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Surgical treatment of an advanced GIST the age of imatinib

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A B S T R A C T

The use of imatinib in the management of gastrointestinal stromal tumours has radically changed their prognosis, particularly in their advanced forms, whether they are metastasic (the majority) or locally advanced. The high rates of response obtained means that, in many cases, surgery can be performed in situations where it was impossible to do so, even to the extent of considering surgery as a first line therapeutic weapon in combination with imatinib. Even so, it must not be used indiscriminately. It will be the different responses of these tumours to imatinib that will determine its usefulness and the way it is used. The combined use of surgery and imatinib is a clear and successful example of multimodal treatment in the context of the so-called targeted molecular therapy.

Tratamiento quirúrgico del GIST avanzado en la era del imatinib

Palabras clave:
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R E S U M E N

La aplicación clínica del imatinib en el manejo de los tumores de la estroma gastrointestinal ha cambiado radicalmente su pronóstico, especialmente en sus formas avanzadas, ya sean metastásicas, la mayoría, o localmente avanzadas. Las elevadas tasas de respuesta obtenidas permiten, en muchos casos, el empleo de la cirugía en situaciones en que antes era imposible, e incluso se llega a considerar la cirugía como un arma terapéutica de primera línea en combinación con imatinib. Aun así, su empleo no debe ser indiscriminado. Serán las diferentes respuestas que estos tumores poseen al imatinib lo que determine su utilidad y su forma de empleo. El uso combinado de cirugía e imatinib supone un claro y exitoso ejemplo de tratamiento multimodal en el contexto de lo que se ha denominado terapia molecular dirigida.

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Introduction

Gastrointestinal stromal tumours (GIST)[1,2] make up less than 1% of all digestive tumours,[3,4] yet are the most common type of mesenchymal neoplasia in the digestive tract.[5,6] Originating in the interstitial cells of Cajal,[6-8] they can settle at any level, although 50% settle at gastric level and 25% in the small intestine.[9-14]

This type of tumour has received a great deal of attention over the past few years, for 3 fundamental reasons. Firstly, it has been now differentiated from other intestinal sarcomas with which it was frequently confused, such as leiomyomata, since more than 95% of GISTs exhibit the differential immunohistochemical marker CD117 (KIT).[1,15,16] This has allowed its epidemiology and natural history to become better understood. Secondly, the mutation from which it originates has been identified. GISTs show a C-kit mutation in 80% of cases: C-kit is a gene which codifies a protein receptor from the tyrosine kinase family (KIT), causing it to become active and giving rise to the development of tumours.[16-19] Thirdly, a drug has become available: imatinib, or STI-571 (Glivec®, Novartis, Basel, Switzerland), specifically blocks this mutated receptor[20,21] and has demonstrated exceptional clinical results.

We have included within the term advanced GIST tumours which appear unresectable at the time of diagnosis, either because of their advanced locoregional stage (locally advanced tumours, 15%) or due to the presence of distant metastasis (20%). It must be emphasised that, following the primary resection of a GIST, some 40%–60% of patients will suffer a relapse within a period of about 2 years, in the form of either metastatic disease or a local recurrence.[8,12,22-25]

This type of advanced GIST, and a potential surgical treatment following the introduction of imatinib, are the subject of this review.

The imatinib revolution

In 2001, Joensuu et al[26] published what is considered to be the first example of the clinical use of imatinib. In their article they describe the extraordinary response of a patient with advanced GIST to the drug. This signified a real revolution, not only because of the excellent result obtained, but also due to the underlying science. Imatinib's mesylate is a selective and potent inhibitor of the tyrosine kinase family, amongst which can be found KIT, the ABL family, and PDGFRα.[20,21,27] Given that GISTs show a mutated form activated by KIT,[17] that most GISTs show mutations of the *C-kit* gene—which leads to the formation of active forms of KIT that generate oncogenic signals[27,28]—, and that imatinib inhibits the KIT receptor, the use of this drug to treat GIST has a solid scientific justification. This is a clear example of what has been defined as molecular-directed therapy.[8] Multiple multi-institutional studies were quickly launched, with the objective of studying the role of imatinib in advanced GIST. As an example we can highlight the US/Finland B2222 study,[22] which incorporated more than 140 patients and reported a response rate of 67%, a disease stabilisation rate of 17% and a progression rate of 13%, with an overall survival rate of 4.8 years. Other similar studies[30-36] published even better results (Table 1). These results meant that patients diagnosed up to that year survived for more than 19 months, while a diagnosis in 2006 meant survival of at least 5 years.[24] Some 75%-85% of patients treated with imatinib were stabilised, with survival rates of 70% at 2 years, and at least 50% of these were free of disease.[37]

