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ΘΕΡΑΠΕΥΤΙΚΗ ΚΛΙΝΙΚΗ ΝΟΣ. ΑΛΕΞΑΝΔΡΑ

ΠΡΟΓΡΑΜΜΑ ΜΕΤΑΠΤΥΧΙΑΚΩΝ ΣΠΟΥΔΩΝ: «ΚΛΙΝΙΚΕΣ ΜΕΛΕΤΕΣ: ΣΧΕΔΙΑΣΜΟΣ ΚΑΙ ΕΚΤΕΛΕΣΗ»

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NEOADJUVANT IMATINIB IN RECURRENT/METASTATIC GASTROINTESTINAL STROMAL TUMORS: A SYSTEMATIC REVIEW AND META-ANALYSIS OF PROPORTIONS

"ΝΕΟΕΠΙΚΟΥΡΙΚΗ ΧΟΡΗΓΗΣΗ ΙΜΑΤΙΝΙΜΠΗΣ ΣΕ ΑΣΘΕΝΕΙΣ ΜΕ ΥΠΟΤΡΟΠΙΑΖΟΝΤΑ ΚΑΙ ΜΕΤΑΣΤΑΤΙΚΑ GISTs: ΣΥΣΤΗΜΑΤΙΚΗ ΑΝΑΣΚΟΠΗΣΗ ΚΑΙ ΜΕΤΑ-ΑΝΑΛΥΣΗ"

Νίκη Σταύρου, Ιατρός, ΑΜ 20190077

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ΑΘΗΝΑ 2024

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<u>Τα Μέλη της Εξεταστικής Επιτροπής</u>

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ΑΘΗΝΑ 2024

«Οὐκ ἔνι ἰατρικὴν εἰδέναι ὅστις μὴ οἶδεν ὅ, τι ἐστὶν ἄνθρωπος»

–Ιπποκράτης, 460-377 π.Χ.

“He who does not know what a man is knows no medicine”

–Hippocrates, 460-377 BC

ACKNOWLEDGEMENTS

I am deeply honored to express my gratitude to my professors for inspiring my engagement in high-quality research focused on bioethics and a patient-oriented approach during this exceptional master's program.

I would like to extend special thanks to my supervisor Dr. Ioannis Ntanasis – Stathopoulos and to the professors of my master thesis board Dr. Flora Zagouri and Dr. Maria Gavriatopoulou for their invaluable guidance in refining my thesis. I am also grateful to Mr. Charalampos Filippatos, scientific associate in the Department of Clinical Therapeutics, whose willingness to share his extensive knowledge of statistical methodology and support in my thesis was instrumental in the completion of this work.

Additionally, I must acknowledge Dr. Nikolaos Memos, the Sarcoma and Rare Tumor Surgeon in Aretaieio Hospital who inspired my interest in sarcomas and rare cancers during my postgraduate studies at the Medical School of Athens. He helped me conceptualize the compelling topic of my master's thesis and has consistently offered guidance and support throughout my unique journey in medical oncology.

Finally, I would like to thank my husband and my family, whose unwavering support has been vital in helping me achieve my highest goals in science and my ethics over the years.

ΕΥΧΑΡΙΣΤΙΕΣ

Νιώθω βαθιά ευγνωμοσύνη και τιμή για την φοίτησή μου στο μεταπτυχιακό πρόγραμμα σπουδών «Κλινικές Μελέτες: Σχεδιασμός και Εκτέλεση» της Ιατρικής Σχολής Αθηνών, για το οποίο εκπόνησα την παρούσα διπλωματική εργασία, καθώς και για όλους τους διδάσκοντες που συμμετείχαν σε αυτό, μεταλαμπαδεύοντάς μου την γνώση τους και τις υψηλές αξίες της βιοηθικής και της προσωποκεντρικής φροντίδας των ασθενών.

Ιδιαίτερα ευχαριστώ τον επιβλέποντά μου κο Ιωάννη Ντάναση- Σταθόπουλο και τις καθηγήτριες της εξεταστικής μου επιτροπής κα Φλώρα Ζαγουρή και κα Μαρία Γαβριατοπούλου για την συμβουλευτική και καθοδήγησή τους στην περάτωση της διπλωματικής μου. Είμαι ιδιαίτερα ευγνώμων στον κο Χαράλαμπο Φιλιππάτο, επιστημονικό συνεργάτη της Θεραπευτικής Κλινικής, ο οποίος με προθυμία συνέβαλε, προσφέροντας τις υψηλές γνώσεις του στην στατιστική ανάλυση και μεθοδολογία και την καθοδήγησή του σε αυτό το εγχείρημα.

Επιπρόσθετα, δεν θα μπορούσα να παραλείψω τις εγκάρδιες ευχαριστίες μου και την αμέριστη ευγνωμοσύνη μου στον κο Νικόλαο Μέμο, Χειρουργό Σαρκωμάτων και Σπανίων Όγκων του Αρεταιείου Νοσοκομείου, με τον οποίο συλλάβαμε την ιδέα της παρούσας εργασίας και ο οποίος ήδη από τις προπτυχιακές μου σπουδές στην Ιατρική Σχολή Αθηνών. Με ενέπνευσε στην βαθύτερη ενασχόλησή μου με τα σαρκώματα και τους σπάνιους όγκους στην ιατρική μου πορεία στην Παθολογική Ογκολογία.

Τέλος, οφείλω να ευχαριστήσω τον σύζυγό μου για την διαρκή στήριξή του στην επιστημονική μου πορεία και την οικογένειά μου που με θυσίες και αυταπάρνηση συμβάλλουν στην εξέλιξή μου ως ιατρός και ως άνθρωπος.

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ABBREVIATIONS

CI	CONFIDENCE INTERVAL
CML	CHRONIC MYELOID LEUKEMIA
CT	COMPUTED TOMOGRAPHY
GI	GASTROINTESTINAL
GISTs	GASTROINTESTINAL STROMAL TUMORS
IM	IMATINIB
MRI	MAGNETIC RESONANCE IMAGING
NF1	NEUROFIBROMATOSIS TYPE 1
OS	OVERALL SURVIVAL
PDGF	PLATELET-DERIVED GROWTH FACTOR
PFS	PROGRESSION FREE SURVIVAL

ABSTRACT

INTRODUCTION

Metastatic and recurrent gastrointestinal stromal tumors (GISTs) present challenging clinical management. Imatinib is the standard first-line therapy, improving survival and reducing tumor burden, in the neoadjuvant use, facilitating surgical intervention. This systematic review and meta-analysis assess the efficacy of neoadjuvant imatinib in metastatic/recurrent GISTs, highlighting its potential to enhance surgical outcomes and overall patient management.

METHODS

A systematic search was conducted in PubMed (end-of-search: 8 October 2024) for records on neoadjuvant imatinib therapy in recurrent/metastatic GISTs. Pooled proportions and 95% confidence intervals were calculated with common-effect and random-effects models. Subgroup and meta-regression analysis were performed, addressing heterogeneity and examining any potential association between the factors that varied, and the outcomes reported. This meta-analysis was performed following PRISMA guidelines.

RESULTS

The search identified 397 articles, and 13 were analyzed. The meta-analysis of proportions indicated that 2-year and 5-year PFS were 72% (95% CI: 53%-86%) and 43% (95% CI: 17%-74%), respectively while 2-year and 5-year OS were 85% (95% CI: 78%-90%) and 60% (95% CI: 51%-68%), respectively. The R0 resection rate was 80% (95% CI: 62%-91%), associated positively with that of radiological partial response before surgery ($\beta = 3.92$, $p<0.001$). Further meta-regression analysis yielded no significant association with preoperative imatinib duration.

CONCLUSION

This meta-analysis, involving 316 patients included in 13 studies, yielded significant outcomes for the neoadjuvant imatinib therapy of recurrent/metastatic GISTs, as it yielded favorable OS rates and high rates of microscopically complete resections. R0 rate was significantly associated with that of radiological partial response to neoadjuvant treatment; however, it was not associated with the preoperative imatinib duration.

KEYWORDS: gastrointestinal stromal tumor; gist; imatinib; neoadjuvant; metastatic; surgery

ΠΕΡΙΛΗΨΗ

ΕΙΣΑΓΩΓΗ

Οι ασθενείς με μεταστατικό/υποτροπιάζον GIST συχνά αποτελούν πρόκληση στην κλινική πράξη. Το imatinib αποτελεί την πρώτη γραμμή θεραπείας αυξάνοντας την επιβίωση των ασθενών και στοχεύοντας στην συρρίκνωση και πλήρη εκτομή του όγκου, όταν χορηγείται νεοεπικουρικά. Η παρούσα συστηματική ανασκόπηση και μετα-ανάλυση μελετά την αποτελεσματικότητα της προεγχειρητικής χορήγησης imatinib σε ασθενείς με μεταστατικό/υποτροπιάζον GIST επισημαίνοντας τα χειρουργικά οφέλη στην συνολική διαχείριση των ασθενών.

ΜΕΘΟΔΟΣ

Πραγματοποιήθηκε συστηματική αναζήτηση και ανασκόπηση στη βάση δεδομένων PubMed (έως: 8/10/2024) και υπολογίστηκαν συνολικές αναλογίες και τα 95% διαστήματα εμπιστοσύνης μέσω μετα-αναλυτικών μοντέλων. Περαιτέρω, έγινε ανάλυση κατά ομάδες και μετα-παλινδρόμηση με σκοπό την αντιμετώπιση της ετερογένειας και την ανεύρεση πιθανών συμμεταβλητών που συσχετίζονται με τα αποτελέσματα που εξήχθησαν. Η παρούσα μετα-ανάλυση διέπεται από τους κανόνες των κατευθυντήριων οδηγιών PRISMA.

ΑΠΟΤΕΛΕΣΜΑΤΑ

Από τη συστηματική αναζήτηση προέκυψαν 13 επιλέξιμα άρθρα από τα 397 συνολικά. Στα 2 έτη, η επιβίωση άνευ προόδου νόσου (PFS) ήταν 72% (95% CI: 53%-86%) και στα 5 έτη 43% (95% CI:17%-74%), ενώ στα 2 έτη η ολική επιβίωση (OS) ήταν 85% (95% CI: 78%-90%) και στα 5 έτη 60% (95% CI:51%-68%). Το συνολικό ποσοστό των πλήρων (R0) εκτομών ήταν 80% (95% CI:62%-91%) και διαπιστώθηκε ότι συσχετίζεται με την ακτινολογική ανταπόκριση των ασθενών προ του χειρουργείου ($\beta = 3.92$, $p<0.001$), ενώ δεν αποδείχθηκε συσχέτιση με την διάρκεια νεοεπικουρικής χορήγησης imatinib.

ΣΥΜΠΕΡΑΣΜΑ

Η παρούσα μετα-ανάλυση που συμπεριέλαβε 316 ασθενείς από 13 μελέτες, ανέδειξε σημαντικά αποτελέσματα στην νεοεπικουρική χορήγηση imatinib σε υποτροπιάζον/μεταστατικό GIST, αναδεικνύοντας οφέλη επιβίωσης και επίτευξης R0 εκτομών. Η επίτευξη των R0 εκτομών φάνηκε να συσχετίζεται σημαντικά με την ακτινολογική μερική ανταπόκριση του όγκου στη νεοεπικουρική θεραπεία, αλλά όχι με την διάρκεια της χορήγησης imatinib νεοεπικουρικά.

