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Difficulties in conducting pure academic research, obstacles in data collection and quality of informations: The example of the INTERCEPTOR study

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ABSTRACT

Purpose/Objective: On September 2009: We started a randomized multicenter phase III study comparing chemoradiation (CRT) (Aldestein RTOG regimen) versus induction chemotherapy followed by Cetuximab radiation (IBRT). The main study's aim was comparison of overall survival but no formal analyses have been made between the two arms because of low accrual and high amount of missing data. The goal of this paper is to identify the reasons of difference in accrual and quality of data among participating centers.

Material/Methods: Statistic: We correlated data collection quality with relevance of the centers, accrual and number of scientific papers (both specific on HNC and other topics) of each PI. We created an HNC publishing score dividing the number of HNC specific papers for the overall number of published papers.

Results: We observed a strong difference in the accrual of pts as well as in the quality of data among the participating centers. The accrual was independent from the quality of data since some centers with low accrual produced high quality data with an excellent follow up. We found a correlation among both number of published papers of each PI and HNC publishing score with the quality of data.

Conclusion: The study demonstrated that expertise in HNC is important not only to ensure a better outcomes but also to provide high quality *data* in phase III trials.

Introduction

Head and neck cancer is a complex disease arising from mucosal layer of oral cavity, nose, paranasal-sinuses, pharynx, larynx, characterized by dismal prognosis in recurrent metastatic disease. Prognosis is affected by both tumor and patients' features such as tumor stage, primary anatomic site, performance status, comorbidities, age, voluptuary habits and biology. The treatment of head and neck cancer requires significant expertise, given the structures and vital functions involved [1].

In 2007 we designed a multicenter phase III trial comparing induction chemotherapy followed by cetuximab concomitant to radiotherapy versus concurrent chemo-radiotherapy in locally advanced, unresectable head and neck cancer. Patients accrual started in 2009. The study did not achieve any economical support by the Institutions or by drug companies and was activated and conducted as a pure academic study.

All the authorization processes and the following conduction of the trial were based on the trial office of the main institution while the data entry and their update (using an available electronic case report form) as well as their quality, was under the responsibility of the participating centers.

After the activation of the study, in order to increase the accrual rate, we accepted more centers than those planned despite the fact that we were not able to control the quality of the data and their update by the participating centers due to the lack of funding for the research that precludes, for example, the organization of the site visits.

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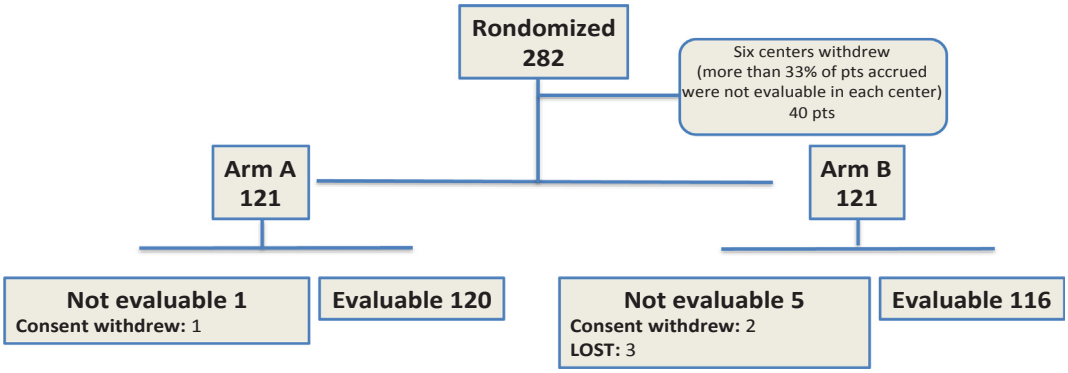


Consort diagram : among 282 randomized patients, 40 were not evaluable because of major missing data; of remnant patients in Arm A 120 were evaluable because of 1 consent withdrew and 116 were evaluable in Arm B because of 2 consent withdrew and 3 lost of contact.

Fig. 1. CONSORT diagram. Consort diagram: among 282 randomized patients, 40 were not evaluable because of major missing data; of remnant patients in Arm A 120 were evaluable because of 1 consent withdrew and 116 were evaluable in Arm B because of 2 consent withdrew and 3 lost of contact.