If a highly effective drug such as imatinib is now available, why not combine its use with surgery?[38-41] The answer to this question lies in 2 distinct clinical scenarios: the neoadjuvant scenario in the case of locally advanced tumours or tumours in "difficult" locations, such as the lower rectum, gastroesophageal junction, or pancreas, and the scenario in which the disease has spread to the liver or peritoneum.

Neoadjuvancy in a GIST that is either locally advanced or in a difficult location

We define a locally advanced GIST as that which, due to its size and/or location, impedes a complete resection or the acquisition of disease-free margins (R0) or makes necessary, in order to meet these objectives, the execution of very aggressive and mutilating surgeries.

The logic to neoadjuvant treatment of a locally advanced GIST is similar to that of other types of tumour.[8,42-45] The majority of GISTs respond to imatinib, and many become smaller and less friable. This causes many tumours to become resectable where they were initially unresectable, allowing a less aggressive and invasive surgery with a lower morbidity and mortality, in both locally advanced tumours and those in difficult locations (stomach, duodenum, oesophagus and cardia, lower rectum, and recto-vaginal space). Furthermore, oncologically the surgery becomes safer, reducing the risk of the tumour spreading outside the operating field.[8,42] Also, the preoperative treatment improves the oncological result of the surgery, in that it treats hidden micrometastases and enables the singling out of patients with a better prognosis for surgery, whilst ruling it out for those who develop metastases during treatment with imatinib.[45-52]

The literature results, although based on isolated cases and small joint institutional studies,[46,51,53-55] seem to support these indications as detailed in Table 2a. In general, the authors emphasise that neoadjuvancy results in an increase of tumour resectability together with an improved preservation of the organs, thanks to a reduction in the tumour size estimated at an average of 85%.

Despite these data, and while reasonable given the above indications, a recommendation for the preoperative use of imatinib can only be given once we have data from a wide range of multi-institutional prospective trials such as RTOG S-0132,[57] whose preliminary data is shown in Table 2b, the German study Apollon[58] (CSTI571BDE43) or MDACC ID03-0023.[25,59-61]

However, neoadjuvant treatment poses several problems, such as electing the optimum time for surgery, which is a key in assessing the response to the treatment, or the right

Table 1 – Primary studies of advanced GIST treated with imatinib (data taken from successive updates with different follow-up periods)

Study	Patients, No.	Imatinib dosage, mg/d	Follow-up, mo	PR, %	DS, %	DP, %	DFS, %
EORTC (phase I)[30,31]	36	400–1000	8–12	69	19	11	82
US/Finland Multicenter B2222 (phase II)[29,32,33]	73	400	53	67[a]	15	15	65
	74	600		66a	18	8	
EORTC U 62005 (phase III)[34]	470	400	24	50	32	13	56
	472	800		54	32	9	50
US Intergroup S0033 (phase III)[35,36]	361	400	12	49	22	–	80
	360	800		48	22	–	82
Total	1845	400–1000	8–24	48–69	15–32	8–15	50–82

DFS indicates disease-free survival; DP, disease progression; DS, disease stabilisation; PR, partial response.
[a]Includes patients in complete response.

Table 2a – Neoadjuvancy in a GIST that is either locally advanced or in a difficult location

	Patients, No.	R0, %	DFS, %
Haller[46]	10	100	–
Andtbacka[54]	11	100	91 (31 months)
Hohenberger[56]	14	86	72 (16 months)
Fiore[99]	15	–	77% (36 months)

DFS indicates disease-free survival.