Λέξεις κλειδιά: στρωματικοί όγκοι του πεπτικού, gist, ιματινίμπη, νεοεπικουρική, μεταστατικός, χειρουργείο

INTRODUCTION

GASTROINTESTINAL CANCER

Gastrointestinal (GI) cancers include a wide array of malignant tumors that affect different components of the digestive system, such as the esophagus, stomach, pancreas, liver, colon, and rectum [1-2]. Data from the Global Cancer Observatory (GLOBOCAN) indicates that GI cancers accounted for about 26% of all newly diagnosed cancer cases globally in 2020, underscoring their substantial impact on public health. [3-7] The rates of incidence and prevalence for these types of cancers differ significantly based on geographical and demographic variables. For example, while colorectal cancer has been experiencing increasing incidence rates in many areas, the rates of gastric cancer have been seeing a decline in several high-income nations, although they remain notably elevated in certain regions of East Asia [8-9].

GASTROINTESTINAL STROMAL TUMORS

Gastrointestinal stromal tumors (GISTs) represent a small proportion of gastrointestinal cancers, accounting for approximately 1-2% of all malignant tumors in the GI tract. GISTs typically arise from the precursors of interstitial cells of Cajal located in the myenteric plexus, which play a crucial role in regulating and sustaining gastrointestinal motility, by generating electrical impulses. They represent the most common mesenchymal tumors in this area and can arise anywhere along the GI tract, although they are most frequently found in the stomach and small intestine [10-12].

The estimated incidence of GISTs ranges from about 10 to 15 per million people per year in Western countries, although this figure can vary based on geography and demographic factors. GISTs can occur at any age, but they are predominantly diagnosed in adults, typically between the ages of 50 and 70, with a slight male predominance indicated by a male-to-female ratio of approximately 1.5:1. Most GISTs arise in the stomach, accounting for roughly 60% of cases, followed by the small intestine, which comprises about 30% of occurrences. They are less commonly found in other areas such as the esophagus, colon, and rectum [13-17].

The biological behavior of GISTs can vary significantly, with some tumors being benign and small, while others may exhibit aggressive and metastatic characteristics. The assessment of risk for aggressive behavior often involves evaluating factors such as tumor size, mitotic rate, and location. GISTs are predominantly diagnosed incidentally during imaging studies or surgical procedures conducted for other medical conditions [18-20].

Risk factors of GISTs

The size of the GIST at the time of diagnosis is one of the most important prognostic indicators. Generally, smaller tumors (less than 2 cm) are associated with a lower risk of metastasis and are often considered benign. As the tumor size increases, particularly those exceeding 5 cm, the likelihood of aggressive behavior, including metastasis, also increases. Tumors larger than 10 cm are especially concerning and usually indicate a higher risk for spread.

The mitotic rate, which refers to the number of mitotic figures observed in a specified area of the tumor (usually counted per 50 high-power fields), is another crucial factor in assessing tumor aggressiveness. A higher mitotic rate suggests a more aggressive tumor that has greater potential for proliferation and metastasis. Typically, a mitotic rate of less than 5 mitoses per 50 high-power fields is considered low risk, while a rate of 5 or more indicates a higher risk of aggressive behavior [4, 18].

The anatomical location of the GIST also affects its prognosis. GISTs located in the stomach generally have a better prognosis compared to those found in the small intestine, especially if the small intestine tumors are larger. This may relate to differences in the biology of the tumors based on their site of origin and the surrounding tissue's characteristics.

GISTs are often discovered incidentally during imaging studies or surgical procedures performed for unrelated medical conditions. For example, a patient may undergo an abdominal ultrasound or CT scan for abdominal pain, and the imaging might reveal an unexpected mass in the

gastrointestinal tract. Because many GISTs do not cause symptoms until they are fairly large, they can often be diagnosed at an advanced stage.

Other risk factors for GISTs include genetic predispositions such as neurofibromatosis type 1 (NF1) and Carney-Stratakis syndrome, as well as mutations in the KIT and PDGFRA genes, which are involved in tumor development in the majority of cases [21,27].

Molecular pathogenesis of GISTs

Once a GIST is suspected based on imaging findings, confirmation of the diagnosis is achieved through histopathological examination of tumor tissue. This examination typically involves obtaining a biopsy or tissue sample, which is then analyzed under a microscope.

Gastrointestinal stromal tumors (GISTs) are predominantly characterized by specific mutations in two key genes: KIT and PDGFRA, which play a critical role in their molecular pathogenesis. The KIT gene, located on chromosome 4, encodes the receptor tyrosine kinase CD117, which is instrumental in normal cell signaling related to proliferation and survival. In about 75-80% of GIST cases, activating mutations in the KIT gene leads to constitutive activation of the receptor, fostering uncontrolled tumor growth. The most frequently observed mutations in KIT occur within the juxta membrane domain (exon 11) and the kinase domain (exons 9, 13, and 17), each of which can result in varying sensitivity to imatinib therapy.

In contrast, approximately 5-15% of GISTs harbor mutations in the PDGFRA gene, which encodes another receptor tyrosine kinase. The most common PDGFRA mutation occurs in exon 18, specifically the D842V variant, which is associated with a distinct clinical profile and often displays resistance to imatinib, necessitating alternative treatment options. These molecular alterations confer not only a growth advantage to the tumor cells but also dictate prognosis and therapeutic response, highlighting the importance of genetic testing in the management of GISTs [22-24].

Primary localized GISTs

Clinically, GISTs can cause symptoms such as abdominal pain, gastrointestinal bleeding, and obstruction, which may lead to delayed diagnosis. The cornerstone of treatment for localized primary GISTs is surgical resection. Complete surgical excision of the tumor with clear margins is the goal, as this approach offers the best chance for a potential cure. The type of surgery may vary depending on the tumor's location; for instance, a GIST in the stomach may require a partial gastrectomy, while a tumor in the small intestine may necessitate resection of a segment of the intestine. When possible, minimally invasive techniques, such as laparoscopic surgery, may be employed to reduce recovery time and surgical complications.

In cases where the risk of recurrence is significant due to larger tumor size or higher mitotic rates, adjuvant therapy with targeted treatments may be considered after surgery. Imatinib is the standard adjuvant treatment for GISTs with high-risk characteristics. Patients typically receive imatinib for a duration that can range from 3 years to indefinitely, depending on the clinician's assessment of risk and patient response. This medication works by blocking the activity of the c-KIT protein, thereby inhibiting tumor growth and reducing the likelihood of recurrence [25-27].

After surgery and any adjuvant treatment, ongoing follow-up is critical. Regular imaging studies, such as computed tomography (CT) or magnetic resonance imaging (MRI) scans, are typically performed every 3 to 6 months for the first few years to monitor any signs of recurrence.

Locally advanced GISTs

The treatment of locally advanced GISTs is more complex than that of localized tumors due to the increased risk of tumor spreading and the potential for incomplete surgical resection. The approach typically involves a combination of targeted therapy, surgical intervention, and careful monitoring, depending on the specific characteristics of the tumor and individual patient factors.

Neoadjuvant therapy with imatinib is often employed. This therapy has several benefits, including tumor shrinkage, which can make the tumor operable and easier to resect. Additionally, the response to imatinib can provide insights into the biology of the tumor, which may assist in guiding further treatment. Neoadjuvant treatment usually lasts several months, and the decision to proceed with surgery is based on the tumor's response to therapy, assessed through imaging studies and clinical evaluation [22].

If the tumor shrinks sufficiently and surgical resection becomes feasible following neoadjuvant therapy, the goal remains to achieve a complete excision with negative margins. The involvement of a surgical team experienced in managing GISTs is crucial due to the potential complexities involved in resecting tumors found in anatomical locations such as the stomach or small intestine. While the aim is to remove the entire tumor along with a margin of healthy tissue, in certain cases where complete resection is not possible, surgical procedures may still be performed to alleviate symptoms, such as obstruction or bleeding, although these procedures are not curative [23].
After surgical resection, adjuvant treatment with imatinib may be recommended to reduce the risk of recurrence, typically lasting from 3 to 5 years depending on patient risk factors and clinician judgment. Regular follow-up with imaging studies and clinical evaluations is essential after treatment, usually occurring every 3 to 6 months for the first few years, as the risk of recurrence is significant during this period.

For locally advanced GISTs that cannot be completely resected or if recurrence occurs, additional targeted therapies become available. Imatinib remains the first-line treatment for unresectable or metastatic GISTs if it was not used in the neoadjuvant setting [24].

Recurrent and metastatic GISTs

Targeted therapies for recurrent and/or metastatic GISTs are crucial. Imatinib is the standard first-line treatment, especially for tumors with KIT exon 11 mutations. Imatinib is typically administered at a dose of 400 mg/day, with a potential escalation to 800 mg/day for exon 9 mutations [28-31]. Since introduction, survival rates for patients with metastatic GISTs have

significantly improved, with median overall survival now exceeding five years in many studies, compared to only 1.5 years prior to imatinib's use [28, 32-35]. Patients harboring KIT exon 11 mutations tend to respond better, showing higher response rates and longer progression-free survival than those with other mutations [36-39].

In cases where the patient has progressed on Imatinib, Sunitinib may be indicated. Sunitinib is administered at a dose of 50 mg orally once daily, typically in a schedule of 4 weeks on and 2 weeks off. Alternatively, Regorafenib is an option for patients who have experienced progression after treatment with both Imatinib and Sunitinib [40-43]. The recommended regimen for Regorafenib is 160 mg orally once daily for 21 days, followed by a 7-day break.

Lastly, Ripretinib is approved for fourth-line treatment and is intended for patients who have progressed on prior therapies, including Imatinib, Sunitinib, and Regorafenib. The typical dosing for Ripretinib is 150 mg orally once daily. While several issues remain, they should be clarified by the current clinical trials and associated laboratory studies [44-47].

Chemotherapy and radiotherapy in recurrent/ metastatic GISTs

Chemotherapy is generally not considered effective GISTs. This is largely due to the distinct biological behavior of GISTs, which typically arise from interstitial cells of Cajal or precursor cells in the gastrointestinal tract. The majority of GISTs are driven by specific genetic mutations, mainly in the KIT gene and, to a lesser extent, in the PDGFRA gene. These mutations lead to the dysregulation of signaling pathways that are not effectively targeted by conventional chemotherapeutic agents [45].

GISTs are resistant to radiotherapy and are rarely treated as a primary option due to their unique characteristics and biological behavior. These tumors typically do not respond well to conventional cytotoxic treatments, and their specific molecular features make them less effective targets for radiation therapy.

However, radiotherapy may have some roles in specific clinical situations. For example, it might be considered for palliative treatment in cases where GISTs cause localized symptoms, such as pain or bleeding, especially when surgical options are not feasible or when there is significant local tumor extension that cannot be resected. In such cases, radiation can help alleviate symptoms by shrinking the tumor or controlling its growth [46].

IMATINIB

Imatinib, marketed under the trade name Gleevec, is a selective tyrosine kinase inhibitor primarily used in the treatment of various malignancies, including chronic myeloid leukemia (CML) and GISTs. This drug strategically targets specific proteins involved in cancer cell signaling pathways, effectively inhibiting their proliferation and promoting apoptosis in cancer cells [48-52].

Pharmacodynamics

Imatinib functions as a selective tyrosine kinase inhibitor, primarily targeting the BCR-ABL fusion protein, which is responsible for the pathogenesis of chronic myeloid leukemia (CML). This fusion protein results from a genetic translocation that leads to the constitutive activation of cell signaling pathways promoting uncontrolled cell proliferation and survival. By inhibiting BCR-ABL, imatinib disrupts these signaling pathways, effectively reducing cell proliferation and inducing apoptosis, or programmed cell death, in cancer cells [53-56].

