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(54) Titre : COMPOSE ANTITUMORAL ET SON PROCEDE DE PRODUCTION
(54) Title: ANTI-TUMORAL COMPOUND AND RELATIVE PRODUCTION PROCESS



(57) **Abrégé/Abstract:**
The present invention relates to an anti-tumoral compound for the localized treatment of neoplastic pathologies of malignant kind that cannot be surgically removed or with a high risk of local recurrence, comprising: a bicomponent injectable biologic glue; an antineoplastic substance; an epinephrine-based solution. Said compound may be used as an independent therapeutic treatment, as it allows to treat tumoral masses that are not surgically removable, or as a therapeutic treatment complementary to surgical removal or to known ablative techniques (laser, radiofrequency, microwaves, etc.) for a maximization of the efficiency of said therapies reducing the risk of neoplastic relapses in the original surgical site. A process for the production of said antitumor compound is also object of the present invention.

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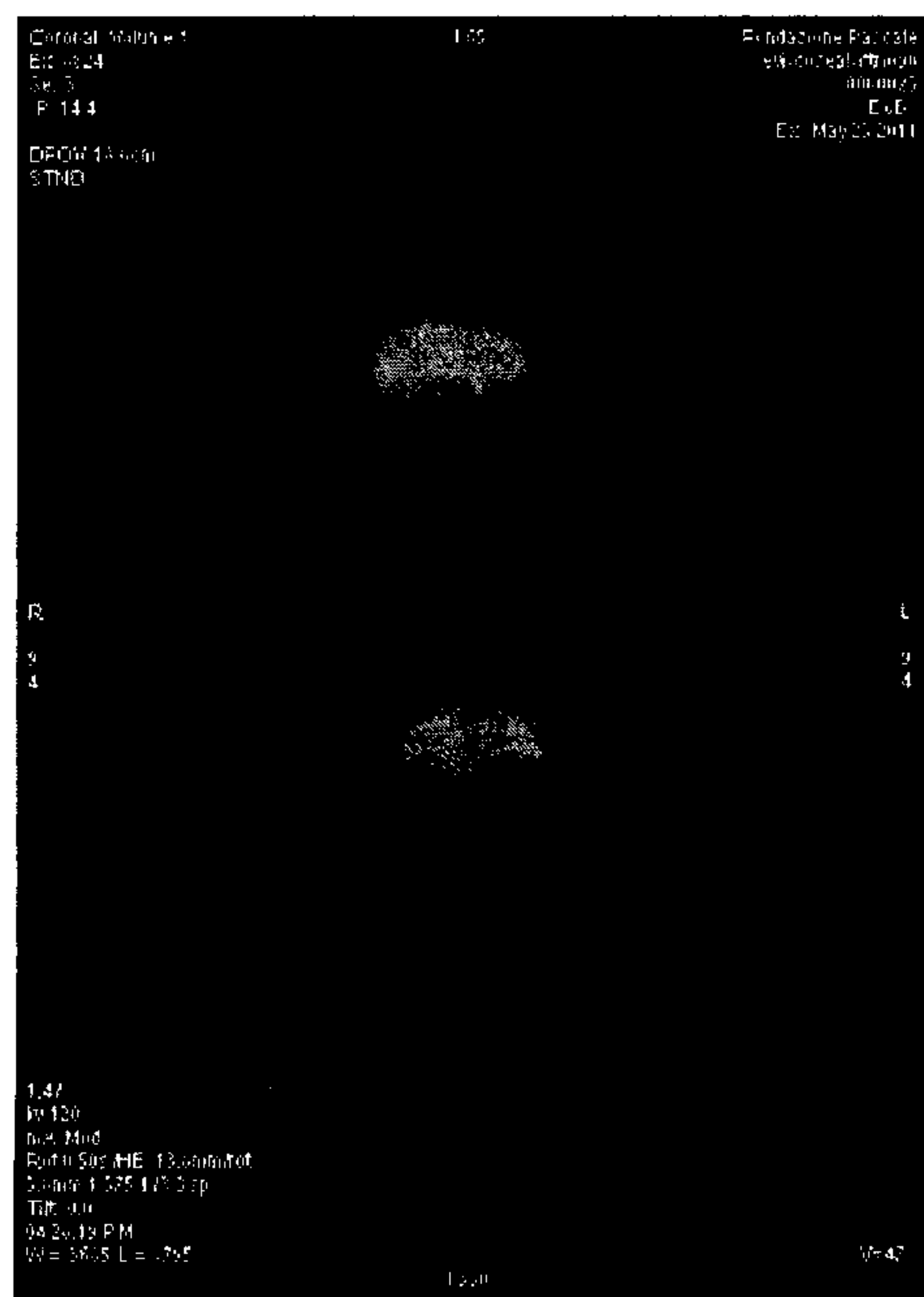


FIG. 4

(57) Abstract: The present invention relates to an anti-tumoral compound for the localized treatment of neoplastic pathologies of malignant kind that cannot be surgically removed or with a high risk of local recurrence, comprising: a bicomponent injectable biologic glue; an antineoplastic substance; an epinephrine-based solution. Said compound may be used as an independent therapeutic treatment, as it allows to treat tumoral masses that are not surgically removable, or as a therapeutic treatment complementary to surgical removal or to known ablative techniques (laser, radiofrequency, microwaves, etc.) for a maximization of the efficiency of said therapies reducing the risk of neoplastic relapses in the original surgical site. A process for the production of said antitumor compound is also object of the present invention.

ANTI-TUMORAL COMPOUND AND RELATIVE PRODUCTION PROCESS

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5 The present invention relates to the field of therapeutic drugs and medicines for antitumor treatments.

More in detail, the present invention concerns an anti-tumoral compound for the localized treatment of neoplastic pathologies of malignant kind that cannot be excised by surgery, or with a high risk of local recurrence.

10 It is well known that in presence of neoplastic pathologies of malignant kind like, e.g., hepatocellular carcinoma, colorectal cancer or breast cancer, the removal of the tumoral mass is the only therapeutic treatment that guarantees the long term survival of the patient.

15 It is furthermore known that, at the light of the present medical knowledge, not all neoplastic pathologies of malignant kind may be removed by surgery, as said therapeutic method is tightly depending on the patient's clinical condition, on the localization of the neoplasias and on the morphologic features of the tumoral mass to be removed.

The removal of a neoplastic mass by surgical resection cannot be performed in the following cases:

- 20 - if in the patient's body there is a non neoplastic pathology (comorbidity) involving the organ attacked by the tumoral mass, or the anatomic region comprising the same;
- if the removal of the tumoral mass determines the alteration of the functionality of the treated organ;
- 25 - if the removal of the tumoral mass determines aesthetic or functional modifications such as to permanently change the lifestyle of the patient.

Furthermore, the surgical removal of a tumoral mass can not be performed without the certainty of obtaining a resection margin of healthy tissue of at least one centimetre from the infiltration limit of the tumoral cells, as it has been widely shown that resection margins less than one centimetre favour
5 the recurrence of neoplastic pathologies of malignant kind in the original surgical site.

It is known that therapeutic methods alternative to surgical resection of a tumoral mass usually comprise:

- chemotherapy or radiotherapy treatments, systemic and/or
10 locoregional;
- intra-arterial treatments like, e.g., chemoembolization, chemoperfusion or radioembolization;
- localized ablative treatments, obtained by means of quick freezing (cryoablation), chemical desiccation (alcohol ablation), or necrosis
15 of tumor cells induced by hyperthermia (ablation by means of laser, microwaves, radio frequency, etc.).

It is further known that said methods have important and numerous limits or side effects, as:

- the high toxicity of the antineoplastic substances used in the
20 treatments like chemotherapy and radiotherapy makes a long term application of said therapies impossible;
- the quick freezing of the tumoral tissues, or the necrosis induced by hypothermia thereof, causes breaks and bleedings in the cell structure of the treated organs;
- 25 - the desiccation of the tumoral tissues, obtained by the localized injection of alcohol, determines an incomplete necrosis of the same due to a non uniform distribution of said substance through the

tissues.

Furthermore, none of said therapies proves to be radical for the purpose of allowing a long term survival of the patient.

In the pharmaceutical field, the method consisting in the inclusion of one
5 or more active principles in a viscous material, functioning as a carrier of the same, for obtaining medical compounds allowing the localized treatment of different pathologies, is well known.

Among the many typologies of compounds that may be commonly obtained with said method, those with anti-inflammatory, antimicrobial,
10 antihemorrhagic, dermoregenerating, analgesic, disinfectant and other action will be reported as an example.

Therefore, it is the aim of the present invention to obtain a compound for antitumor use that may be applied for the local treatment of neoplastic pathologies of malignant kind that cannot be surgically treated or showing
15 a high risk of local recurrence by the inclusion, in a viscous material functioning as a carrier, of a substance having appropriate neoplastic capacities and functioning as a therapeutic agent.