Table 2b – Neoadjuvancy in a GIST that is either locally advanced or in a difficult location

	2 years				
	R0	R1	R2	DFS	S
Locally advanced, %	77	15	8	82	93
Recurring/metastatic, %	58	5	32	73	91

DFS indicates disease-free survival; S, survival.

time to interrupt and reinstate the imatinib in relation to surgery. Another issue is that initially resectable tumours which are located in difficult positions do not respond to neoadjuvant treatment, and end up becoming unresectable. It is for these reasons that most authors recommend biopsy with mutational analysis coupled with a positron emission tomography (PET) in locally advanced and metastatic GISTs, particularly if neoadjuvant treatment is planned.[58] It has been observed that the response to imatinib varies according to the type of mutation involved in the formation of the tumour.[62-64] Furthermore, carrying out a PET in the first 15 days of treatment allows us to predict the response to treatment, since the functional results far precede the morphological.[3,65,66] Thanks to these 2 techniques the response to imatinib can be predicted and the approach modified (adjusting of dosage, employment of second-line agents, or moving straight to surgery).[67-70]

Imatinib treatment can be maintained right up to the optimum time for surgery, ie, until the tumour becomes resectable, normally after a period of 6-12 months.[24,43,46] The maximum response can be defined as an absence of radiological improvement after 2 control computed tomographies (CT). Despite the above, it is not always necessary to wait for the maximum response before carrying out surgery; it is enough to have reached a result which allows it.[3] For this reason an interdisciplinary assessment of this response is key in choosing the best time for surgery.[3]

Adjuvant surgery in metastatic GIST

The usefulness of surgery in a metastatic GIST treated with imatinib is not clearly defined. The logic behind its employment is based on the concern that patients who respond to treatment usually develop, over about two years, an apparent resistance to imatinib.[34,62] In the US/Finland B2222 study[29,32,33] it was observed that up to 40% of patients died as a result of this problem.[71] Furthermore, a complete pathological response is rare (<5%),[34,44,47,72] and cells remained viable even after complete response.[73,74] Surgery, in eliminating remaining tumour foci (cytoreduction), helps to delay or prevent a recurrence of the tumour and avoid the development of secondary mutations, thus increasing the rate of sustained response.[58,75] Surgery can also help to eliminate potential secondary symptoms such as pain or haemorrhage. However, only retrospective data is available, as these hypotheses have not been demonstrated in a prospective study.[41]

Imatinib is the treatment of choice for first-line therapy in advanced GISTs.[3,60] Immediate surgery can be indicated only in the small number of patients who have primary tumours and synchronic small-volume metastatic disease, which is therefore localised and resectable, in an attempt to achieve an R0 resection.[8,62] Other authors consider that these patients should be treated immediately with imatinib.[24] The data provided in the BFR14 study[76] favour the latter option. Thus, the rate of survival and disease-free survival (DFS) at 2 years in patients with metastatic GIST who were operated on immediately were 83% and 55%, respectively, compared with 70% and 52% of those who were treated initially with imatinib (with no statistically significant differences between groups). These data demonstrate that surgery in the context of advanced GIST is adjuvant to treatment with imatinib, and not the reverse, and should be employed to prolong the time during which patients can be treated with the drug.[24]

Not all patients with advanced disease who are treated with imatinib are candidates for surgery. Patient selection should be based on the grade and duration of response to imatinib and the resistance pattern observed. A fresh look at the available literature reveals that the majority of studies published employ their own selection criteria, generally fairly imprecise, which stem from the modification and adaptation of pre-existing radiological criteria,[43,54,74-80] making their interpretation extremely difficult. For a better account of the available data, we will differentiate between patients showing a complete response (total disappearance of all measurable or evaluable disease), partial response (reduction of more than 50% in the size of evaluated lesions), disease stabilisation (response does not meet the criteria for either complete or partial response), focal resistance (one-point growth of the tumour), and disease progression (growth of >50% in tumour size).

The major studies published to date are detailed in Table 3a.[43,54,56,74-80] We must emphasise that the resectability rates, ie, the percentage of patients with advanced disease undergoing surgery following a period of treatment with imatinib, are in reality low, between 10% (Bonvalot et al[43]) and 24% (Gronchi et al[74]).