In addition to BCR-ABL, imatinib also inhibits other key tyrosine kinases, such as c-KIT, which is implicated in gastrointestinal stromal tumors, and platelet-derived growth factor (PDGF) receptors. By blocking the activity of these kinases, imatinib interferes with various processes essential for tumor growth and dissemination. Its selective action minimizes impact on normal cells, distinguishing it from conventional chemotherapeutics that affect a broader spectrum of rapidly dividing cells [57-60].

Imatinib's pharmacodynamic properties are also characterized by its ability to produce effects that are both dose-dependent and time-dependent. Higher drug concentrations lead to increased inhibition of the target kinases and, consequently, greater antitumor efficacy. Resistance to imatinib can arise due to mutations in the BCR-ABL gene or related signaling pathways, which can result in altered drug binding and reduced therapeutic effectiveness. This resistance poses significant challenges in long-term treatment and highlights the necessity for ongoing monitoring and potential modification of therapeutic strategies [61-63].

Pharmacokinetics

The pharmacokinetic profile of imatinib describes its absorption, distribution, metabolism, and excretion in the body. When administered orally, imatinib is well absorbed, with peak plasma concentration typically achieved within 2 to 4 hours after ingestion. However, its bioavailability can be influenced by food, resulting in higher absorption when taken with a meal.

Once in the bloodstream, imatinib is extensively distributed throughout the body. It has a large volume of distribution, estimated to be between 30 to 300 liters, indicating significant tissue penetration. The drug's protein binding is also noteworthy, with approximately 95% of imatinib bound to plasma proteins, particularly albumin and alpha-1 acid glycoprotein. This high protein binding affects its distribution and may influence both efficacy and safety profiles, as only the unbound fraction of the drug is pharmacologically active [64-67].

Metabolism of imatinib primarily occurs in the liver via cytochrome P450 enzymes, particularly CYP3A4, and it generates several active metabolites, with one known as CGP62221 contributing to the drug's overall pharmacological activity. In terms of excretion, the elimination half-life of imatinib ranges from 15 to 20 hours, allowing for its general recommendation of once-daily dosing. About 20-25% of the administered dose is excreted unchanged in the urine, while the majority is eliminated as metabolites

It is noteworthy that due to its metabolism by CYP3A4, imatinib may interact with other medications that induce or inhibit this enzyme, which could potentially affect its efficacy and toxicity. Therefore, careful monitoring is warranted when combining imatinib with other drugs to optimize patient outcomes.

Variability in pharmacokinetics among patients can be influenced by genetic factors, such as polymorphisms in the CYP3A4 gene, as well as external factors like age, weight, and the presence of comorbid conditions. This interindividual variability underscores the importance of personalized medicine approaches, where monitoring the plasma concentration of imatinib may guide dose adjustments and optimize the therapeutic outcome [68-70].

Patients find that they can manage these complications effectively. The overall treatment plan requires careful monitoring to assess the tumor response, which is typically evaluated through imaging studies. The assessment of tumor response is crucial, as it guides further decisions regarding surgery, including the timing of the surgical intervention in relation to the neoadjuvant therapy [71-74]

Surgical approach in recurrent/ metastatic GISTs

Surgical intervention remains a critical component of care when feasible. If metastatic disease is confined and resectable, the NCCN advises considering surgical options, particularly for localized progression. In some cases, palliative surgery may be indicated to relieve symptoms or prevent complications. Surgical intervention for metastatic GISTs, particularly in patients already on imatinib, can be considered in managing disease progression [75-78]. When patients exhibit localized metastatic disease that is amenable to resection, surgery can significantly enhance survival rates, even after systematic therapy has begun. Studies indicate that imatinib may reduce tumor burden and facilitate resection, emphasizing the importance of a multidisciplinary approach to evaluate surgical options in this context [18-20, 85-86].

The NCCN guidelines also strongly encourage the consideration of clinical trials for patients with metastatic GISTs. Participation in clinical trials may provide access to novel therapies and could be a viable treatment option for those who have exhausted standard treatments. Ongoing monitoring is crucial to evaluate the response to treatment and detect any disease progression. Routine imaging studies, such as CT scans, can help assess tumor burden and treatment efficacy, while blood tests may be conducted to evaluate overall health and the presence of disease markers [47, 87-88].

In this context, we conducted a comprehensive systematic-review and meta-analysis of studies and clinical trials on recurrent/metastatic GISTs to assess the efficacy of neoadjuvant imatinib therapy, highlighting its potential to enhance surgical outcomes and overall patient management.

MATERIALS & METHODS

The present meta-analysis was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [79]. The study protocol was discussed and agreed upon in advance by all authors.

A systematic search was conducted in the PubMed database from inception until October 8, 2024, to identify literature on the use of neoadjuvant imatinib in recurrent and/or metastatic GIST. The search algorithm used was ensured to adhere to PubMed's unique characteristics, implementing variations of key terms such as: neoadjuvant, pre-operative, imatinib, therapy, gastrointestinal stromal tumors, GIST, cancer, metastasis, metastatic, recurrent, relapse. Additionally, a snowball approach was used to capture all relevant records by reviewing the reference lists of included studies, ensuring comprehensive coverage and minimizing the risk of omitting previously cited literature.

Eligible studies included clinical trials (randomized or not) and prospective or retrospective studies focusing on adults diagnosed with recurrent/metastatic GIST that were treated with imatinib prior

to surgery. Exclusion criteria encompassed case reports, case series, reviews, in vitro and animal studies and records not available in English.

Data abstraction and effect estimates

The data abstraction encompassed: general information (first author's name, publication year, database ID), study characteristics (design, cohort size, follow-up, geographic region, number of males, age), population characteristics (locations of primary malignancy, sites of metastases, number and size of lesions, KIT mutations), intervention characteristics (preoperative imatinib therapy duration, preoperative imatinib dosage) and outcomes overall survival (OS), progression free survival (PFS), resection rates (R0 for microscopically complete resection, R1 for macroscopically complete resection and R2 for macroscopically incomplete resection) and RECIST criteria assessing the radiological response (CR for complete response, PR for partial response, SD for stable disease and PD for progressive disease). Extracted effect estimates included crude number and percentages for the outcomes alongside their 95% confidence intervals (CI).

There was no shortage of required data for the purposes of the meta-analysis. Data were independently extracted, analyzed and recorded. The finalized data form was reached after team consensus.

Statistical analysis

Extracted data for continuous numerical variables such as age and follow-up, reported in the original studies as either means or medians, were standardized to means using the method proposed by Hozo et al [80]. This conversion ensured consistency across data points, allowing for uniformity in their use for statistical analysis.

An overall analysis of proportions of OS and PFS at 2-year and 5-year timepoints and R0/R1/R2 resections was chosen as the base-case analysis to evaluate the effect of preoperative therapy with

imatinib in patients with recurrent and/or metastatic GIST. When proportions of OS and PFS at 2-year and 5-year time points were unavailable, these were either extracted from published Kaplan-Meier survival curves or calculated directly from patient outcome data provided in the eligible records.

Statistical analysis included pooling of studies as well as post meta-regressions. Common and Random-effects models were appropriately used to calculate the pooled effect estimates (proportions). Study heterogeneity was assessed by Q-test and I^2 estimations. When heterogeneity was not low (I^2 and Q-test conclusions), random-effect models results were deemed appropriate. Subgroup analysis was performed based on design and geographic region, in case of more than 5 entries. Post hoc meta-regression analysis was performed to assess whether other moderators within the study sample modified the reported effect estimates. Variables included were prespecified key study aspects from the extracted data that introduced heterogeneity and had 10 or more entries.

Across this analysis, $I^2 < 40\%$ or p(Q-test) < 0.10 was considered low heterogeneity and statistical significance was achieved by p-values < 0.05.

All statistical analysis were performed using R/R-Studio version 2024.04.2+764) (Posit Software, PBC).

Assessment of Study Quality and Risk of Bias

All records included prospective or retrospective cohort or case-control studies. Risk of bias was assessed with the implementation of RoB:2 algorithm by Cochrane and the Newcastle-Ottawa scale to our analysis tools [79,81].

A publication bias assessment was decided not to be conducted in this study, as in such cases of meta-analyses of proportions it has been associated with misleading results and its use is not recommended [82-83].

RESULTS

Three hundred and ninety-seven records were identified by utilizing the pre-specified search algorithm. Each article underwent an evaluation for relevance to the designated topic, leading to the exclusion of 159 publications that were deemed irrelevant, per initial review. The remaining 238 reports were screened in accordance with the eligibility criteria outlined in the methods section.

This further comprehensive review resulted in the exclusion of 153 records that did not meet the study criteria, 60 that were not available in English, 9 due to study design and 3 for other reasons. The following PRISMA flowchart depicts the successive steps in the selection of studies, which ultimately resulted in 13 articles that were included in the final analysis [85-97] (Figure 1).

These 13 records report results from 13 independent prospective and retrospective studies or clinical trials, involving 316 patients with recurrent/metastatic GISTs that were treated with imatinib prior to surgery. Descriptive characteristics of the included are portrayed in Table 1.