It is furthermore the aim of the present invention to overcome some of the problems and of the limits deriving from the use of therapeutic methods
20 commonly used for the treatment of neoplastic pathologies of malignant kind which cannot be treated surgically, or having a high risk of local recurrence.

The aim set forth is reached by means of an anti-tumoral compound, characterized in that it comprises:

- 25
- an injectable biological glue consisting of two distinct chemical mix;
 - an antineoplastic substance;
 - an epinephrine-based solution;

wherein said injectable biological glue is arranged for solidifying, keeping the antineoplastic substance in loco in cooperation with the vasoconstriction effect induced by epinephrine.

In accordance with one embodiment, there is provided an anti-tumoral composition for injection into a treatment site, comprising: an injectable
5 biologic glue consisting of two distinct chemical mixes: (i) a first chemical mix and (ii) a second chemical mix comprising an activating agent; and an antineoplastic substance comprising biocompatible microspheres with diameters between 20 and 60 microns labelled with yttrium radioactive
10 isotope (^{90}Y) having an activity between 259 to 3000 MBQ; wherein said injectable biologic glue is arranged for solidifying after mixing said two mixes upon injection to keep the antineoplastic substance in loco and homogeneously distributed in the biologic glue.

According to a preferred embodiment of the present invention, the
15 injectable biological glue is a haemostatic gel, or a hydrogel.

According to a further embodiment, the compound according to the present invention may comprise an antineoplastic substance with radiotherapy or chemotherapy effect.

A process for the production of said anti-tumoral compound is also the
20 object of the present invention.

In accordance with one embodiment, there is provided a process for the production of a compound for antitumor use, comprising: preparing a first injectable compound; preparing a second injectable compound comprising an activating component; pre-dosing said first and second compounds
25 inside disposable syringes, and subsequently storing said compounds at a low temperature; warming said compounds, when they are to be used, up to the temperature of 37°C; adding to said compounds a solution of

biocompatible microspheres with diameters between 20 and 60 microns,
labelled with yttrium radioactive isotope (^{90}Y) having an activity between
259 to 3000 MBq to generate a homogenous distribution of microspheres
in the biogluce; injecting said compounds using a coaxial catheter with a
5 double lumen.

The compound according to the present invention has many and important
advantages:

- it may be given at an intra-tumoral level, for the purpose of
determining the complete necrosis of the tumoral tissues around
10 the inoculation area, thus allowing the treatment of tumoral masses
of malignant kind that cannot be surgically removed;
- it may be applied as a filling material of surgical wounds deriving
from a surgical resection, or from ablative treatments, of tumoral
masses of malignant kind, for the purpose of determining the
15 complete necrosis of possible residual tumoral cells localized along
the edges of said wounds;
- it determines a greater efficiency of antineoplastic substances,
producing a favourable increase of the administration period and of
the dosage of said substances at a local level, due to the
20 concentration of the same inside the treated tumoral masses, or
inside said surgical wounds deriving from surgical removal, or from
ablative treatments, of the same;

- it prevents the free diffusion of said antineoplastic substances in the body of the patient, consequently limiting the systemic exposure to the toxic components of the same;
- it allows overcoming of the side effects deriving from the application of the therapeutic methods substitute for the surgical resection of the tumoral masses of malignant kind;
- besides, the inclusion of neoplastic substances into a material having viscous structure limits the exposure of the medical staff to the toxic components of said antineoplastic substances when the drug is given to the patient.

The anti-tumoral compound according to the present invention is based, as said before, on the principle of including a substance with suitable antineoplastic capacities into a special material with a viscous structure, arranged for functioning as a carrier for said substance.

- Special biocompatible microspheres have been labelled with a radioactive high energy isotope for therapeutic use, then including the radiolabelled microspheres into a quick solidification haemostatic gel, thus obtaining a compound for antitumor action that may be directly inoculable inside tumoral masses that cannot be surgically treated, or that may be applied as a filling material in surgical wounds deriving from surgical resection of said tumoral masses.

Actually, histologic examinations have shown that said compound induces a favourable necrosis of the neoplastic cells in the area corresponding to inoculation into the tumoral mass of interest, or near the application area in the wound deriving from surgical resection of said tumoral mass.

The necrosis of the tumoral cells of interest is induced by means of an appropriate internal radiotherapy with electrons (IRE), determined by the

localized emission of radioactive particles by said radiolabelled microspheres.

Laboratory examinations, carried out in a gamma camera and with PET/CT, have surprisingly shown that the compound spreads in an almost
5 homogeneous manner inside the tumoral mass into which it has been inoculated, or inside the surgical wound onto which it has been applied, due to the viscous structure of the haemostatic gel forming the matrix thereof, and that such homogeneous diffusion is highly functional to the necrosis of the neoplastic cells localized in such areas.

10 The same examinations have also surprisingly shown that, if a haemostatic gel with a sufficient solidification speed is used as a carrier of said radiolabelled microspheres, the possible dispersion of said microspheres in the patient's body – potentially deriving from factors like gravity, their diffusion in the blood and/or lymphatic vessels, the presence
15 of serosanguineous collections and other – is strongly limited, consequently avoiding any possible side effect deriving from possible dispersion of radioactive material in the patient himself.

Finally, further laboratory examinations have shown that the dispersion of the radiolabelled microspheres in the patient's body may be further limited
20 including a substance in the compound arranged for determining a temporary vasoconstriction of the tissues surrounding the inoculation or application point of the same.

According to the present invention, and in a not restrictive exemplification, an anti-tumoral compound for local use according to the present invention
25 mainly consists of:

- a quick solidification, bicomponent haemostatic gel resulting from the localized injection of two distinct chemical compounds, dosed in

adequate ratio of quantity, one of which is fibrinogen and aprotinin-based, and the other one of which is trombine and calcium chloride-based;

- 5 - a solution of biocompatible microspheres, arranged for being included in the chemical solutions forming above mentioned haemostatic gel, labelled with a high energy radioactive isotope for therapeutic use, like e.g. the radioactive yttrium (^{90}Y), such as to determine the necrosis of the tumoral tissues around the inoculation or application area of the anti-tumoral compound;
- 10 - an epinephrine-based solution, also arranged for being included in the chemical solutions forming said haemostatic gel, such as to determine a temporary vasoconstriction effect to the tissues around the inoculation or application area of said anti-tumoral compound.

According to the present invention, above described anti-tumoral
15 compound is arranged for being directly inoculated into tumoral masses of malignant kind that cannot be surgically treated, for determining the complete necrosis of the neoplastic cells that are near the inoculation point thereof.

It is also arranged for being applied as a filling material in surgical wounds
20 deriving from surgical resection, or from ablative treatments, of tumoral masses of malignant kind, for determining the complete necrosis of possible residual neoplastic cells along the edges of the wounds, so that said edges are surrounded by at least one centimetre of healthy tissue thus reducing the risk of a possible recurrence of the neoplasia in the
25 original site.

Said anti-tumoral compound induces the complete necrosis of the neoplastic cells near its inoculation or application point by means of an

adequate internal radiotherapy with electrons (IRE) determined by the localized emission of radioactive particles by the radiolabelled microspheres comprised in the haemostatic gel forming the matrix thereof. Moreover, the complete necrosis of the neoplastic cells is favoured by the
5 homogeneous distribution of the compound inside the tumoral mass into which it is inoculated or inside the surgical wound onto which it is applied, which is made possible due to the viscosity of the haemostatic gel forming the matrix thereof.

Evidence of the homogeneous distribution of the compound in cavity is
10 given in enclosed figures 1 and 2 wherein, by a gamma-camera in front and back projection, the distribution of 1 mCi (37 MBq) of microspheres is shown, said microspheres being radiolabelled with the radioactive yttrium isotope (^{90}Y) and comprised in a quick solidification bicomponent haemostatic gel, inside a 2,5 ml syringe barrel.

15 Figures 3 and 4 show – respectively by means of PET/CT and CT – the distribution of 340-370 microspheres MBq, radiolabelled with the radioactive yttrium isotope (^{90}Y) and comprised in a quick solidification, bicomponent haemostatic gel, inside 5 ml volume plastic spheres.

Such figures also show that the anti-tumoral compound does not reveal
20 any dissociation between the solutions and the solidified gel, and that said gel does not reveal alterations of its distribution and of its solidification near the cavity of interest.

The quick solidification of the haemostatic gel, forming the matrix of the anti-tumoral compound, determines the confinement of the radiolabelled
25 microspheres inside the inoculation or application site of said compound, advantageously producing a prolongation of its administration time and a consequent increase of its local dosage, deriving from the strong

concentration of said microspheres inside each single tumoral mass, or of each single surgery wound treated.