From analysis of the data shown,[43,54,56,74-80] what is striking is the extraordinary difference observed in survival and DFS rates between patients operated on who were in response (100% and over 60%, respectively, at 2 years) and those who were in progression (0%-60% and 0%, respectively, at 2 years). It is evident that surgery in the case of disease in progression which is not controlled with imatinib offers poor results, such that it should be indicated only for palliative reasons, to control complications such as pain, bleeding or fistulas. Indeed, some centres, such as Villejuif,[43] Essen,[79] or Milan,[74] exclude patients who are in progression from surgery. These patients should be treated with high doses of imatinib, according to tolerance, or with second-line agents such as sunitinib.

Adjuvant surgery remains reserved for those patients in response. The results obtained for this group are excellent, with survival rates of 100% and DFS rates of more than 60% at 2 years.[74,75] Furthermore, neither the average survival nor average DFS have yet been reached in some studies.[12,77,80]

One point of great interest is that the type of surgical resection, that is, its "quality" (R0, R1, or R2), depends on the type of response to imatinib. A recent study of 35 patients at the MD Anderson Cancer Center[54] found that up to 91% of patients in response achieved an R0 resection, while in

Table 3a – Studies of adjuvant surgery following imatinib in advanced GIST.

Study	Year	Resectability, No. (%)	Survival		Disease-free survival	
			R	PE	R	PE
Sun Jin Sym, Seoul[80]	2008	34 (13)	–[a]	23.5 months	21.8 months	3 months
DeMatteo, MSKCC[75]	2007	40	100% (2 years)[a]	0 (1 year)	61% (2 years)[a]	0 (1 year)
Gronchi, Milan[74]	2007	38 (24)	100% (2 years)	60% (2 years)	69% (2 years)	0 (1 year)
Andtbcka, MDACC[54]	2007	25	R0, 95% (2 years), R, 91%. R1.2, 79% (1 year), R, 4%	R0, 55% (2 years). R1.2, 0 (1 year)		
Raut, Dana-Farber[77]	2006	69	95 (5%) (1 year)[a]	0 (1 year)	80 (9%) (1 year)[a]	0 (1 year)
Bonvalot, Villejuif[43]	2006	17 (10)	62 (2 years)	–	23.4 months	–
Rutkowsi, Warsaw[78]	2006	32 (23)	100% (1 year)	75% (1 year)	100% (1 year)	12.5% (1 year)
Bauer, Essen[79]	2005	12 (13)	100% (2 years)	–	92% (2 years)	
Bui, France[76]	2007[b]	96 (36)	80.7% (2 years)	25 (interval, 20-34) months		
Hohenberger, Germany[56]	2006[b]	99	–	–	16 (7–39) months	7 (2–25) months

MDACC indicates MD Anderson Cancer Center; MSKCC, Memorial Sloan Kettering Cancer Center; PE, patients in progression; R, patients in response (RC, RP, and EE).
[a]Average not reached.
[b]Data contributed in abstract form.

the case of progression, R1 or R2 resections were obtained in 96% of cases. These differences have prognostic implications, since patient survival in those where an R0 was achieved was 100% at 30 months, compared to 80% at 12 months where R1 or R2 resections were achieved. Other authors such as DeMatteo et al,[75] Hohenberber et al,[56] and Raut et al[77] also found this link between imatinib response, surgery quality and survival. Survival and quality of surgery depend, therefore, on the response to imatinib, so, which is the determining factor in survival: an R0 resection or a response to imatinib? In other words, does surgery contribute anything in terms of survival to those patients with advanced disease who have responded to imatinib? It could be argued that these studies suffer from a selection bias in operating only on patients with a better prognosis, since these are the patients who responded to imatinib.[75,81] Pending the results of the EORTC-62063 study,[24,82] there is currently no available data from and prospective clinical study which compares patients in response under observation versus adjuvant surgery.[75,81] Only Bauer et al[79] provide data in this respect, although retrospective, reporting survival and DFS rates of 100% and 76%, respectively, at 3 years in the group undergoing surgery following a response to imatinib, compared to rates of 81% and 53% in the group treated with imatinib but not undergoing surgery.

In the case of stable disease, the role of surgery, either immediately or following a brief initial period of response, is controversial. For some the tumour is metastatic, and surgery is ineffective for this. Others, in contrast, believe that surgery can act as a "cytoreducer," in that it may minimise the residual disease and avoid the appearance of resistant clones.[3,8,25] The majority of studies[43,54,56,74-80] include patients with stable disease in the "patients in response" group, making it difficult to extract specific data and assess the role of surgery.