Figure 1. PRISMA 2020 Flowchart of study selection

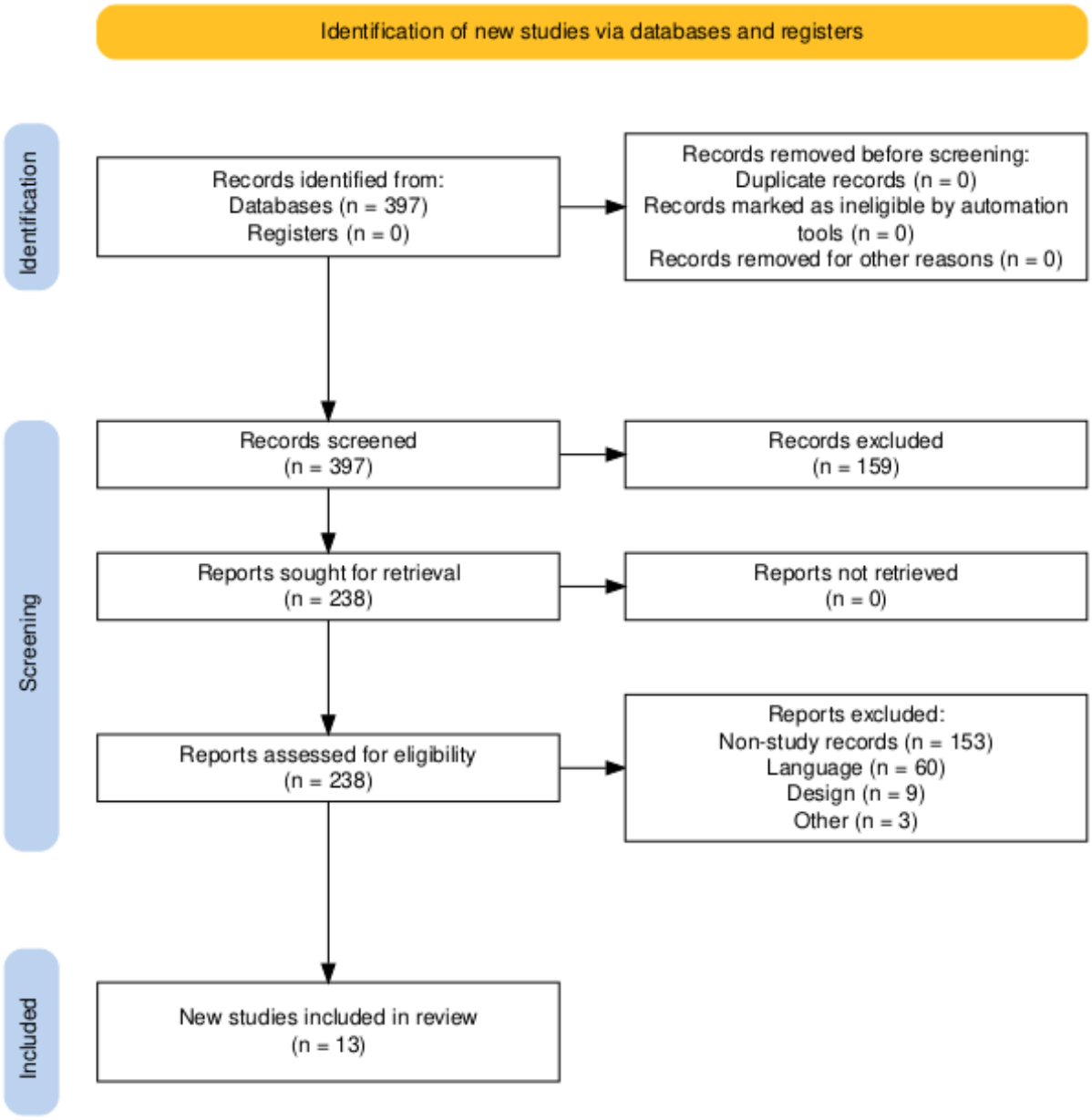


Table 1. Descriptive table

Study	Design	Region	N	Males (%)	Age (years)	Median FU (mo)	Primary site Stomach S.I. L.I. Other	Site of metastasis Liver Peritoneum Other	Preoperative IM duration (mo)	Preoperative IM dosage (mg/d)	KIT mutation	Lesions (=1) (>=2)
Qi et al (2020)	R	Asia	7	85.7	47	55.12	3 2 0 2	1 - 2	8	400-600	Exon 11: 5 Exon 9: 2	- -
Wang et al (2020)	R	Asia	12	91.7	56.2	39.9	3 3 2 4	- - -	11.4	400	-	- -
Chen et al (2019)	R	Asia	15	60.0	53	26	5 - - 10	15 0 0	10	400-800	-	- 12
Roland et al (2018)	R	USA	87	54.0	55	51	33 38 10 6	27 24 36	22.2	-	Exon 11: 22 Exon 9: 4 Wild-type: 8 Exon 2: 6 Other: 6 Unknown: 41	24 63
Ramaswamy et al (2014)	R	Asia	9	-	-	24	6 1 2 0	- - -	-	-	-	-
Cananzi et al (2014)	R	EU	11	36.4	51	65	5 - - 6	11 - -	38	-	-	4 7
Shen et al (2014)	P	Asia	5	80.0	42	9.5	0 3 2 0	2 - 3	8	400-600	Exon 11: 2 Exon 9: 2 Unknown: 1	-
Bednarski et al (2014)	R	USA	53	67.9	59	28.8	16 29 4 3	- - -	17.9	-	Exon 11: 28 Exon 9/13/17: 7 Wild-type: 6	-
Du et al (2014)	CT	Asia	19	57.9	49	23	5 10 2 2	- - -	6.3	400	-	10 9
Wang et al (2013)	R	Asia	22	59.1	49.3	53	7 7 4 4	3 2 17	14	400-800	Exon 11: 12 Exon 9: 4 Exon 13: 1 Wild-type: 1 PDGFRA ex18 D842Vmut: 4	-
Wang et al (2012)	CT	Global	22	59.1	53	66	- 2 - -	7 10 3	2.1	600	-	-
Xia et al (2010)	CT	Asia	19	52.6	53	36	11 5 1 2	19 - -	6	600	Exon 11: 7 Exon 9: 3 Unknown: 8	7 12
Andtbacka et al (2007)	R	USA	35	-	55.7	36.2	- - - -	7 - - -	15.2	400-800	-	9 23

Note: R= Retrospective, P= Prospective, CT= Clinical trial, N= number of patients, FU= follow-up, mo= months, S.I.= small intestine, L.I.= large intestine, IM = Imatinib, Preoperative IM duration per study presented as medians, mg/d = milligrams per day.

2- and 5-year PFS rates

A total of 5 out of the 13 studies reported PFS data at the 2-year timepoint, including 117 patients. Meta-analysis results indicate that 72% (95% CI: 53%-86%) of the patients treated with imatinib prior to surgery survive two-years after surgery without exhibiting disease progression. The pooling of the reported PFS outcomes demonstrated high heterogeneity (I^2 = 75%, p < 0.01) (Figure 2). Furthermore, 4 out of the 13 included studies reported PFS rates at the 5-year timepoint, including 96 patients. The meta-analysis of proportions resulted at a 43% (95% CI: 17%-74%) 5-year PFS rate while heterogeneity was high (I^2 = 80%, p < 0.01) (Figure 2).

Subgroup analysis by study design and geographic region revealed no statistically significant differences between groups (Figures 3 and 4).

Figure 2. Meta-analysis of 2-year PFS (A) and 5-year PFS (B) rates.

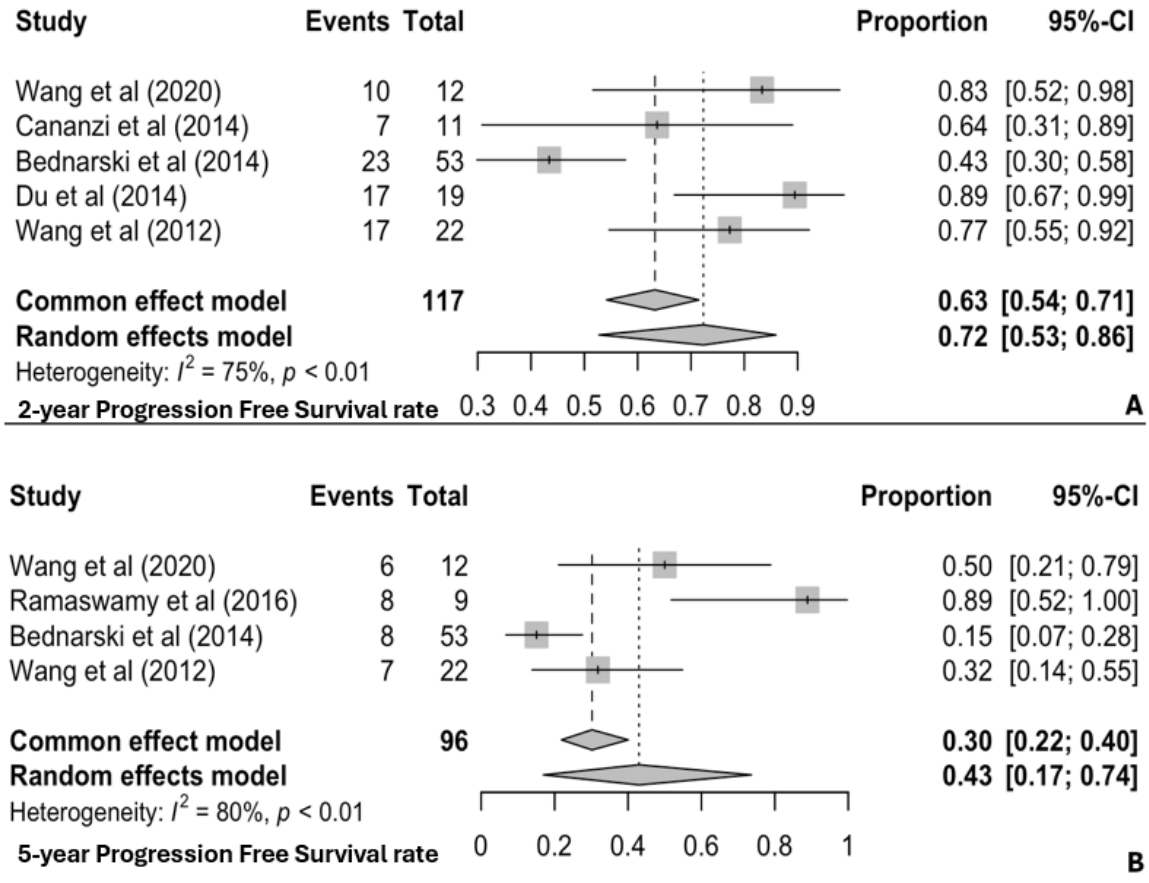


Figure 3. Meta-analysis of 2-year PFS rates, subgroup analysis by design

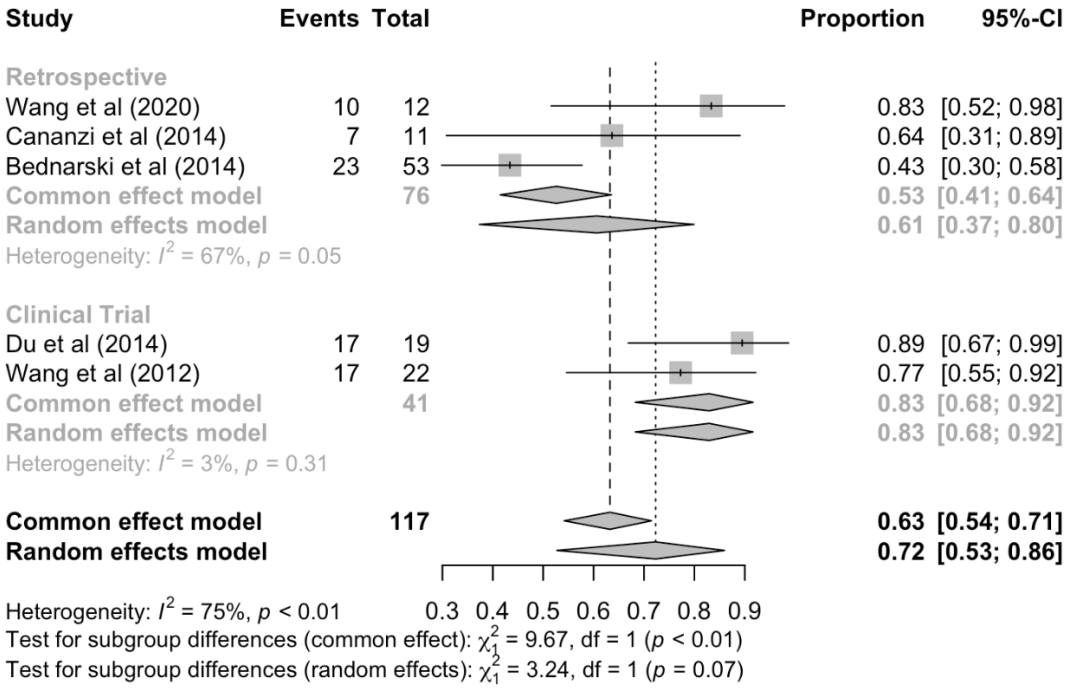
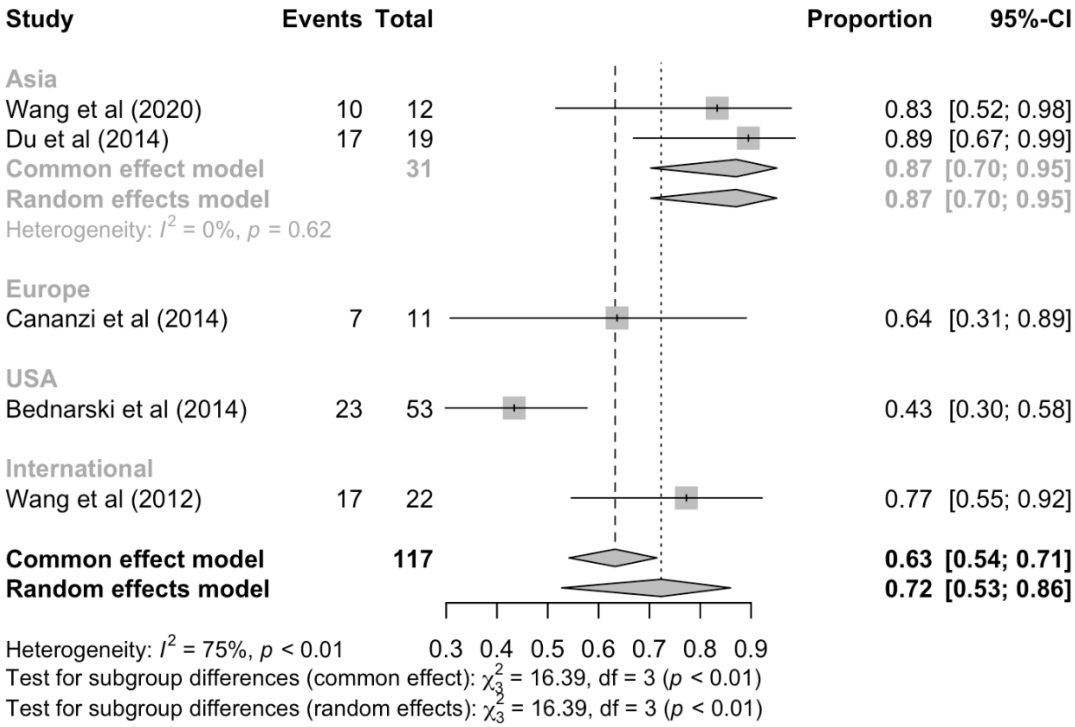