The quick solidification of said haemostatic gel also limits the dispersion of the radiolabelled microspheres in the patient's body, potentially caused by
5 factors like the gravity, the diffusion in blood and lymphatic vessels, the presence of serosanguineous collections and other, consequently avoiding the setting in of common side effects due to the dispersion of radioactive material in the patient himself.

Said haemostatic gel is obtained by the local injection of a couple of
10 distinct chemical solutions, according to appropriate ratios, one of which fibrinogen and aprotinin-based, with a dosage of 1ml, and the other one trombine and calcium chloride-based, with a dosage of 0,75 ml.

The injection of the two chemical solutions forming said haemostatic gel by means of a coaxial catheter with double lumen, e.g. of the kind
15 disclosed in patent application MI2009A000969 of 3rd June 2009.

Said gel comprises a solution of biocompatible microspheres labelled with a radioactive isotope for therapeutic use, characterized in the emission of high energy electrons and with a penetration power in the tissue >5 mm, equal to 500-625 cellular layers, and preferably represented by the yttrium
20 radioactive isotope (^{90}Y).

With a dosage of 0,25 ml, said solution allows to include inside said haemostatic gel a quantity of biocompatible microspheres equal to 30-60x10⁶ with a diameter comprised between 20 and 60 micron and labelled with the radioactive yttrium isotope (^{90}Y), having an average life of 64,1
25 hours and a tissue penetration coefficient of 11 mm, with an average penetration of the same of 2,5 mm, such as to determine the complete necrosis of the cancer tissues surrounding the inoculation or application

area of the examined anti-tumoral compound.

Said microspheres, which are unassimilable by the human body, release 94% of the radioactivity of the yttrium isotope (^{90}Y) contained therein, in a time period superior to the average physical and biological life of said isotope, evaluated in 10-13 days from the moment of inoculation or application of said anti-tumoral compound.

Figure 5 shows in a graph the results of the measurements, done through a gamma camera and PEC/CT, of the absorption percentage of the radioactivity released by said microspheres in contiguous shells with dimensions of 1 mm, near cavities of different volumes A, B, C, respectively equal to 0,5ml, 4,2 ml and 11,5 ml.

Figure 6 shows in a graph the results of the measurements of the activity percentage of the yttrium radioactive isotope (^{90}Y), according to its distance from the centre of said reference cavities.

The data shown in the graphs in figures 7 and 8 have been processed from the activity values of the yttrium isotope (^{90}Y), released for each reference cavity, and said figures respectively show:

- the entity of radiation dosage (Gy/MBq) absorbed per unity, in adjoining shells of cavities of different dimensions, with reference volumes respectively equal to 0,5 ml, 4,2 ml and 11,5 ml;
- entities of radiation dosage (Gy) absorbed in a whole, in adjoining shells of cavities of different dimensions, with reference volumes respectively equal to 0,5 ml, 4,2 m and 11,5 ml.

Following table 1, on the other hand, reports the results of the measurements of the radiation dosage absorbed by wounds of different dimension, with the reference radius respectively equal to 0,5 cm, 1 cm and 1,5 cm.

Table 1

Volume	Radius	Act.	Volume	Radius	Act.	Volume	Radius	Act.
0,5 ml	0,5 cm	185 MBq	4,2 ml	1 cm	370 MBq	14,1 ml	1,5 cm	1110 MBq
cm	Gy/MBq	Gy	cm	Gy/MBq	Gy	cm	Gy/MBq	Gy
0,5	62,9	11640	1,0	10,1	3732,3	1,5	3,46	3843,2
0,6	35,0	6467	1,1	6,7	2488,2	1,6	1,15	1281,1
0,7	14,0	2587	1,2	2,2	829,4	1,7	0,81	896,7
0,8	5,6	1035	1,3	1,0	373,2	1,8	0,35	384,3
0,9	2,1	388	1,4	0,6	207,4	1,9	0,12	128,1
1,0	0,559	103	1,5	0,112	41,5	2,0	0,06	64,1
1,2	0,070	13	1,6	0,004	1,7	2,1	0,0092	10,2
1,5	0,0002	0,04	1,7	0,001	0,4	2,3	0,0012	1,3

The results of the measurements, and of the processing deriving therefrom, confirm the strong concentration of the radiotherapy action of the radiolabelled microspheres near the inoculation or application point of the examined anti-tumoral compound.

Besides, the results confirm the limited dispersion of radioactive elements in the areas around the inoculation or application point of said compound, and consequently their limited dispersion in the patient's body.

As an alternative to above mentioned biocompatible microspheres, common antineoplastic substances with chemotherapy action may be comprised inside said haemostatic gel forming the matrix of said anti-tumoral compound.

Furthermore, an epinephrine solution is included inside said haemostatic gel, with a dosage equal to 0,1 ml/mg, arranged for determining a temporary vasoconstriction of the tissues around the inoculation or application area of the compound.

Said solution determines an advantageous increase of the haemostatic effect already given by the gel forming the matrix of said compound and, strongly reducing the bleeding of the tissues treated, it further limits the

dispersion of the antineoplastic substances in the patient's body and thus avoids the arising of common side effects deriving from the systemic exposure to the toxic components of the same.

The particular features of the anti-tumoral compound above described, like
5 the highly localized administration and the limited dispersion of the antineoplastic substances contained therein, allow an advantageous use of said compound in the field of the therapeutic treatment of tumoral masses localized in the area of the head and in the brain tissues, in the area of the neck, of the chest cavity, of the abdominal cavity and in the
10 area of the retroperitoneal space, in the area of the pelvis as well as in the bones and in the soft tissues in general.

Said features also allow the use of said compound as an independent therapeutic treatment, suitable for allowing the treatment of tumoral masses that cannot be surgically removed, or as a therapeutic treatment
15 complementary to surgical resection, or to alternative surgical techniques, suitable for maximizing the efficiency of those therapies and reducing the risk of neoplastic recurrences in the original site.

Best results have been obtained, with respect to similar substances, with the use of TISSUCOL (BAXTER) or Beriplast P (Nycomed), as a biological
20 glue of SIR (SIRTeX) spheres as biocompatible microsphere solution; and of epinephrine (adrenaline) belonging to the adrenergic activity catecholamines of A and B type, as a local vasoconstrictor agent on the smooth muscles.

Best results have been obtained also with the use of the biological glue
25 Coseal (BAXTER), a surgical sealant resulting from the localized injection of two different synthetic polyethylene glycols (PEGs), of a diluted solution of hydrochloric acid and of a solution of sodium phosphate/sodium

carbonate.

During administration, said polyethylene glycols and said solutions form a hydrogel that adheres to the tissues and covalently binds itself to the same.

- 5 The pharmacologic behaviour of the anti-tumoral compound according to the present invention has been examined in different species, making use of animals with spontaneous or implanted neoplasias.

The results of said studies have shown – in imaging mode – that following to the administration of the compound in the wound, no loss of
10 radiolabelled microspheres occurs in the tissues around the area of its inoculation or application.

By means of autoradiography it has been proved, in particular, that the dose injected in the tested animals remains active inside the solidified gel until 13 days after its injection.

- 15 Histological examination in a number of pigs has shown the necrosis of all neoplastic cells comprised in the area of administration of the anti-tumoral compound and said area varies between 0,6 and 3,2 mm.

The dose given to the animals has been considered tumoricidal for wounds between 3 and 22 cc, and no radioactivity has been found in the
20 blood of the same.

Besides, different dosages of yttrium radioactive isotope (^{90}Y) have been evaluated, according to the volume of the residual surgical cavity to be filled up or to the dimensions of the wound to be treated, as appropriately summed up in following Table 2.

25

Table 2

<i>Volume of the remaining cavity or of the wound (cc)</i>	<i>Activity of the ⁹⁰Y isotope (MBq)</i>	<i>Volume of injected medicine (ml)</i>
1	259-370 (7-10 mCi)	3
3	444-555 (12-15 mCi)	4
5	592-740 (16-20 mCi)	6
10	1110-1480 (30-40 mCi)	12
20	2220-2960 (60-80 mCi)	24
>20	3000	24

The precondition for the dosimetric evaluation is that the yttrium radioactive isotope (⁹⁰Y) is homogeneously distributed inside the residual surgical cavity and inside the solidified gel forming the matrix of said compound, obtained through the co-injection of TISSUCOL (BAXTER), or Beriplast P (Nycomed), and epinephrine.

The different components of the haemostatic gel forming the matrix of the anti-tumoral compound have been given through a 2,5 ml syringe by means of a slow infusion carried out through a special coaxial catheter with double lumen.

The ratio between the fibrinogen-aprotinin solution, the trombine-calcium chloride solution and the microsphere SIR solution was respectively of 1 ml:0,75 ml:0,25 ml.