The study couldn't report a formal comparison between the two arms because of the insufficient accrual and the censoring of many centers due to the low quality of their data.

The present paper reports the difficulties encountered during the INTERCEPTOR conduction, and analyses the impact of expertise in the quality of data record.

Materials and methods

Interceptor trial is a phase III multicenter randomized trial on LA-HNC (stage III–IV) started in 2009.

After 8 years from the start of patients' enrolment, 282 patients had been accrued, but some Centers where censored because their performance was grossly inadequate in terms of data provided to the Trial Coordinating Center (with > 33% of enrolled patients with major data missing post randomization). Therefore only 236 patients were considered available for the analyses (Fig. 1).

Due to the long time since the study start, and to the fact that patients' enrollment was very slow, it was decided to proceed with an unplanned interim futility analysis.

Additionally considering the amount of missing data we decided to correlate quality of data with center relevance, accrual and principal investigator expertise.

We considered the ratio among evaluable and enrolled patients for each center, and we correlated this value with the relevance of the center and the experience of PI either specifically in HNC or generically in the conduction of oncology trials.

Relevance of center in this paper was established considering position in the regional oncologic network (HUB and spoke model), the experience of PI was measured as number of published paper in HNC or generically in any oncology field.

Finally, we create a "HNC publishing score" (HNPS) for each P.I., dividing the number of HNC specific papers for the overall number of published papers.

Results

Participating centers

Centers were selected on the basis of their interest in participating into the study and on the presence of a head and neck surgical team, a medical oncology department and a radiation oncology department operating inside a multidisciplinary board (MDB) in the same institution.

In addition, centers missing one of these services in their structure but with a consolidated cooperation with a comparable service operating in their geographical proximity were also admitted.

However, due to the slow accrual observed during the first 3 years, we decided to increase the number of participating centers, accepting also some institutions initially excluded.

Twenty centers achieved the Ethical Committee approval but only 16 of them enrolled patients into the INTERCEPTOR study (Table 1).

Among them, only 3 centers accrued more then 20 pts and they account for 61% of the whole study population. Seven centers among the remaining 13 accrued less than 10 pts each (27 pts cumulatively). In addition, six centers had more than 33% not evaluable pts and were excluded.

However the cumulative accrual does not necessarily reflects the accrual per year. Indeed some center join the study since its begin while other were affiliated later. In general centers with 9 ± 3 accrual per year performed as those with high total cumulative accrual.

It might be stressed that among centers with low accrual there are some with high performance: some centers with low accrual/per year (3.6 ± 2 pts) had 80% evaluable patients.

In contrast other centers with the same low accrual rate had more than 33% of not evaluable patients.

Evaluable patients

The consort diagram (Fig. 1) reports the reasons for exclusion from the analysis.

Overall, 46 pts (16%) were randomized but cannot be analyzed for the primary endpoint (overall survival) and have been withdrew (see Fig. 1 Consort Diagram). Data on Progression free survival were reported on 228 patients. Due to the long time since the study start, missing data and slow accrual we decided to proceed with an unplanned interim futility analysis.

Futility analyses are widely used to assess if a study can be concluded because its interim results allow ruling out, with adequate confidence, that even if continued to its planned end, the study could provide a positive result. Due to results of the analyses the study was stopped.

Analysis of missing data

Data missing by centers are summarized in Table 1.

Table 1
Evaluable patients. Centers with > 20% not evaluable pts are censored.