Figure 4. Meta-analysis of 2-year PFS rates, subgroup analysis by region



2- and 5-year OS rates

Six out of the 13 studies included, reported 2-year OS rates, encompassing a total of 136 patients. Meta-analysis results indicate that 85% (95% CI: 78%-91%) of the patients treated with imatinib prior to surgery survived two-years of post-operation. Given the low heterogeneity observed (I^2 = 4%, p = 0.39) the interpretation of the common-effect model was deemed appropriate (Figure 5). Again, six studies out of the 13 included (not the same as in the 2-year analysis), reported OS data at the 5-year timepoint. Pooled proportion analysis revealed a 60% (95% CI: 51%-67%) 5-year OS rate. Heterogeneity was once again particularly low (I^2 = 0%, p = 0.66), allowing for the interpretation of the common-effect model estimates (Figure 5). Subgroup analysis by study design and geographic region revealed no statistically significant differences between groups (Figures 6-9).

Figure 5. Meta-analysis of 2-year OS (A) and 5-year OS (B) rates.

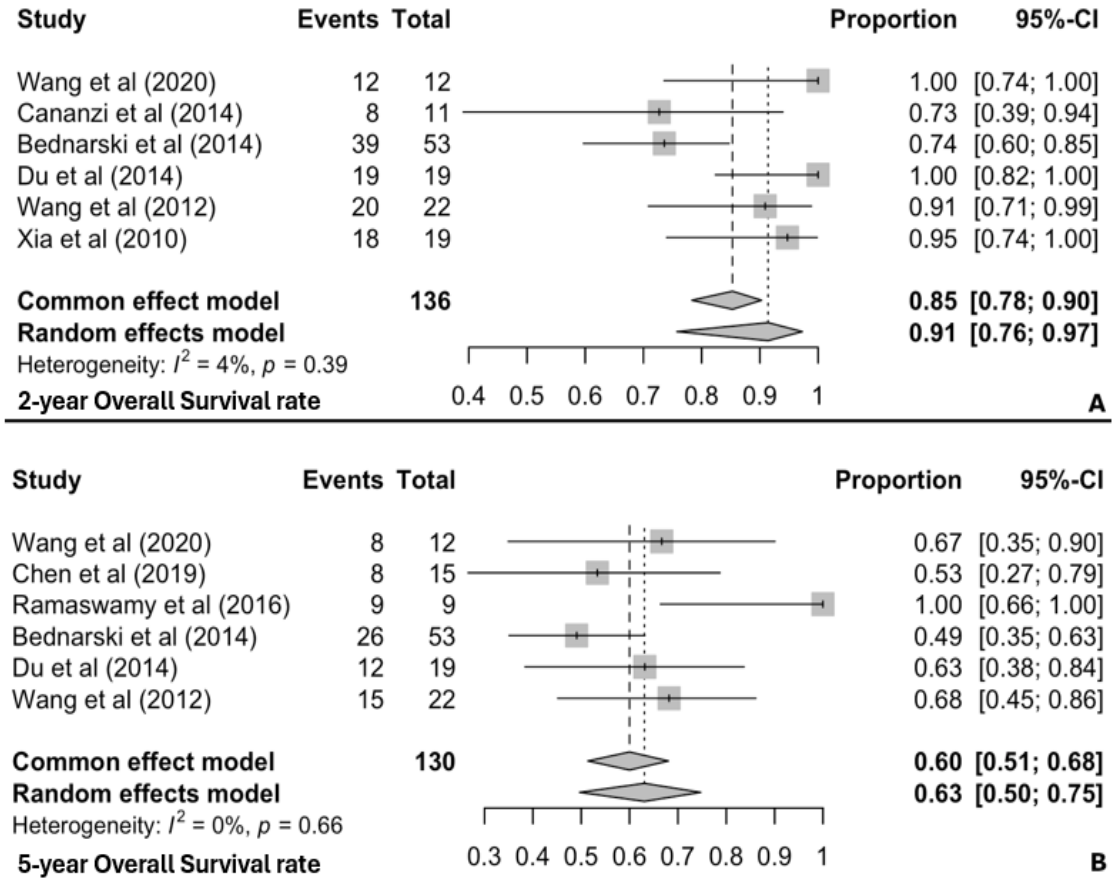


Figure 6. Meta-analysis of 2-year OS rates, subgroup analysis by design

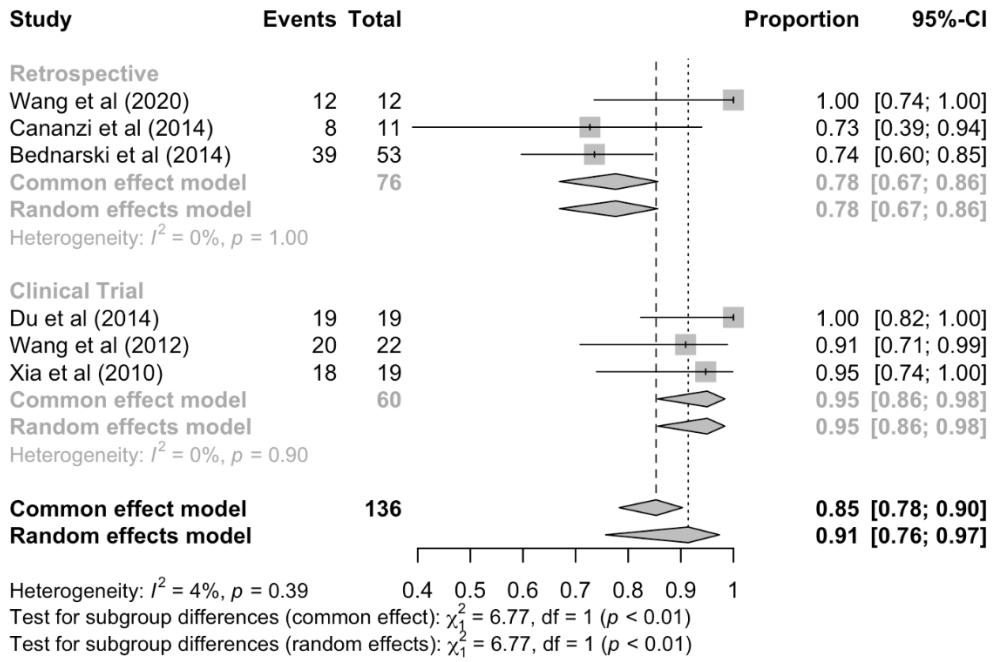


Figure 7. Meta-analysis of 2-year OS rates, subgroup analysis by region