In this preparation, the activity of the yttrium radioactive isotope (⁹⁰Y) has been of 22 MBq (0,6mCi).

The exposure of the staff to the components of the compound has been evaluated by means of a dosimetric thermoluminescence detector (TDL),

because the preparation and the administration procedure of the compound must be considered as potentially dangerous.

Such exposure has been estimated supposing to manage a 3 GBq device with a time for preparing the dose of 30 minutes (for technical staff) and
5 suggesting an average dose of 2 GBq in the patients and a time for the injection of the dose of 20 minutes (for medical staff).

During work, the detector has been placed near the pelvis, on the collar of the T-shirt and on the fingers.

The results are summed up in following table 3.

10 Table 3

<i>Technical staff</i>	<i>Surface dosage (0,07 mm)</i>	<i>Deep dosage (10 mm)</i>
Pelvis mSv (mrem)	0,027 (2,7)	0,003 (0,3)
Eyes mSv (mrem)	0,026 (2,6)	0,004 (0,4)
Hands mSv (mrem)	0,35 (35)	
<i>Medical staff</i>	<i>Surface dosage (0,07 mm)</i>	<i>Deep dosage (10 mm)</i>
Pelvis mSv (mrem)	0,038 (3,8)	0,004 (0,4)
Eyes mSv (mrem)	0,12 (12)	0,054 (5,4)
Hands mSv (mrem)	0,35 (35)	

In a non-limiting example, the production process of the anti-tumoral compound according to the present invention comprises:

- a preparation phase of a chemical fibrinogen and aprotinin-based injectable compound;
- 15 - a preparation phase of a chemical trombine and calcium chloride-based injectable compound;

- a phase of pre-dosing of said chemical compounds, inside special disposable syringes, and the subsequent low temperature storage of the same;
 - a warming phase of said compounds, when they are to be used, up to the temperature of 37°C;
 - a first phase of adding said compounds carried out by means of a solution of biocompatible microspheres, labelled with a high energy isotope for therapeutic use, like the yttrium radioactive isotope (⁹⁰Y);
 - a second phase of adding said compounds, carried out by means of an epinephrine-based solution;
 - an administration phase of equivalent doses of said compounds, determining the localized formation of a haemostatic gel comprising above listed adding substances, carried out by means of a special coaxial catheter with double lumen.
- 15 In a possible embodiment, the process for the production of said anti-tumoral compound comprises:
- a preparation phase of a chemical injectable compound consisting of a synthetic polyethylene glycol and of a diluted solution of hydrochloric acid;
 - a preparation phase of a chemical injectable compound consisting of a synthetic polyethylene glycol and of a solution of sodium phosphate/sodium carbonate;
 - a pre-dosing phase of said chemical compounds inside special disposable syringes, and the subsequent low temperature storage of the same;
 - a warming phase of said compounds at the moment of use up to the temperature of 37°C;

- a first phase of adding said compounds, carried out by means of a solution of biocompatible microspheres, labelled with a high energy isotope for therapeutic use, like the yttrium radioactive isotope (^{90}Y);
 - a second phase of adding said compounds, carried out by means of an epinephrine-based solution;
 - an administration phase of equivalent doses of said compounds, determining the localized formation of a hydrogel comprising above mentioned adding substances, carried out by means of a special coaxial catheter with double lumen.
- 10 As an alternative, the phase of adding the compounds, common to both described procedures, and carried out with a solution of biocompatible microspheres labelled with a high energy isotope for therapeutic use, may be replaced by a phase of adding chemotherapy drugs.

* * * * *

CLAIMS

1. An anti-tumoral composition for injection into a treatment site, comprising:
 - an injectable biologic glue consisting of two distinct chemical mixes: (i) a first chemical mix and (ii) a second chemical mix comprising an activating agent; and
 - an antineoplastic substance comprising biocompatible microspheres with diameters between 20 and 60 microns labelled with yttrium radioactive isotope (^{90}Y) having an activity between 259 to 3000 MBQ;

wherein said injectable biologic glue is arranged for solidifying after mixing said two mixes upon injection to keep the antineoplastic substance in loco and homogeneously distributed in the biologic glue.

2. The anti-tumoral composition according to claim 1, characterized in that the injectable biologic glue is a haemostatic gel.
3. The anti-tumoral composition according to claim 2, characterized in that said first chemical mix comprises a fibrinogen and aprotinin-based mix, and said second chemical mix comprises a trombine and calcium chloride-based mix.
4. The anti-tumoral composition according to claim 1, characterized in that the injectable biologic glue is a hydrogel.
5. The anti-tumoral composition according to claim 4, characterized in that said first chemical mix comprises a synthetic polyethylene glycols and diluted hydrochloric acid-based mix, and said second chemical mix comprises a synthetic polyethylene glycols and sodium phosphate/sodium carbonate-based mix.
6. The anti-tumoral composition according to claim 1, characterized in that said injectable biologic glue is arranged for being given to patients by a double lumen catheter.

7. The anti-tumoral composition according to claim 1, characterized in that said biocompatible microspheres have a tissue penetration capacity of >5 mm.
8. A process for the production of a compound for antitumor use, comprising:
 - preparing a first injectable compound;
 - preparing a second injectable compound comprising an activating component;
 - pre-dosing said first and second compounds inside disposable syringes, and subsequently storing said compounds at a low temperature;
 - warming said first and second compounds, when they are to be used, up to the temperature of 37°C; and
 - adding to said first and second compounds a solution of biocompatible microspheres with diameters between 20 and 60 microns, labelled with yttrium radioactive isotope (90Y) having an activity between 259 to 3000 MBq to generate a homogenous distribution of microspheres in the first and second compounds.