In the case of progression or focal resistance, where a differential response to imatinib is observed in which some lesions respond and others do not, or in situation where, after observing a response, tumour growth foci are identified (clones resistant to imatinib), the role of surgery becomes controversial.[83] The majority of authors advocate the early resection of "hot" focal lesions.[77,84] The available data (Table 3b),[75,77,85,86] albeit using a small number of patients, shows that surgery offers worse results than a complete response but better than in progression, with survival rates of 86%-100% and DFS rates of 25%–48% at 1 year. Surgery can prolong DFS and overall survival while the remainder of the disease is controlled using imatinib. Other therapeutic options include radiofrequency (RF) or chemoembolisation.[87,88]

Table 3b – Studies of adjuvant surgery in advanced GIST with focal progression

	1 y	No. (%)	DFS, %	S, %
DeMatteo (2007)[75]		13 (32)	48	90
Al-Batran (2007)[85]		9 (36)	40	90
Hasegawa (2007)[86]		16	25	100
Raut (2006)[77]		32 (47)	33	86

DFS indicates disease-free survival; S, survival.

In conclusion, the indications for surgery in metastatic GIST following treatment with imatinib are: *a)* stable disease or in response if surgery can achieve an R0; *b)* focal progression with clones resistant to imatinib following an initial response to the drug, if the remainder of the disease is controlled; and *c)* development of complications such as haemorrhage, perforation, obstruction, or abscesses. Surgery is contraindicated in the case of generalised disease progression.[3,60,89]

From a technical point of view, surgery in these patients should have R0 resection as the primary objective, and it is essential to sustain treatment with imatinib until the day prior to surgery. Any decision regarding the timing of surgery, should be joint and coordinated between surgery, radiology, and oncology.[3,60]

Adjuvant surgery usually consists of very aggressive resections, owing to the dissemination of the disease. On other, fewer, occasions, surgery consists of a simple sampling of small intraperitoneal nodules.[41] It is generally necessary to combine an omentectomy with peritoneal stripping when performing intestine and liver resections. In some studies, such as the MSKCC,[75] hepatectomies account for up to 43% of surgical procedures carried out. Management of metastatic liver disease is very complex, since it is frequently diffuse or bilobar, thus impeding standard resections. This usually results in a necessary combination of atypical resective surgery with RF[88] or cryotherapy.[58,74,78] Some authors argue in favour of RF in cases of fewer than 5 lesions that are less than 4 cm in diameter, and arterial embolisation in cases of larger disease.[58,87,90] The possibility of liver transplant with imatinib treatment in metastatic GIST has been reported, although only in anecdotal form.[91]

This type of surgery, given its aggressiveness, is associated with a higher rate of morbidity. The MSKCC[75] reports a complication rate of 58% without perioperative mortality, while the Milan group[92] reports a 38% incidence of postoperative pneumonia and 14% rate of major surgical complications. Other authors[79,93] report figures close to 27%.

One issue of concern is the possibility that, secondary to the effect of the imatinib, some tumours bleed or perforate and require urgent surgery.[83,94] While this argument is logical, it comes more from a theoretical point of view, since the number of patients who are subject to surgery for haemorrhage or perforation is anecdotal.[43,74,75,77]

All patients who undergo adjuvant surgery, whether or not this achieves a complete cytoreduction, should be given postoperative treatment with imatinib,[95] which can be reinstated 2 weeks following the intervention. Not only does this influence postoperative scarring, it also helps prevent premature relapse.[74]

An issue that remains unresolved is deciding how long to treat patients with medication before undergoing surgery.[39] Advocates of early surgery argue that it reduces the possibility of resistance, a possibility that is directly proportional to the number of viable tumour cells and the duration of medical

therapy.[38] They argue that it also reduces the risk of digestive or intraperitoneal haemorrhage, occurring in up to 5% of patients. Other authors, in contrast, favour later surgery in order to attain the best response rate possible and, therefore, a better rate of R0 resections, organ preservation and lower surgical morbidity.[39] Given that the average time before the appearance of resistance to imatinib is approximately 2 years[29,71] and from nine months no response is observed,[75,96] the majority of studies advocate surgery 3 to 5 months after starting treatment, whenever stabilisation or morphological response is observed.