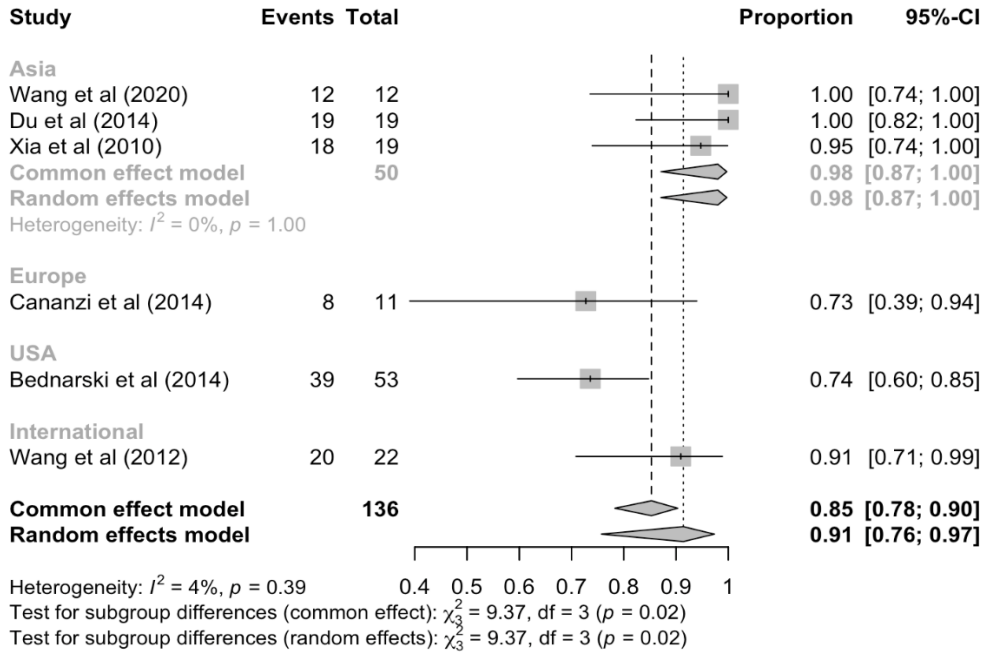


Figure 8. Meta-analysis of 5-year OS rates, subgroup analysis by design

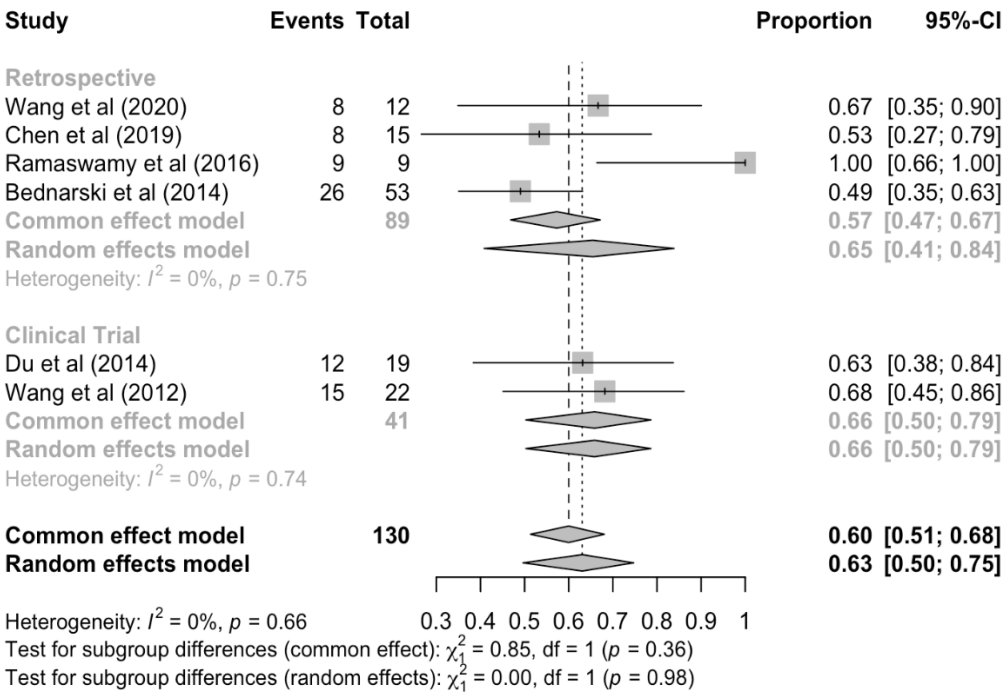
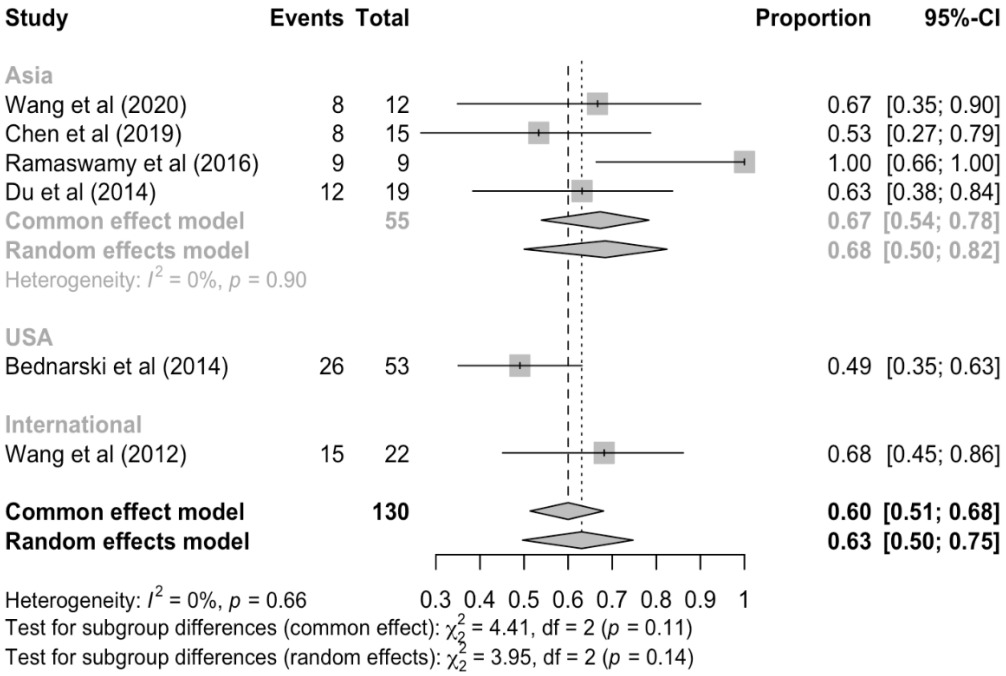


Figure 9. Meta-analysis of 5-year OS rates, subgroup analysis by region



Microscopically complete resection (R0) after neoadjuvant imatinib therapy

The meta-analysis of proportions of R0 resections in 210 patients across 11 studies yielded a pooled overall success rate of 80% (95% CI: 62%, 91%) for microscopically complete resections after neoadjuvant imatinib therapy (Figure 10). A high level of heterogeneity is demonstrated (I^2 = 74%, p < 0.01) across the reported R0 resection outcomes, while pooled effect estimates did not differ between study designs.

Subgroup analysis by study design and geographic region revealed no statistically significant differences between groups (Figures 11 and 12).

Figure 10. Meta-analysis of R0 resection proportions

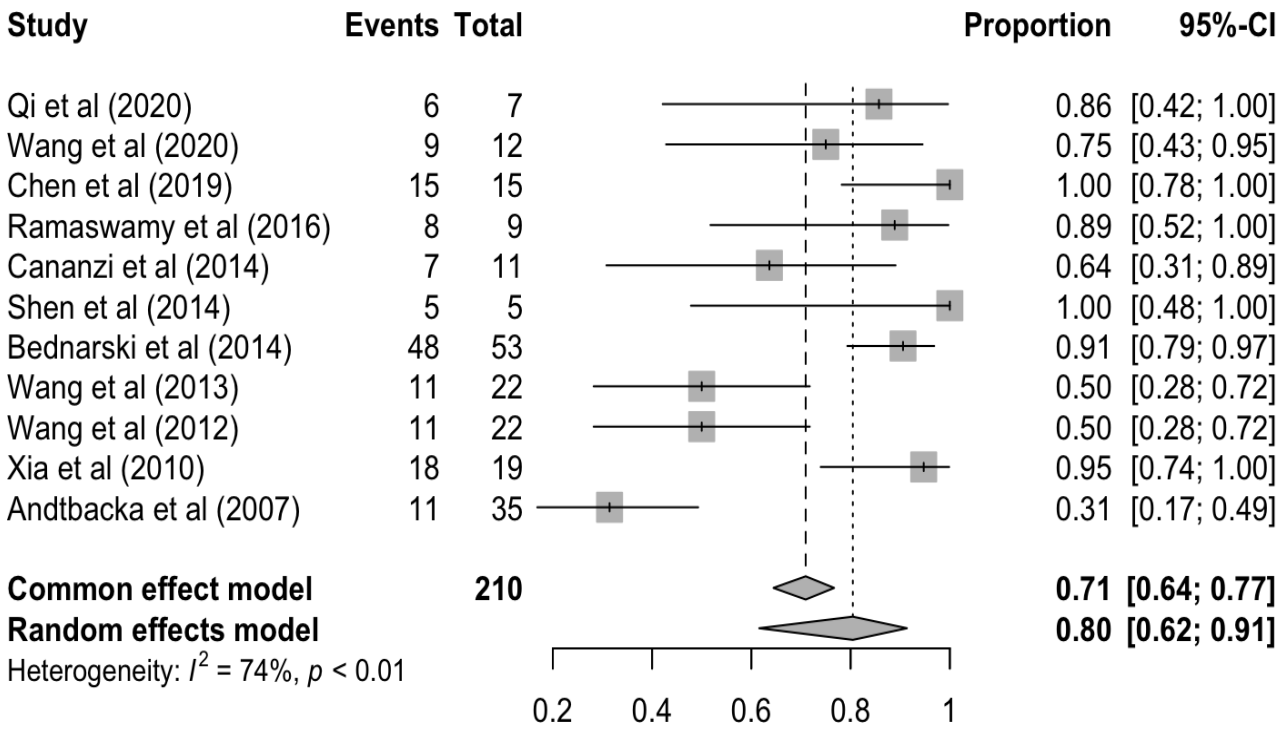


Figure 11. Meta-analysis of R0 resection proportions, subgroup analysis by design

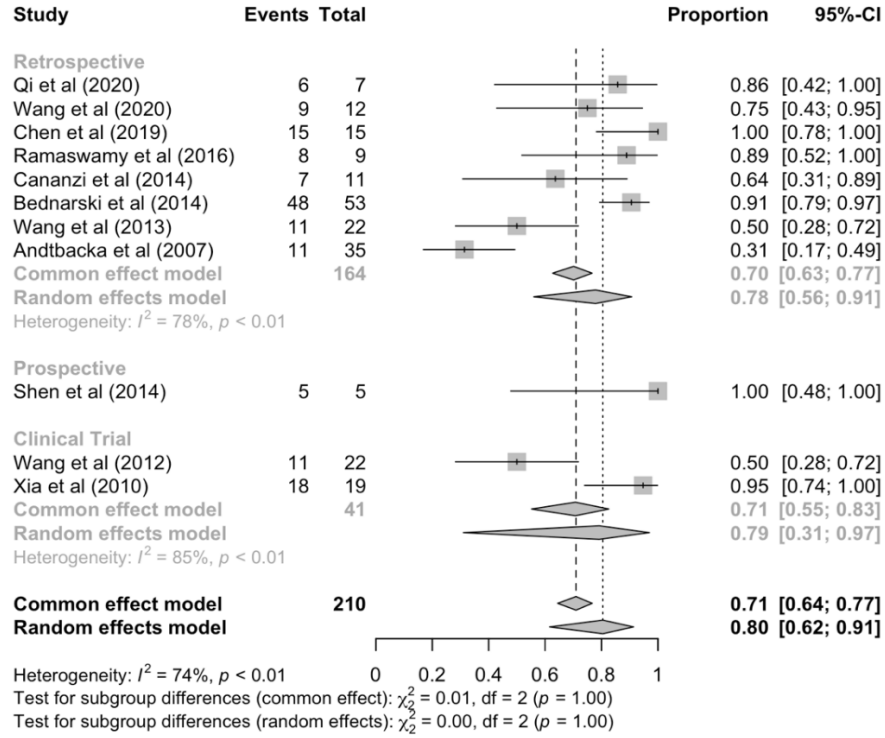
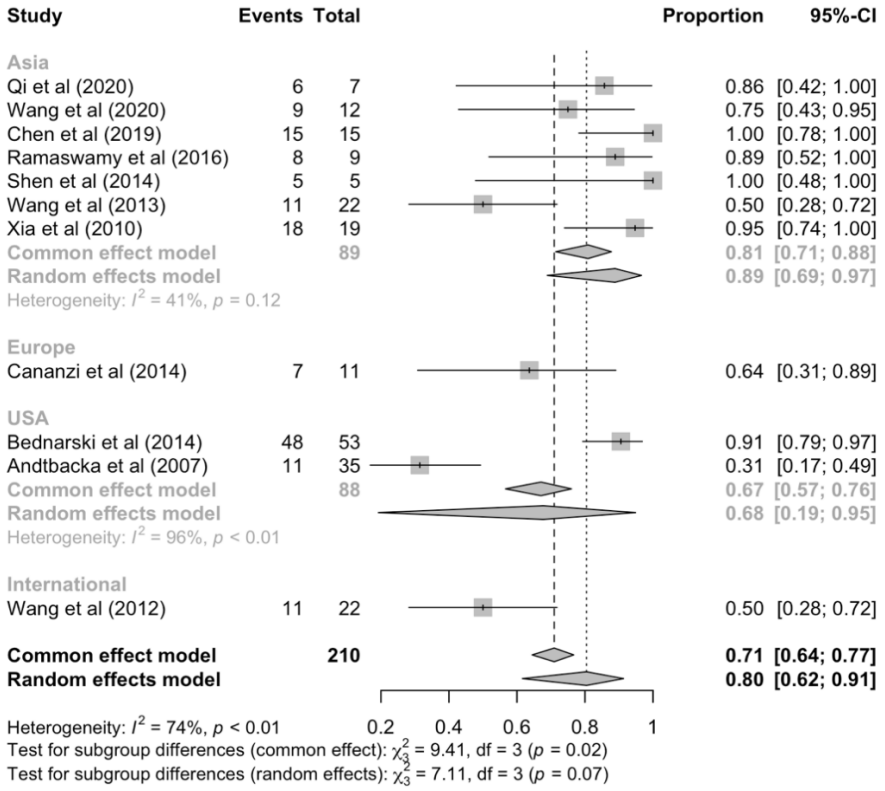


Figure 12. Meta-analysis of R0 resection proportions, subgroup analysis by region