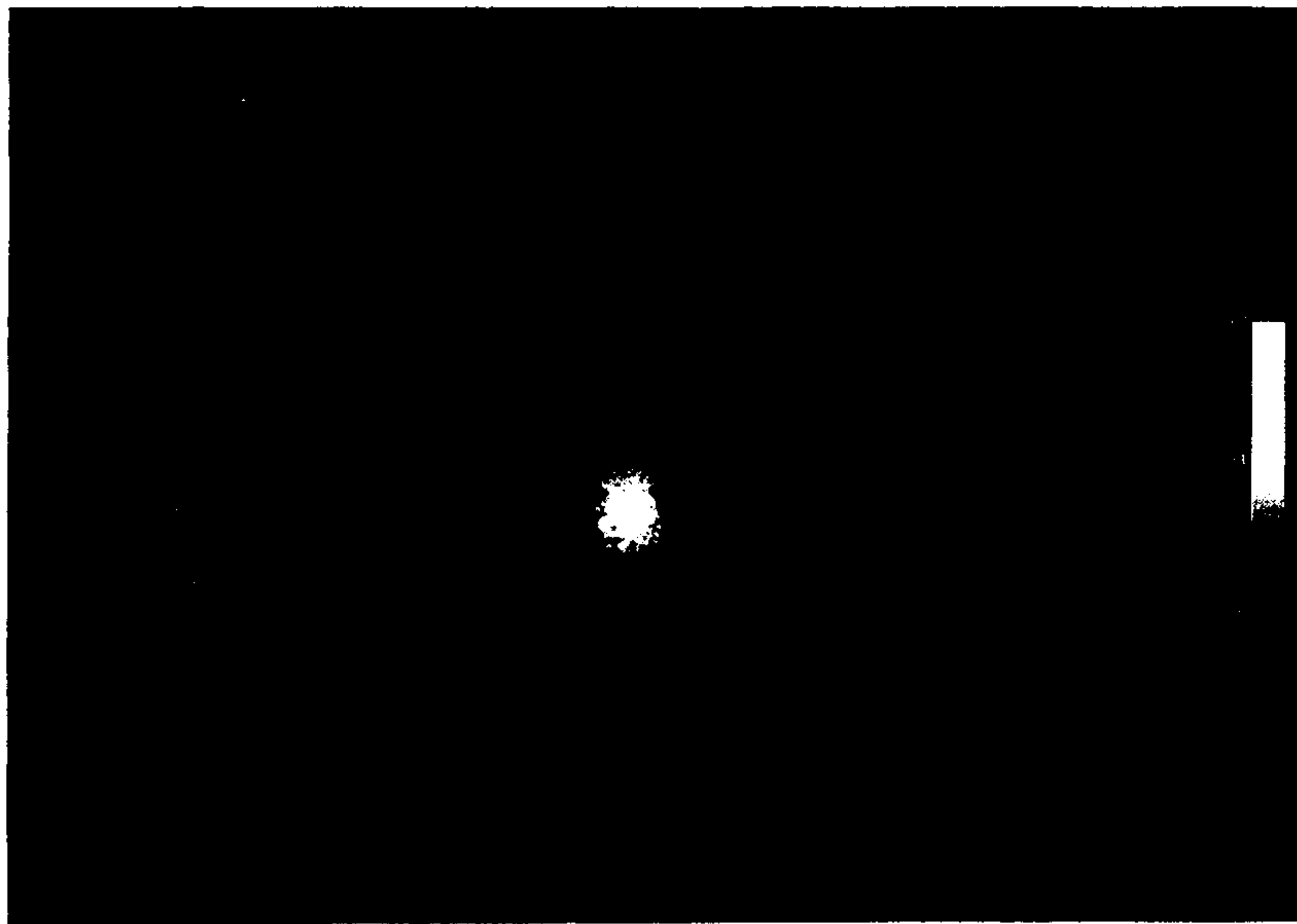


FIG. 1

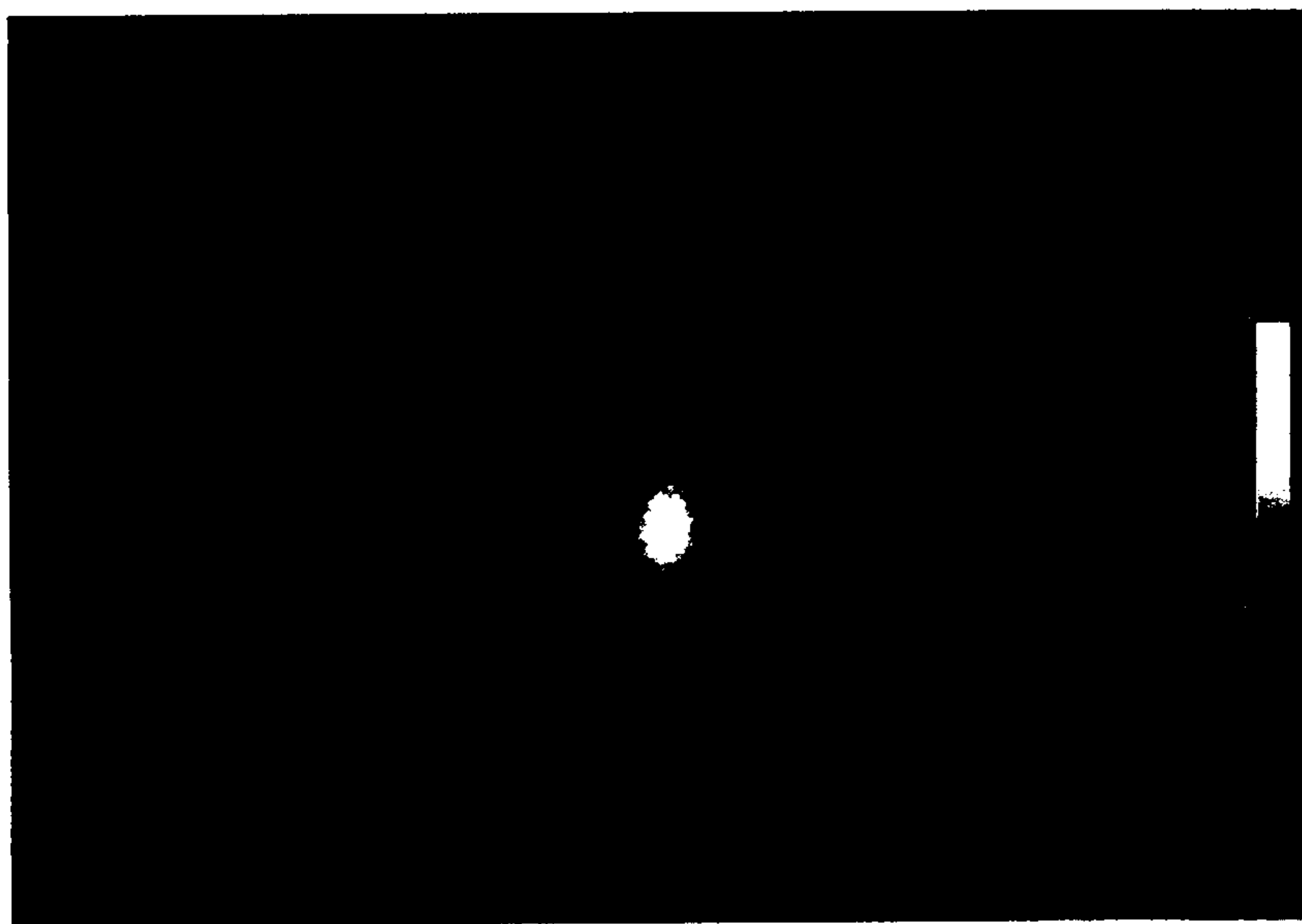