Center	Enrolled pts	Evaluable pts (%)	Non elig.	Never treated worsening clin conditions	Consent withdrawn (treatm.) (%)	Missing life status (%)	Any data missing (%)
7 -	74	73 (98%)	0	0	1 (BRT) (1%)	0	5 (7%)
6 –	76	74 (97%)	2	0	0	0	0
46 –	14	7 (50%)	0	1	4 (4 CRT) (28%)	2 (14%)	5 (36%)
57 -	22	22 (100%)	0	0	0	0	2 (9%)
54 -	14	13 (93%)	0	0	1 (CRT) (7%)	0	1 (7%)
51 –	18	15 (83%)	1	0	1 (CRT) (5%)	1 (5%)	3 (16%)
53 -	13	12 (92%)	0	1	0	0	1 (7%)
44 –	13	8 (62%)	0	0	2 (2 BRT) (15%)	3 (23%)	4 (30%)
47 -	8	7 (87%)	0	1	0	0	3 (37%)
64 –	6	0	0	0	3 (3 CRT) (50%)	3 (50%)	3 (50%)
56 –	2	0	0	0	0	2 (100%)	2 (100%)
67 –	11	11 (100%)	0	0	0	0	0
69 -	2	0	0	0	2 (2 CRT) (100%)	0	0
16 -	3	0	0	0	1 (BRT) (33%)	2 (66%)	2 (66%)
40 -	5	4 (80%)	0	0	0	1 (20%)	1 (20%)
9 –	1	1 (100%)	0	0	0	0	0
TOT 16 Cent	282	247 (87%)	3	3	4 (BRT) + 11 (CRT) = 15	14	32 (11%)
10 cent	242	232 (82%)	3	2	1 (BRT) + 2 (CRT) = 3	2	16 (5.5%)

Note: Centres are identified with a number, we decided to not reveal name of centres and principal investigator.
Abbreviation Cent = center BRT Cetuximab-radiotherapy; CRT cisplatin radiotherapy.

Only 1 center (code 7) among those 3 that recruited 172 pts, recorded a single case of consent withdraw, compared to 14 cases reported in the 13 remaining centers that recruited 110 pts cumulatively (1/172 versus 14/110; Yates' $X^2 = 17.1354$, $p = 0.000031$).

Consent withdraws occurred in 4 pts in arm A and in 11 pts in arm B (Yates' $X^2 = 2.53$, $p = 0.11$).

Curiously, those centers recording more then 1 withdraw had withdraws always in the same study arm.

Finally, 19 pts (12 and 7 in arm A and B respectively) were lost before the first response analysis. Whereas all the data were missed in 14 patients, the life status of five of them (2 in arm B and 3 in arm A) was retrieved by the general register office. These latter pts were considered in survival analysis.

Data missing (excluding survival)

Only 4 centers did not miss any data,. However one of them enrolled 2 pts and they both withdrew the consent and another one enrolled only 1pt. The median data missing ranged between 0% and 100% (median 25%) in the remaining centers (Table 1).

Among the 4 Centers that recorded more than 1 consent withdraw, 3 centers (code 46, 64, 44) had also a high percentage of pts with data missing (36%, 50% and 30% respectively), with the exception of a single institution (code 69) that did not treat any pt.

One or more data is missed in 16% of pts overall.

Six centers (46, 44, 64, 56, 69, 16) account for 71% of not evaluable pts.

Considering the rate of not-evaluable pts, it shows an inverse relationship with pts accrual: 1.7% in the 3 centers recruiting more than 20 pts each, 20.4% in those recruiting 10 to 20 pts and 55.5% in those recruiting less than 10 pts ($X^2 = 69.209$; $p = 0.000$) (Table 2).

Table 2
Relationship between the pts accrual by center and the rate of not evaluable pts.

Centers by accrual	Enrolled	Evaluable	% not evaluable
> 20 pts (3 centres)	172	169	1.7
10–20 pts (6 centres)	83	66	20.4
< 10 pts (7 centres)	27	12	55.5

$X^2 = 69.209$.
$p = 0.000$.

Correlation between accrual volume and papers per Principal Investigator

At the end of the study, due to the poor quality of many of the data collected, we retrospectively verified the expertise of local PI in the INTERCEPTOR study.

To do that, we analyzed the overall published papers and those specifically based on HNC by each local principal investigator since the beginning of this century (Table 3).

The P.I. of six centers published 25 papers or more each on HNC. These centers randomized 215/282 pts and only 7 of them were not evaluable (3.2%). The P.I. of the remaining centers published 0 to 2 HNC papers each and account for 67/282 pts, 28 of them where not evaluable (41.8%) ($X^2 = 69.77$; $p = 0.000$) (Table 3).