Guidelines for action in advanced GIST

Pending the results of a range of prospective multi-institutional studies currently being carried out, very few recommendations can be made that are backed up with a high level of evidence. Despite this, various organisations, both national and international, have published their own guidelines for the management of advanced GIST. Among these guidelines are those of: GEIS (Spanish Sarcoma Research Group),[97] the NCCN (National Comprehensive Cancer Network),[3,98] and ESMO (European Society of Medical Oncology).[60]

All patients should be managed from the start by a multidisciplinary team that should include radiologists, surgeons and oncologists.[3,60,98] If the tumour presents as advanced from the start, a biopsy is obligatory in order to establish that it is a GIST and ascertain the mutational state of the tumour. Once confirmed, there are 2 scenarios, that of a locally advanced tumour or tumour in a difficult location, and that of unresectable metastatic disease.

With the first scenario it is essential to bear in mind that these patients, given their disease progression, can quickly become unresectable, therefore a continued and strict monitoring is obligatory. The management of these patients should, following a CT with or without a basal MRI together with a PET, be neoadjuvant treatment with imatinib. The initial dosage should be 400 mg/day, unless the tumour shows a mutation in exon 9 of the *c-Kit*, in which case the dosage should be 800 mg/day. To find out whether a premature response has occurred, a control PET should be carried out together with a CT with or without an MRI, which will inform us of any response and its grade. If there is a response, treatment with imatinib can continue until the maximum possible response is reached, normally after 3-6 months and always determined with a multidisciplinary approach, in order to proceed to surgical resection. If, in contrast, no response is observed and the disease is showing progression confirmed by a CT, the patient should undergo surgery if it is possible. Otherwise, treat as a patient in progression (see below). Following the resection, and if the resection is an R0, the patient can be treated with imatinib if they showed a preoperative response. The monitoring should be carried out using a CT every three months until recurrence or progression of the disease. We must emphasise that neoadjuvant management of a GIST is not a common procedure and should only be carried out by specialist teams.

In the case of metastatic GIST, management is similar to that described above; however, assessment of the response to imatinib should be carried out within the first 3 months of beginning treatment, using a CT with or without PET. In the case of the disease showing no progression, ie, if a response is observed or the disease stabilises, a surgical resection should be considered if an R0 resection can be achieved. Following this, treatment with imatinib should be continued while monitoring the patient every 3 months, using an abdominopelvic CT, until recurrence or progression of the disease. In the case of a resection not being possible, ongoing treatment with imatinib should be continued The ESMO guidelines[60] recognise the possibility of immediate surgery in metastatic GIST where an R0 resection is possible. However, the available data tells us that surgery is not curative in these situations, and imatinib is the treatment of choice. The choice between surgery and imatinib should be discussed with the patient.

In the case of disease progression, it is necessary to differentiate between limited progression (focal resistance) and generalised progression (overall disease progression). In the first case, if surgery is possible, it should be attempted. Other options include RF and embolisation, with an increase in the imatinib dose or an exchange with second-line agents such as sunitinib. In all cases, re-evaluation of the response is obligatory (PET or CT). Radiotherapy should only be used for palliative purposes in cases of osseous metastases. In cases of disease progression, and where the patient can clinically tolerate it, imatinib is continued, the dose is increased, or sunitinib is used. Again, re-evaluation is obligatory. In either of the 2 situations described, if faced with a lack of response to the therapeutic measures applied, a definitive interruption of treatment should be considered.

In conclusion, the treatment of GIST has benefited from advances and the practical application of evidence-based medicine; proof of this lies in the multiple multi-institutional prospective studies carried out and the many guidelines published to date, a change in the surgical mindset, since the surgeon's repertoire now includes the concepts of neoadjuvancy and cytoreduction, and transferable molecular biological research (imatinib).

We must consider that, even though imatinib is the standard treatment for advanced GISTs, surgical resection is the best therapeutic option, and should therefore be considered for all patients and in every stage of the natural history of the disease. For this, interdisciplinary coordination between surgery, radiology, and oncology is essential, as decisions must be made on an individual basis.

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