FIG. 2

FIG. 3

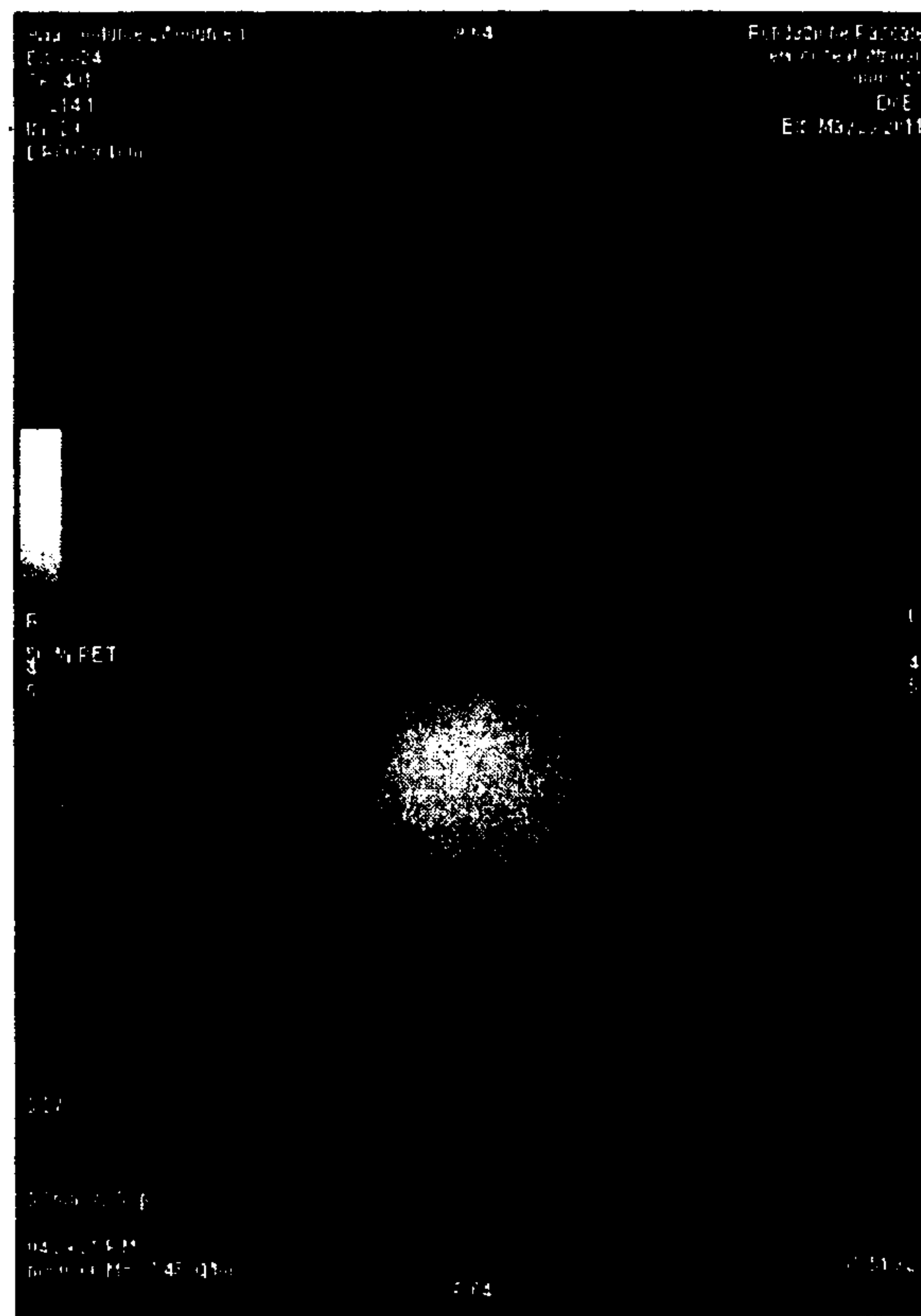
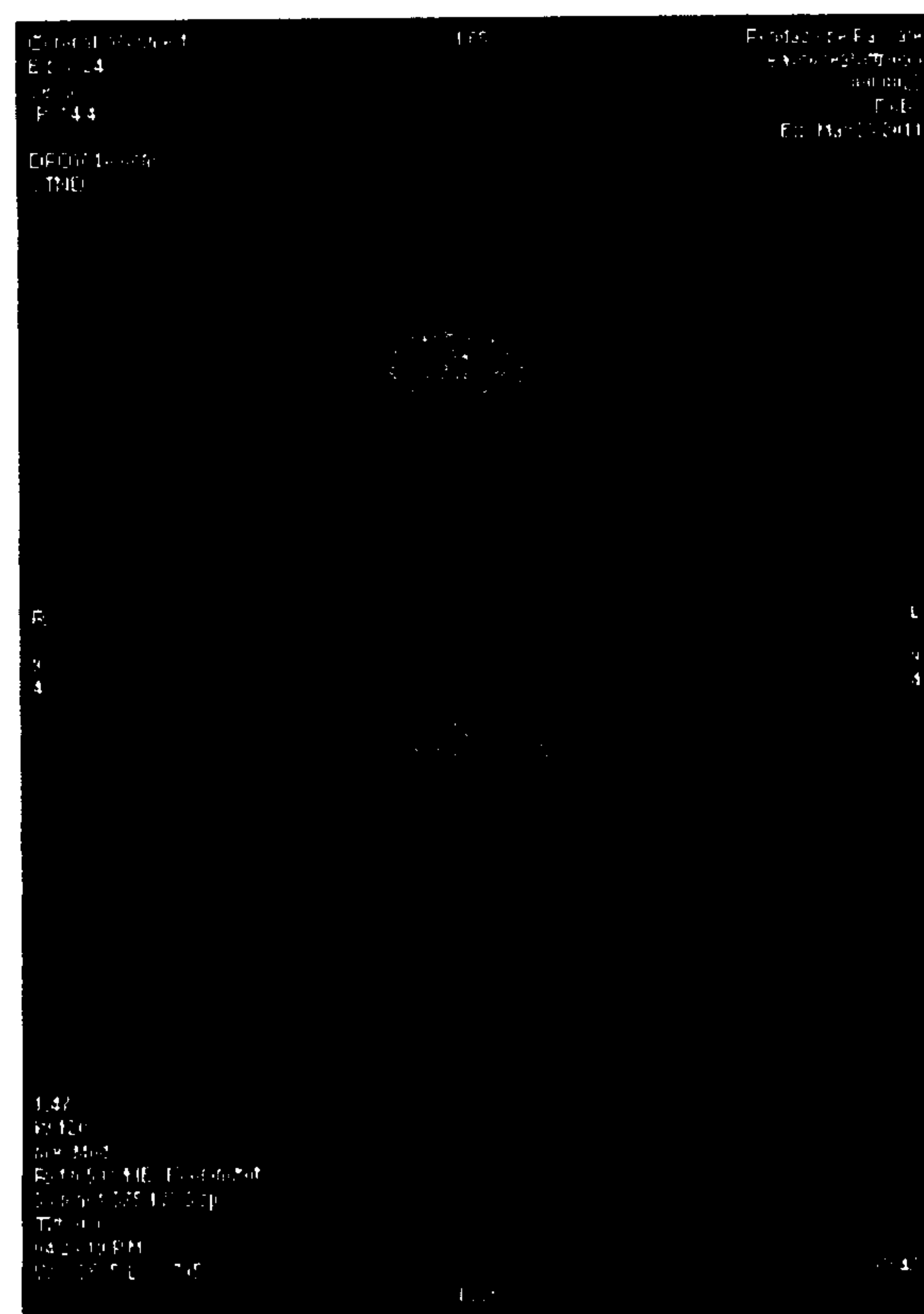