Interestingly, among the P.I.s of centers who published papers in the HNC field (ten P.I.s), only four of them published HNC papers also based on translational research, supportive care, epidemiology or other aspects not strictly related to controlled clinical trials albeit clinical trials was the core of their scientific production. All of them belong to the group with 25 or more papers on HNC. They cumulatively accrued 125 pts, 121 of them were fully evaluable (97%).

The P.I. of 8 centers published more than 60 scientific paper overall each since year 2000. They account for 209/282 pts including 16 not evaluable (7.6%). The other P.I. published less than 60 paper and they account for 73/282 pts 19 of whom not evaluable (26%) ($X^2 = 16.79$; $p = 0.000$).

Then we considered the HNPS for each P.I.

Seven P.I. have a HNPS ≥ 0.25 and they account for 228/282 enrolled pts. Among them only 8 were not evaluable (3.5%). Nine P.I. have a HNPS < 0.25 and they account for 54/282 pts 27 of whom not evaluable (50%) ($X^2 = 86.80$; $p = 0.000$).

Further, we have applied the correlation test of Spearman to HNPS/not evaluable rate and to the number of papers specific in HNC per P.I./not evaluable rate. Both analyses are highly significant ($p = 0.0016$ and $p = 0.0054$ respectively) (Figs. 2–3).

We also try to analyze the not evaluable rate according to the importance of the centers involved. We divided the 16 centers in: group N (HUB centers of national relevance, 7 centers) and group R (spoke centers of regional relevance, 9 centers). The two groups accrued a similar number of patients (134 and 148respectively).

Evaluable pts were 115 and 132 in N and R respectively ($X^2 = 0.73$; $p = 0.39$, NS).

Table 3
Principal Investigator/publications per center.

Center	P.I.	Paper 2000- >	Paper HNC	Enrolled pts	Evaluable pts	Not evaluable rate
7 -	7	139	58	74	73	2%
6 –	6	111	37	76	74	3%
46 –	46	8	0	14	7	50%
57 -	57	30	25	22	22	0
54 -	54	91	28	14	13	7%
51 –	51	67	35	18	15	17%
53 -	53	8	2	13	12	8%
44 –	44	11	2	13	8	38%
47 -	47	85	0	8	7	13%
64 –	64	81	1	6	0	100%
56 –	56	114	1	2	0	100%
67 –	67	262	204	11	11	0
69 -	69	58	0	2	0	100%
16 -	16	33	0	3	0	100%
40 -	40	3	0	5	4	20%
9 –	9	10	1	1	1	0
TOT	16 Centers			282	247	35 pts

Centers withdrawn were 46, 44, 64, 56, 69, 16.

Discussion

Our goal was to focus on the obstacles to conduct an academic trial. We focused on the reasons of difference in accrual and quality of data among participating centers.

Centers were selected on the basis of their declared interest for the study and on the availability of the clinical facilities necessary to perform the treatments. Moreover most Centers had known expertise in the participation in multicenter clinical trials.

Of course, these selection criteria may be biased by other factors. For example, the availability of a MDB may not be strictly correlated with a propensity to perform clinical research.

In addition, due to the initial slow accrual, we adopted less strict selection criteria, in particular with regard to the potential recruitment of new cases or the experience in conducting clinical trial.

We were aware that increasing the number of centers weakening the selection criteria to ensure a better patient accrual would have represented a risk for the quality of data, but, honestly, we underestimated this risk.

Moreover the absence of a financial support did not allow a close monitoring of data entry and contributed to the lack of information.

In our opinion the lack of financial support may represent a key issue.

For example, the study of Ghi et was performed in the same Country (Italy) and was also an academic trial. It faced the same patient population (locally advanced head and neck cancer) and accrued patients