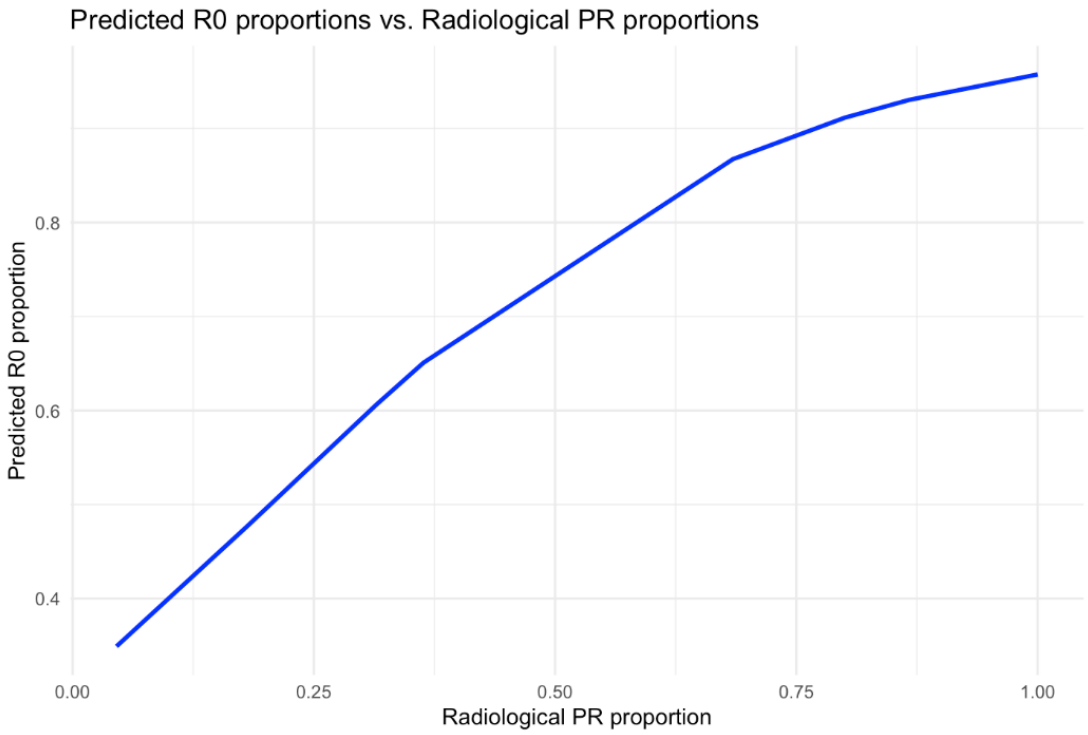


Post-hoc meta-regression analysis revealed a strongly statistically significant and positive association between the proportion of patients achieving radiological PR and the proportion of R0 resections (α= -0.80, β = 3.92, $p<0.001$) (Table 2). More specifically, a linear association on the logit-scale was translated to a near-linear association on the proportion-scale, flattening out close to max values (Figure 13). The negative intercept α=-0.80 denotes a negative association when the moderator is absent; in this case, when a radiological PR is not achieved. The coefficient β = 3.92 means that, for each percentage point increase in radiological PR, the log-odds of resection increase by approximately 3.92 times. Finally, the proportional of radiological PRs explained the rate of 25% of the initial heterogeneity (initial I^2 = 74%, new I^2 = 49%).

Table 2. Meta-regression results for R0 resection proportions

Variable	**Estimate (Logit scale)**	**p-value**
Age (median)	-0.07	0.456
# of patients	-0.02	0.491
% of males	0.02	0.191
Preoperative IM duration (months, median)	-0.03	0.514
% of Radiological PR	3.92	<0.001***

Figure 13. Meta-regression fit curve of association between R0 and radiological PR proportions



Microscopically and macroscopically incomplete resections (R1 and R2) after neoadjuvant imatinib therapy

Proportions of R1 and R2 resections were available from 6 and 9 studies, involving 181 and 198 patients, respectively. Meta-analysis of proportions resulted in 35% (95% CI: 2%-93%) and 16% (95% CI: 7%-32%) for R1 and R2 resection rates, respectively (Figures 14 and 15).

Figure 14. Meta-analysis of R1 resection proportions

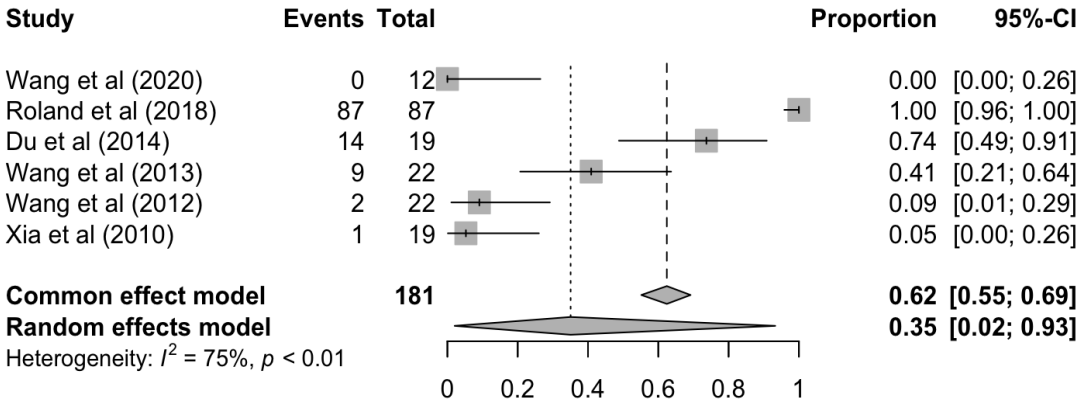
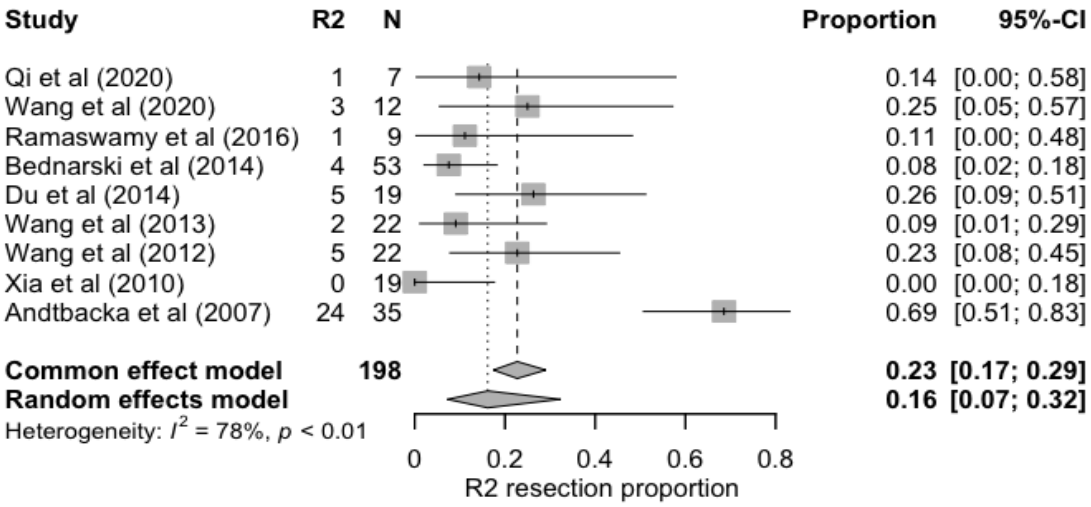


Figure 15. Meta-analysis of R2 resection proportions



Subgroup analysis by study design and geographic region revealed no statistically significant differences between groups (Figures 16-19)

Figure 16. Meta-analysis of R1 resection proportions, subgroup analysis by design

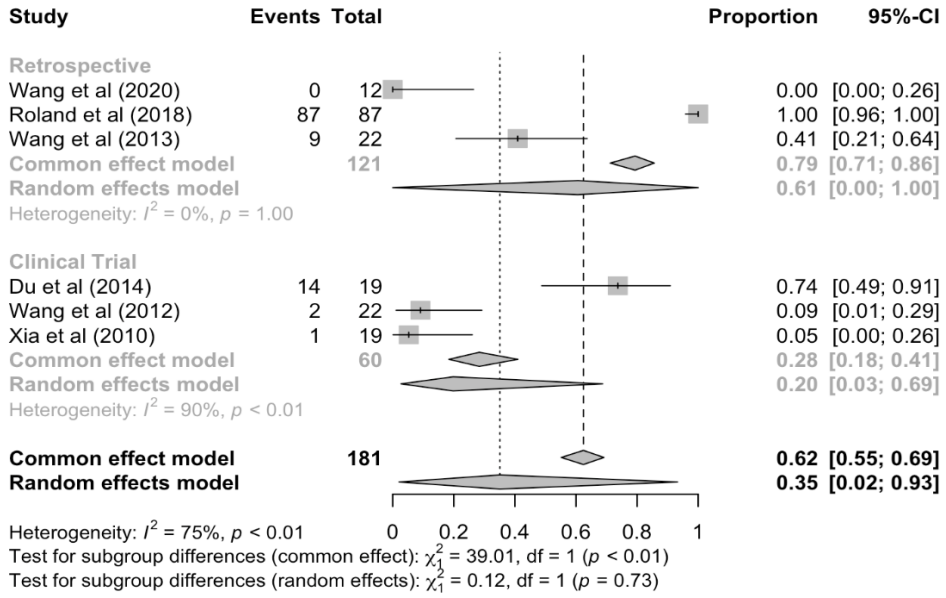


Figure 17. Meta-analysis of R1 resection proportions, subgroup analysis by region

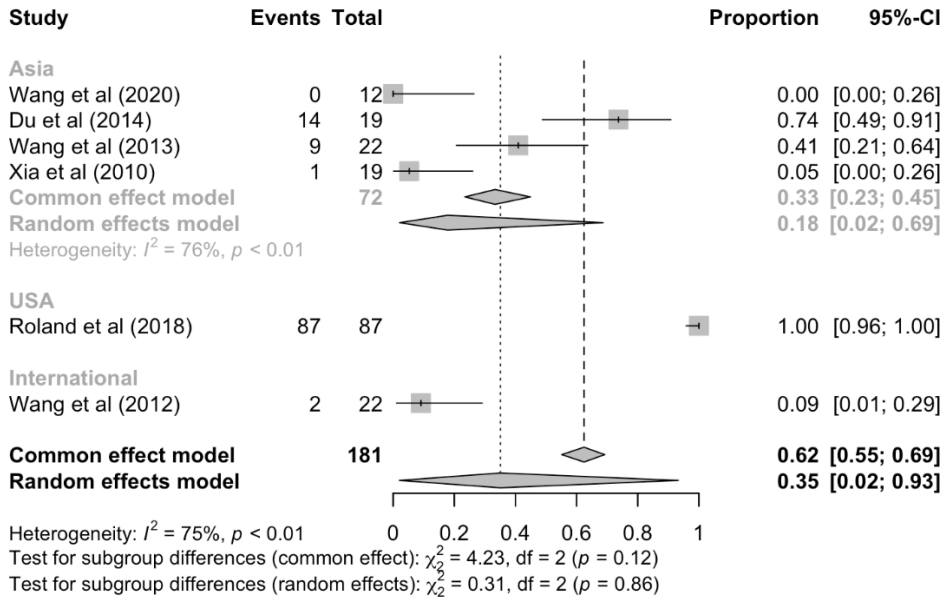


Figure 18. Meta-analysis of R2 resection proportions, subgroup analysis by design