FIG. 4



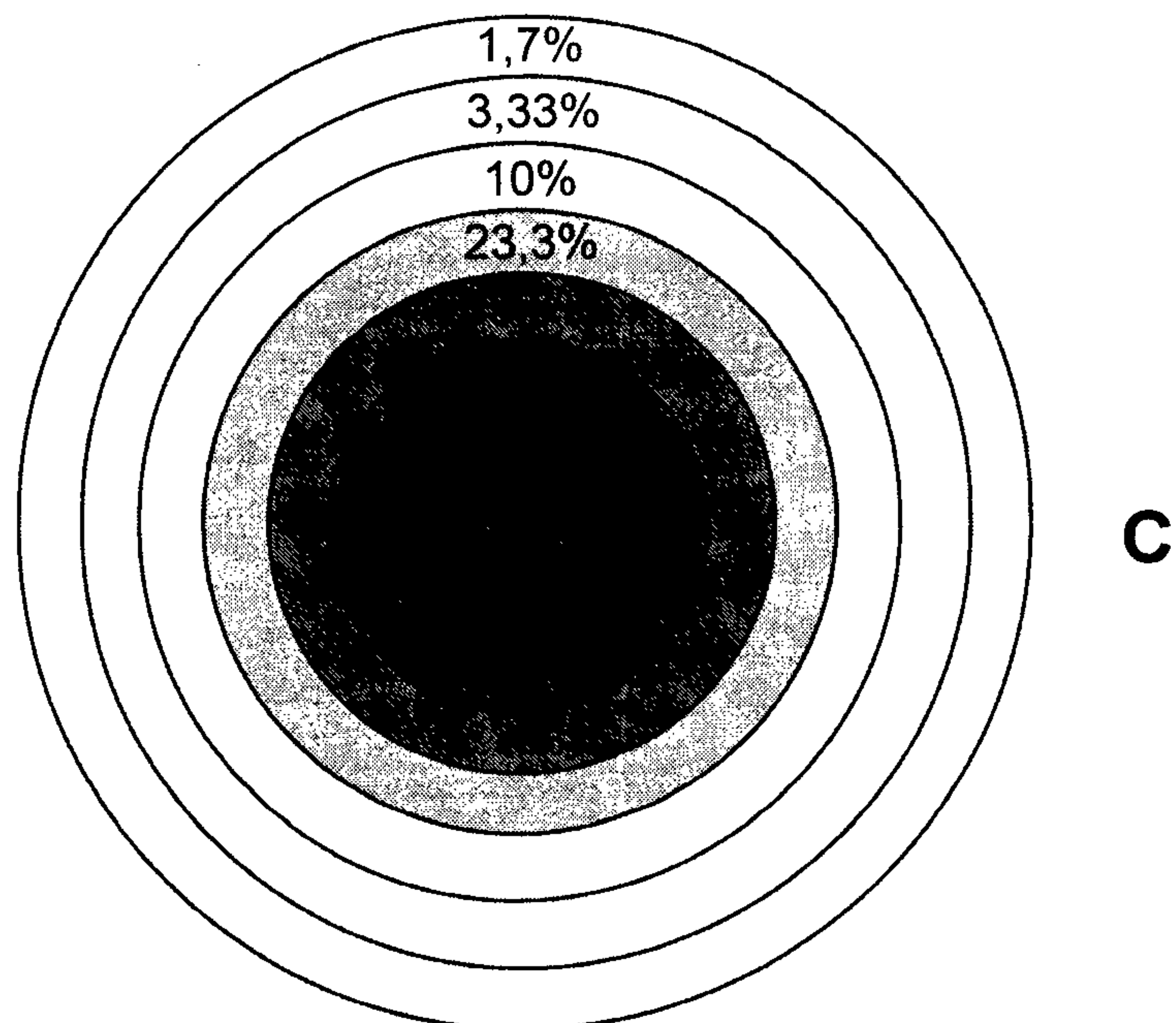
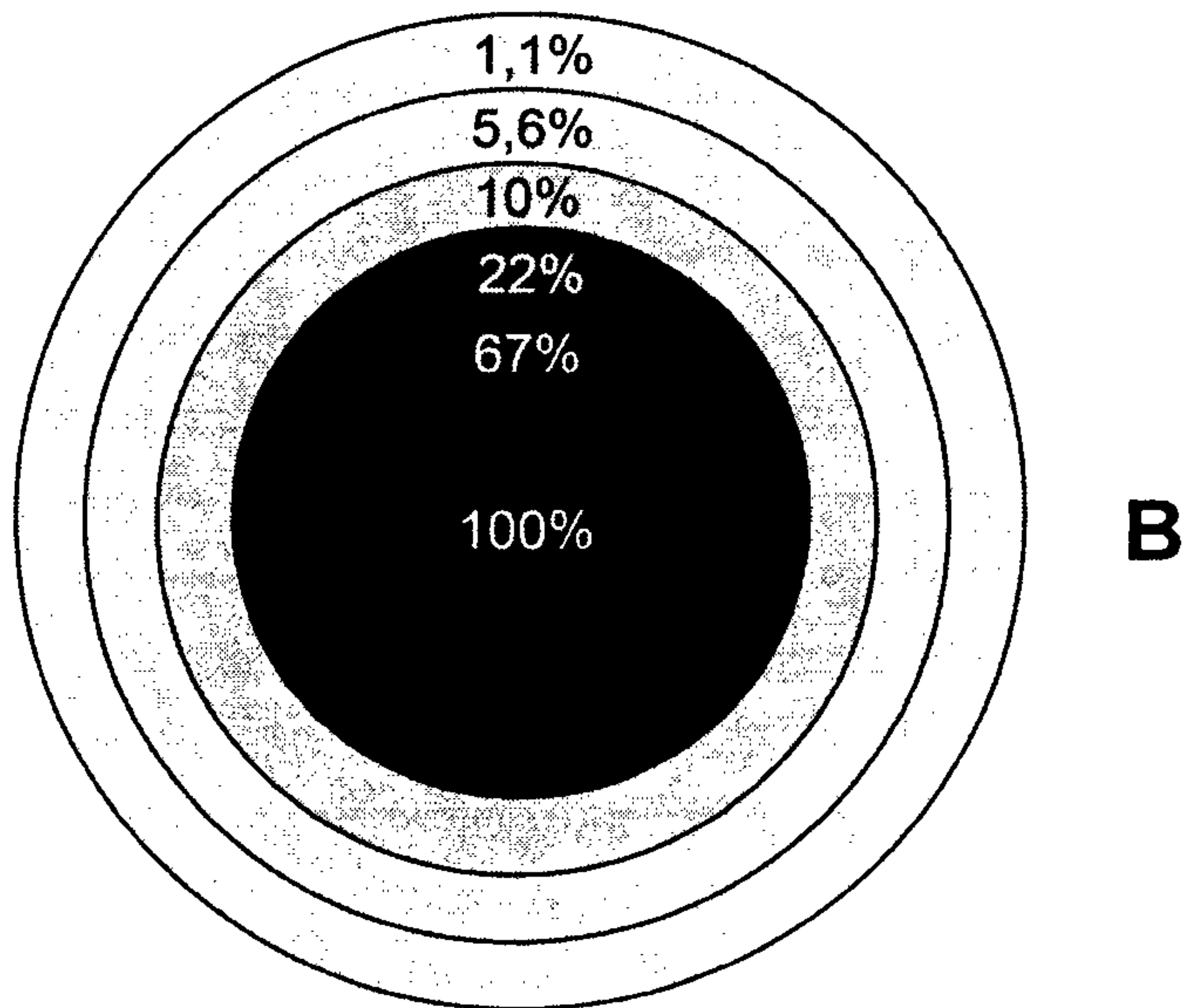
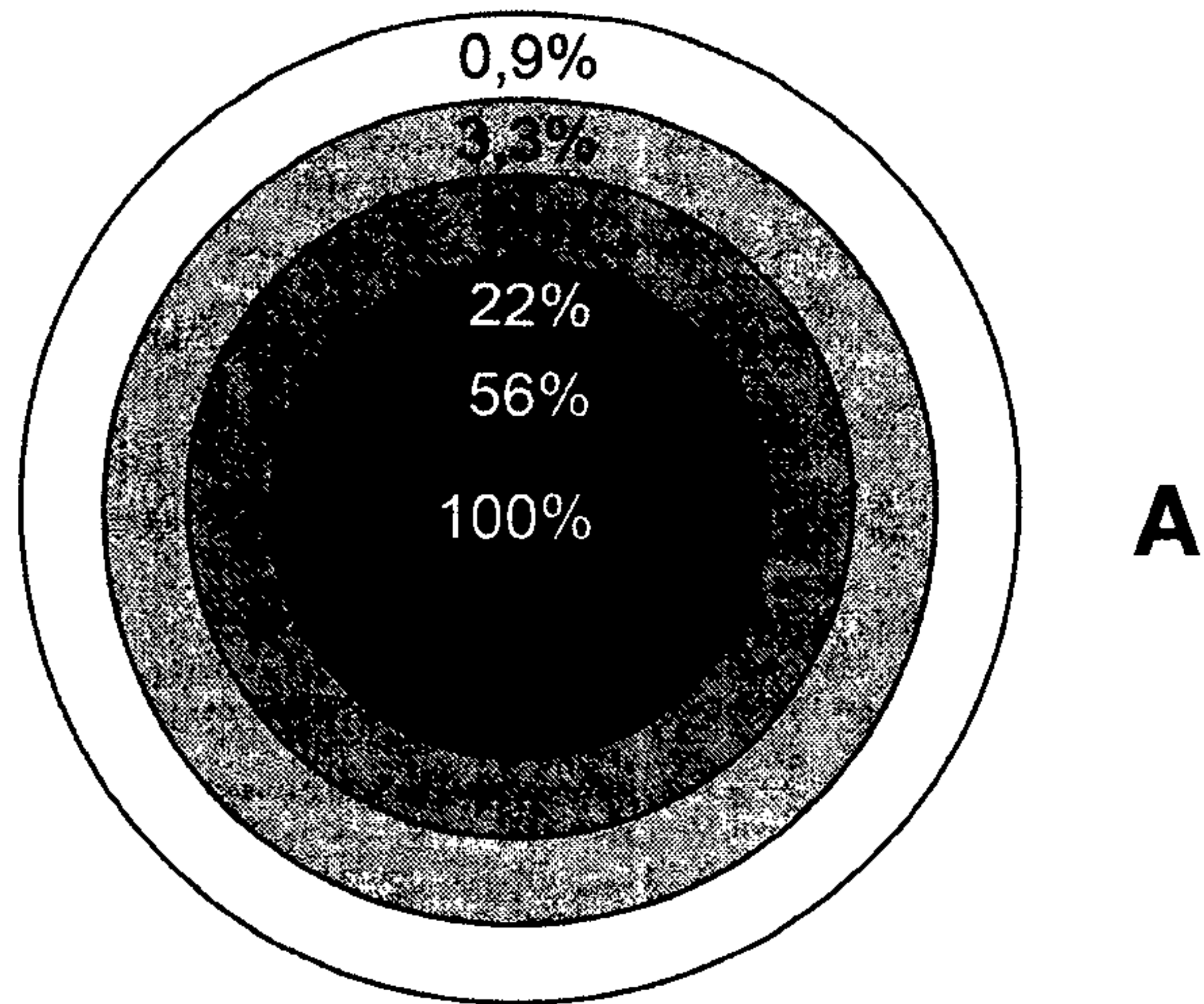