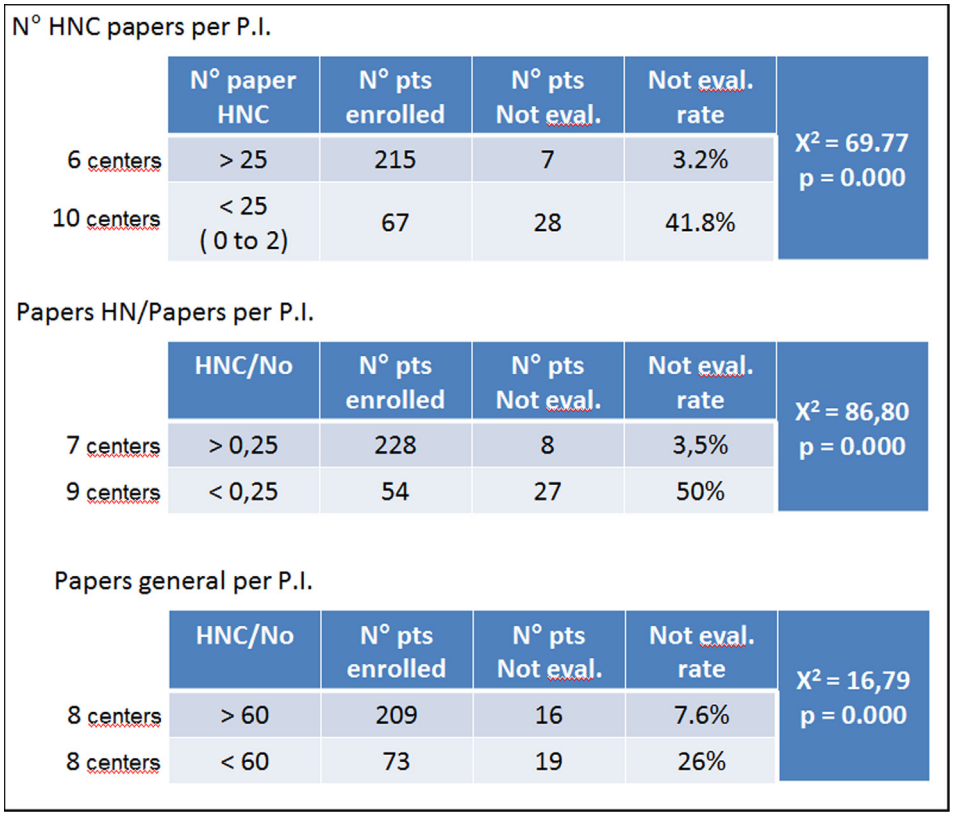
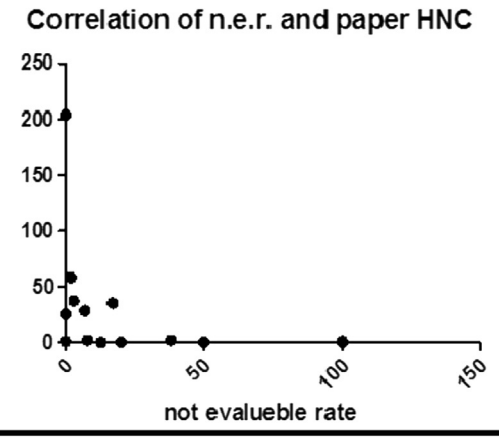


Fig. 2. "HNC publishing score" (HNPS) for each P.I., (number of HNC specific papers/overall number of published papers).

Correlation Tabular results		A paper HNC
		Y
1	Number of XY Pairs	16
2	Spearman r	-0.6601
3	95% confidence interval	-0.8747 to -0.2291
4	P value (two-tailed)	0.0054
5	P value summary	**
6	Exact or approximate P value?	Gaussian Approximation
7	Is the correlation significant? (alpha=0.05	Yes



Correlation Tabular results		A paper HNC
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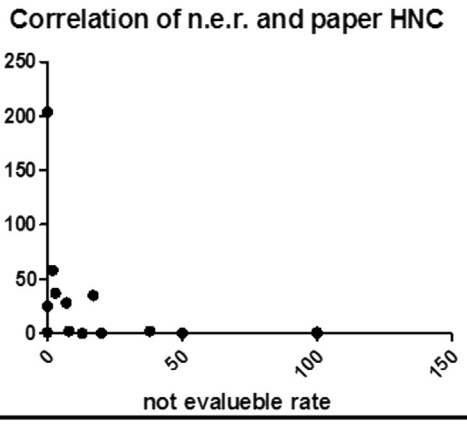

Fig. 3. The correlation test of Spearman to HNPS/not evaluable rate and to the number of papers specific in HNC per P.I./not evaluable rate.

in part during the same years (2003–2012).