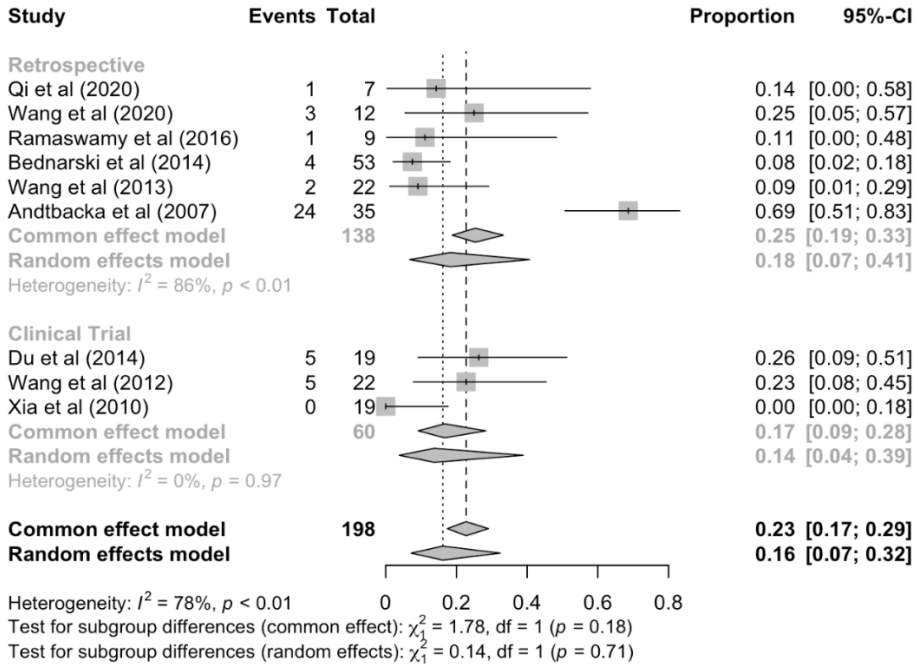
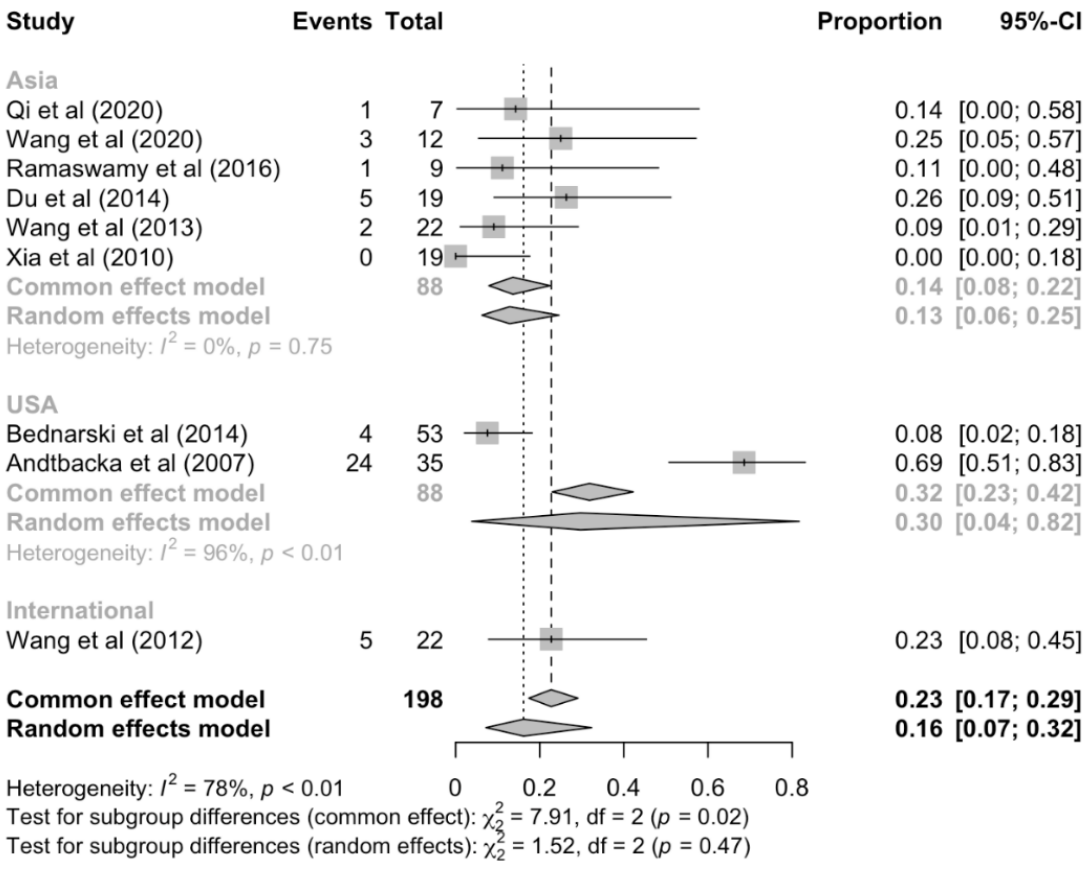


Figure 19. Meta-analysis of R2 resection proportions, subgroup analysis by region



Risk of bias

Both retrospective and prospective studies included were assessed by Newcastle-Ottawa assessment scale [81] and characterized according to score as high- or low-quality studies. Three studies were of low quality (score=6) and eight studies were high quality (score=7) (Table 3). RoB:2 algorithm by Cochrane was utilized for the two randomized clinical trials included and resulted in some concerns, mainly in the measurement of the reported outcome [98].

Table 3. Newcastle-Ottawa scale assessment

STUDY	SELECTION	COMPARABILITY	OUTCOME/ EXPOSURE	NUMBER OF STARS
Qi et al (2020)	**	**	**	6
Wang et al (2020)	**	**	**	6
Chen et al (2019)	**	**	***	7
Roland et al (2018)	**	**	***	7
Ramaswamy et al (2014)	**	**	***	7
Cananzi et al (2014)	**	**	***	7
Shen et al (2014)	**	**	**	6
Bednarski et al (2014)	**	**	***	7
Wang et al (2013)	**	**	***	7
Wang et al (2012)	**	**	***	7
Andtbacka et al (2007)	**	**	***	7

DISCUSSION

In our investigation, we identified the 2- year and 5-year PFS rate at 72% (95% CI 53%-86%) and 43% (95% CI 17%-74%), respectively as well as 2-year OS at 85% (95% CI 78%-90%), which subsequently diminished to 5-year OS at 60% (95% CI 51%-68%). Also, the R0 resection rate was 80% (95% CI 62%-91%) and it was strongly related to tumor response, according to RECIST criteria [112]. It is noteworthy that there was no association between R0 rate and preoperative imatinib duration.

This meta-analysis exclusively considers patients with metastatic and/or recurrent GISTs, distinguishing it from the majority of previous published studies that have combined both locally advanced and metastatic/recurrent cases [84]. A recent meta-analysis conducted by Lam et al. [99], evaluated an heterogeneous cohort of both locally advanced and metastatic GISTs and they reported a commendable R0 resection rate of 88.9% (95% CI 84%-93.2), alongside OS rates of 100% (99.2%-100%), 94% (95% CI 89.7%-98%), and 87.6% (95% CI 78.7%-94.6%) at the 1-year, 3-year, and 5-year intervals, respectively. The extant literature elucidates that individuals with locally advanced GISTs typically manifest more favorable survival trajectories compared to their counterparts with metastatic or recurrent disease. In particular, Gheorghe et al. [9] documented a remarkable 5-year life expectancy of 80% for patients with locally advanced GISTs, contrasted with a mere 55% survival rate among those afflicted by metastatic disease.

Furthermore, several reviews have been published about metastatic/recurrent GISTs under first-line treatment with imatinib. For example, Ford et al., [100] supported an operation in metastatic setting in those patients responding to imatinib or having a limited focal progression, resulting in a marginal improvement in PFS and OS. More, specifically, Patel [76] summarized survival outcomes from major trials which were designed to study survival outcomes in metastatic and unresectable GISTs under first-line imatinib. An open-label phase III trial of Blanke et al [101] reported PFS and OS rates according to daily imatinib dosage between 400mg and 800mg. They published that 2-year PFS was 41% and 46% of those who were treated by 400mg/d and 800mg/d of imatinib, respectively. Accordingly, 2-year OS was 76% and 72% for patients at 400mg/d and those at 800mg/d. Blanke et al., in another trial [102] in a phase II randomized study reported 5-

year OS rate close to 50%. Another study by Serano et al., reported that 2-year PFS in metastatic patients treated with 400mg of imatinib per day was 52% and in the escalated dose of 800mg/d was 44% (HR: 0.78). On the other hand, Blay et al., [103] presented more favorable survival results, when they studied non-metastatic advanced GISTs and represents the results in a few relevant studies (3-year PFS= 92%, 5-year PFS=92%) [104-111].

Wang et al. [95] reported findings from the RTOG 0132/ACRIN 6665, a prospective phase II trial that assessed neoadjuvant imatinib therapy for metastatic and recurrent GISTs involving 22 patients (Group B) with a median follow-up of 5.5 years. They observed that the 2-year and 5-year overall survival rates were 90.9% (95% CI 78.9%-100%) and 68.2% (95% CI 46.9%-89.5%), respectively, while the estimates for 2-year and 5-year PFS were 77.3% (95% CI 59.8%-94.8%) and 29.8% (95% CI 8.8%-50.7%), respectively. In the same trial, Eisenberg et al. [111] reported a R0 resection at 58% in Group B. Additionally, Wang et al. [95] conducted a further analysis on R status and found no apparent correlation between R status and tumor progression. Bednarski et al. [92] conducted a retrospective analysis of 53 patients and reported findings that align closely with our analysis concerning OS and R0 resection rates. They found that the 2-year OS was 74% (95% CI 60%-85%) and the 5-year OS was 49% (95% CI 35%-63%). Additionally, they reported a R0 resection rate of 91% (95% CI 79%-96%).

In the process of evaluating our analysis' results, we noted that the PFS rate observed in our study of [72% (95% CI: 53%-86%)] exhibited substantial heterogeneity, as indicated by an I^2 value of 75% ($p < 0.01$). This suggests considerable variability in the results across the studies incorporated in the analysis [96, 100]. Similarly, the examination of R0 resection rates also revealed a significant degree of heterogeneity, characterized by an I^2 value of 74% ($p < 0.01$) [95-96, 99-101]. These findings imply that clinical outcomes may differ markedly based on the specific populations and methodologies employed in the individual studies. The elevated levels of heterogeneity observed in both the PFS and R0 resection rates underscore the imperative for further investigations aimed at elucidating the factors that may influence survival outcomes and R0 rates in patients diagnosed with GISTs.

Furthermore, our analysis revealed potential publication bias in the case of R0 rates, which is evident in the asymmetrical appearance of the funnel plot (Figures 20, 22). By applying the trim and fill method, as pre-specified in the methods section, we observed an improved symmetry in the distribution. This finding suggests an alternative pooled rate within the trim and fill model, estimated at 50% (95% CI: 27%-73%). Such results raise some concerns regarding the generalization of the overall pooled-effect estimate generated in our study. Subsequent meta-regression analysis (Table 2) highlighted no potential moderators (demographics, preoperative IM duration) of factors that varied and the R0 reported rates. A notable exception was that tumor response demonstrated a statistically significant and positive association with R0 resection rates ($\beta = 3.92$, $p < 0.001$); specifically, for each percentage point increase in radiological partial response, the log-odds of achieving a R0 resection increased approximately 3.92 times.

Finally, it is crucial to acknowledge the rarity of the condition investigated in this study, as well as the scarcity of publications addressing the scientific implications of surgical interventions in patients with metastatic or recurrent GISTs.

CONCLUSION

In conclusion, selected patients with metastatic and/or recurrent GIST who respond to first-line imatinib may be candidates for surgery, as they often achieve higher rates of complete resection, leading to improved survival results compared to those with metastatic GISTs who remain on first-line therapy. However, their survival rates do not match those of locally advanced GISTs receiving neoadjuvant imatinib treatment.

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