FIG. 5

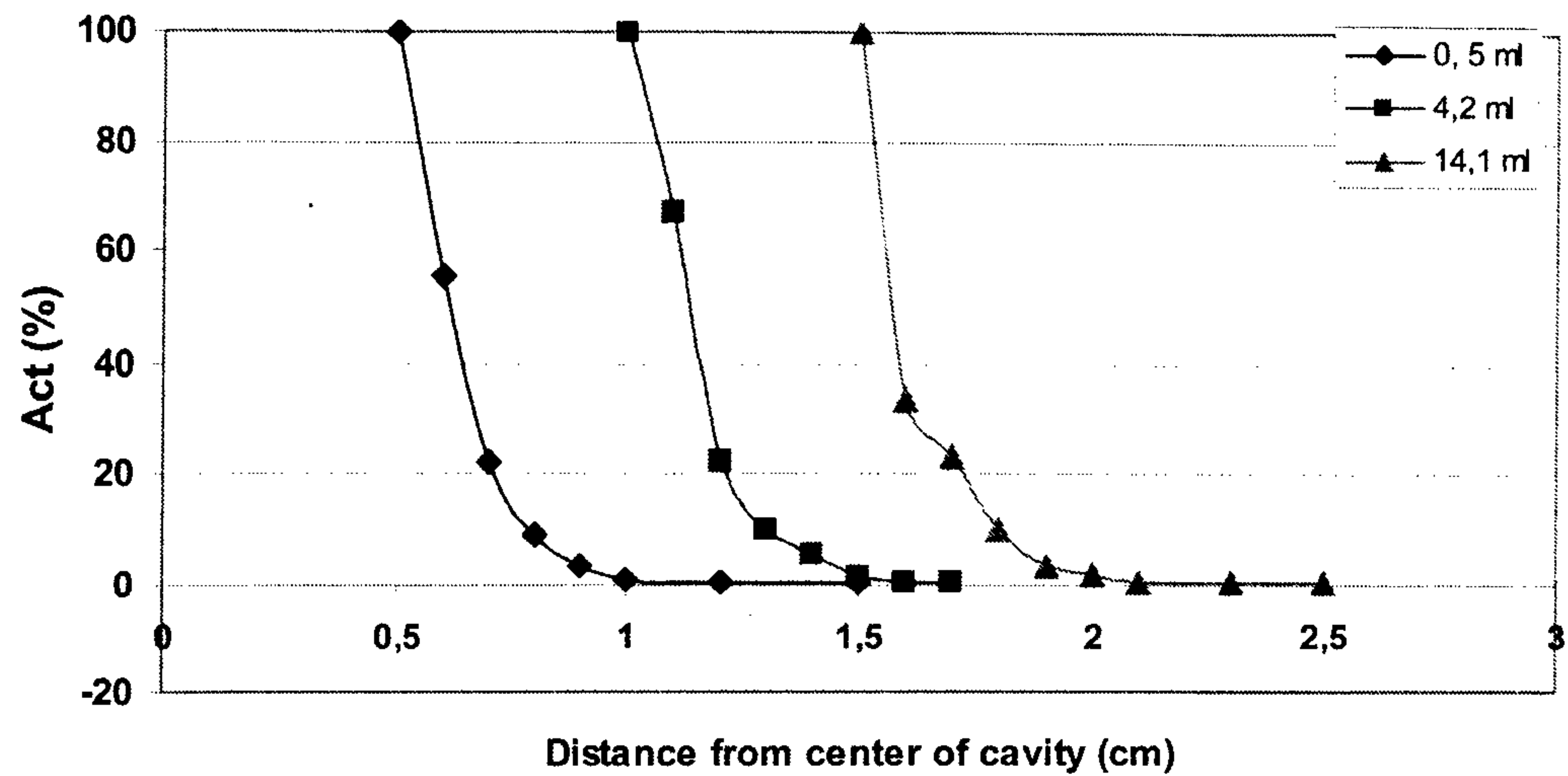


FIG. 6

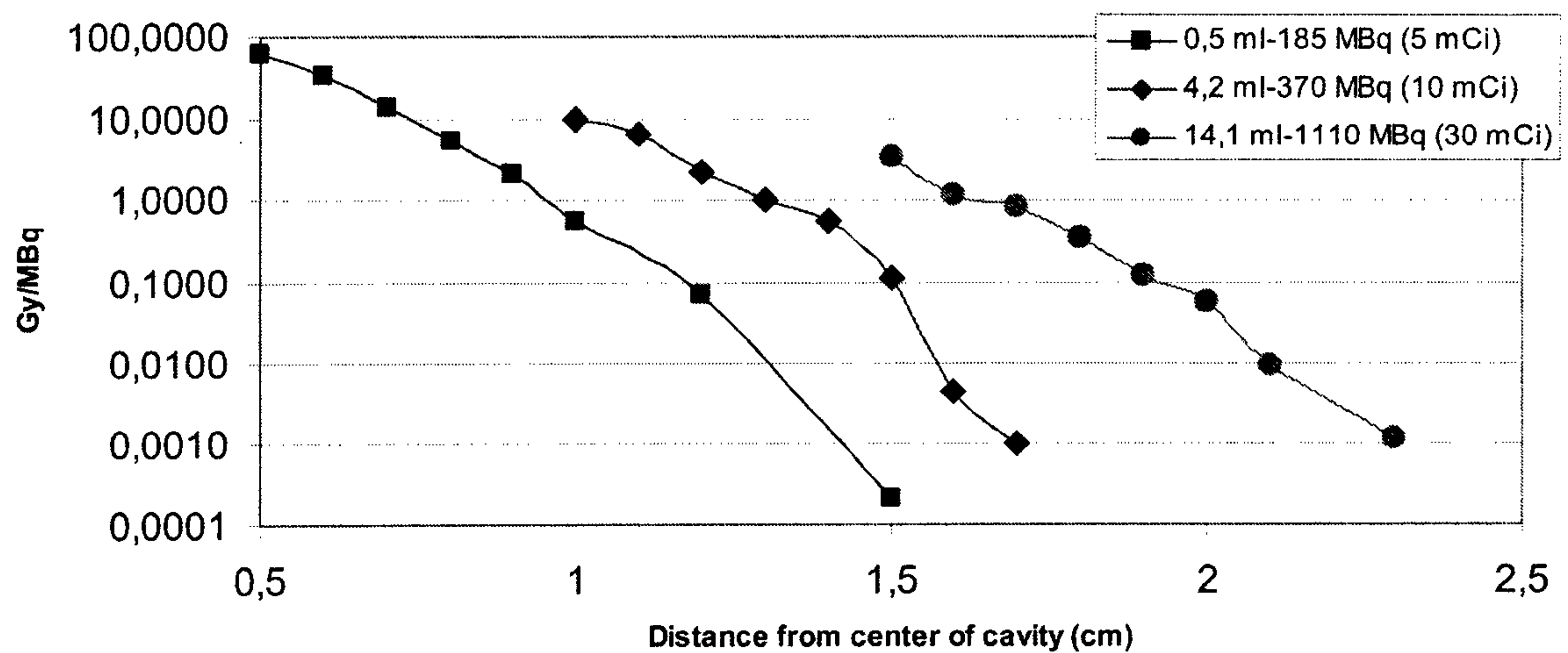


FIG. 7

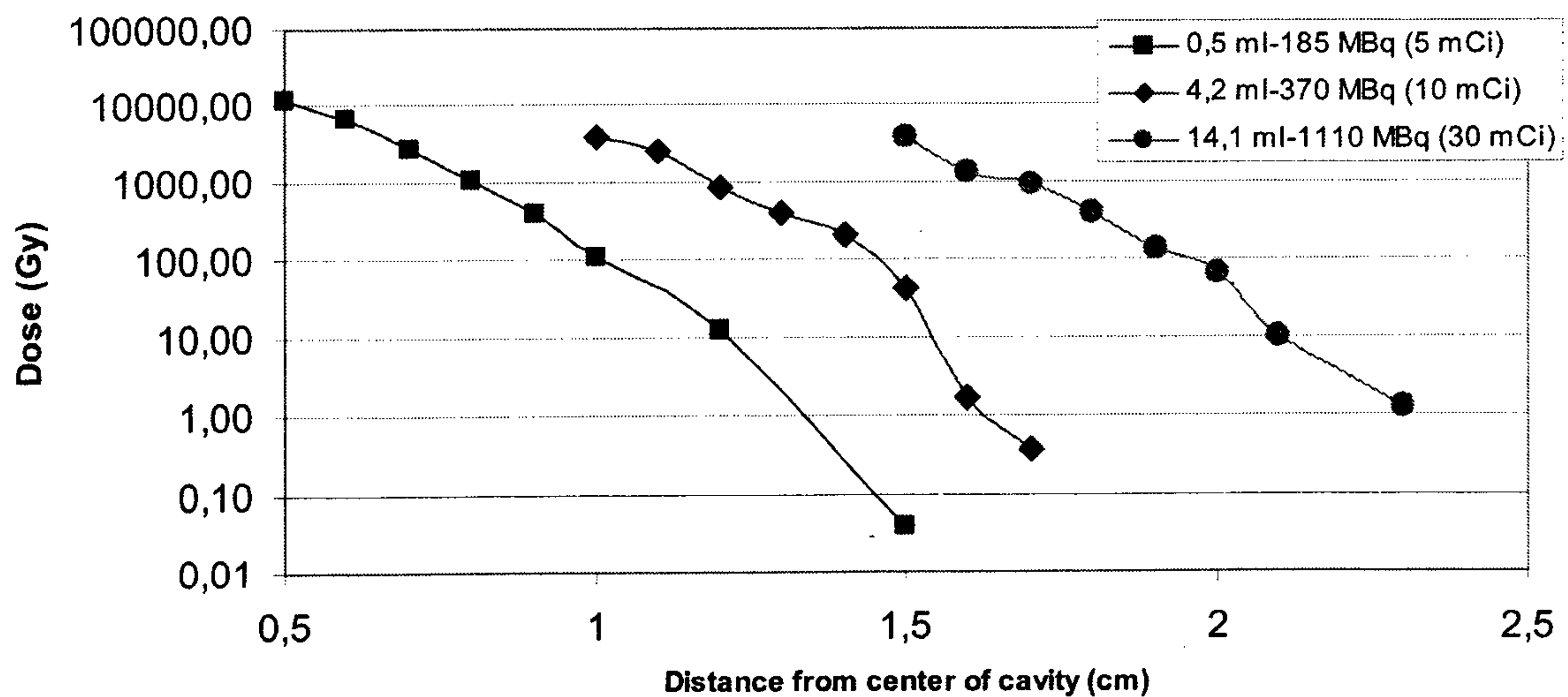


FIG. 8

11.4

^a $n = 6$.

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14.

【附註】1. 本表係根據「中華民國七十七年第一次全國人口及戶口統計」資料編製。

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Environ Biol Fish (2015) 98:1037–1047

2008, p. 278, fn. 11.

Table 1

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