin and lymph node assessment. However, reports from pathology are often far from perfect when there are missing lymph nodes in resection specimens [27]. A systematic review on 179 consecutive study reports on surgery in oesophagogastric and gynaecologic cancer assessed how adverse events are reported according to the Consolidated Standards of Reporting Trials (CONSORT) statement [28]. The authors concluded that there was a poor standard of adequate reporting, which did not improve over time and also was not better when reports were published in journals with high impact factors [28]. Improvements in reporting could be made by immediate postoperative web reporting, offering the surgeon to report details of the procedure performed [29]. Unfortunately, often it is not clear at the time of surgery whether the patients will qualify for a postoperative trial. EORTC 62024 allowed entering patients in the study until three months after surgery.

The detailed analysis we took on the surgical procedures might be limited by the fact that we could only review 79.1% of the patients. We experienced that in certain countries or hospitals, a written operative record is not required and a surgical drawing sometimes was the only detail to be found. In addition, semantics play a role. Gastrectomy or colectomy is understood as total removal of that organ in Central Europe. In Anglo-American–oriented areas, respective procedures might mean only a partial gastrectomy or a hemicolectomy. As a consequence, only those people knowledgeable of what really has been done should fill out the forms at trial entry, not data managers or study nurses. Surgical oncologists must be involved in trial planning [24,26]. The Children's Oncology Group analysed 956 patients with data available for central review for the extent of surgical resection, and the overall discordance rate for the cohort was 43% [30]. The authors concluded that reporting of adverse events in cancer trials investigating surgery needs to be improved. Consequently, surgeons or surgical oncologists must be involved from the very beginning of planning a study in an adjuvant setting.

Conflict of interest statement

All authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2019.07.028.

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