The CONSORT diagram of the Ghi's study reports missing data to evaluate response in only 21 patients out of 421 enrolled (5%). This data compares favorably to the INTERCEPTOR study.

However, the Ghi's study was funded in part by a drug company and in part by a private foundation [8].

Chan et al have already reported the importance of research funding for the conduction of clinical trials [8] thus emphasizing the fragility of

a multicenter study lacking economic support.

We report a significant relationship between the pts accrual and the rate of not evaluable pts.

There is limited literature on the challenges encountered during no profit research in HNC.

Several findings support the idea that experienced HNC MDB likely execute superior treatment plans and may better support patients through treatment [3].

However, as reported above, an existing MDB is not a guarantee per se of the collection of good quality data during clinical trials.

Prior research showed a correlation among treatment center experience and survival [2].

Moreover definition of expertise differs among published papers varying from provider's volume, historical accrual in trials, and number of treated patients.

In 2003 Benasso et al compared outcome of patients involved in two multicenter randomized trials coordinated by National Institute for Cancer Research of Genoa (IST). They demonstrated that 3-year OS was significantly higher for patients treated with CTRT at the coordinating centre vs the affiliated centers (46% vs 27% P = 0.0001) [2].

The effect of institutional experience on OS in patients with stage III or IV HNC was investigated within a randomized trial of the Radiation Therapy Oncology Group (RTOG 0129). They reported significantly worse OS and PFS among patients with HNC treated at institutions with historically low- (HLACs) as compared with historically high-volume accrual (HHACs). Risk of death or progression was 90% greater for patients at HLACs. There was higher loco-regional recurrence rates at HLACs compared with HHACs. Deviations from protocol therapy were more common at HLACs than HHACs. The authors showed that unacceptable RT protocol noncompliance was higher in HLACs compared with HHACs (11% vs 5% p = 0.04) [4].

In 2010 another HNC trial TROG02.02 (Trans Tasman Radiation Oncology Group 02.02) reported no compliance in RT in 25% of patients. These patients compared with those compliant with protocol plans, had double the 2 year locoregional failure rate (46% vs 22%) and an absolute reduction in 2 year OS of 20% (50 vs 70%). In this study the probability of receiving poor-quality RT was correlated with the number of patients who were enrolled at centers [5].

Lassing et al confirmed in a retrospective analysis a different OS among academic and community center [6].

However, in our study the not evaluable rate was not significantly dependent by the characteristic of the centers.

A significant correlation between the number of accrued patients and the not evaluable rate was also reported by others [3].

Nevertheless among centers with low accrual there are some with excellent outcome (code 67).

We found a strong correlation existing between the scientific production in HNC of the P.I. and the not evaluable rate of the center.

Albeit most P.I. have experiences in clinical trials, and have a good scientific production, the data show that the specific expertise in HNC studies is required.

It could reflect both the relative rarity of the disease and its complexity, which requires a strong familiarity with a multidisciplinary approach.

Our analysis suggests that the conduction of an academic clinical study lacking economic support in a complex field such as head and neck tumors requires the profound interest of the P.I. in this specific field.

The interest of the P.I. can be measured from its scientific background and represents a fundamental element for the success of the study.

On the contrary, no correlation emerged between the importance of the center and the quality of the data, thus reinforcing the role of the P.I.

The analysis of the literature data [8,7] suggests that funding of academic clinical trials could at least reduce the risk of failure.

Many paper along the last two decades have analyzed the impact of the center expertise on the outcome but for the first time this study analyzes the impact of the expertise of researchers on the quality of collected data.

Declaration of Competing Interest

MCM has served on Ad Boards for Meck KGaA, Merck Sharpe and Dohme and BMS and had a speaker role in Merck-promoting meeetings.

L Licitra served on Ad Boards for Meck KGaA, Merck Sharpe and Dohme, Eisai, BMS, Novartis.

MB has served on Ad Boards for Meck KGaA, Merck Sharpe and Dohme.

PB has served on Ad Boards for Meck KGaA, Merck Sharpe and Dohme.

LLo has served on Ad Boards for Meck KGaA, Merck Sharpe and Dohme, Eisai

All the other authors decline conflict of interest

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The authors are fully responsible for the content of this manuscript, and the views and opinions described in the publication reflect solely those of the authors.

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