CHAPTER 3
Classification

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Introduction

As a general principle, classification rules have a hierarchy which must always be followed. The rules of the current ICD-O edition take precedence over other sources, with the exception of IARC technical norms (but only those issued after publication of the ICD-O); this is because although the rules published in the ICD-O update all IARC technical norms, the delay in between planning and publication/diffusion of the current edition of the ICD-O may require subsequent official changes by the IARC (e.g., the technical rule for the registration of multiple primaries in ICD-O-3 was revised with *Internal report* no. 2, 2004). The technical indications of the IACR rank next, and those of the ENCR follow. The hierarchy ensures that rules of the lowest rank cannot contradict those higher up and that their use is limited in directing previously unaddressed procedures. National technical rules, such as the Italian rules found in this handbook, rank last. Each registry may collect and record additional information that does not conflict with higher ranking information nor with the information contained in this handbook. Technical rules used in relation to secondary research (EUROCARE, EUROCIM) are only binding within the context of individual projects.

ICD-O rules

Rule A: topographic areas and ill-defined sites

If the diagnosis does not specify the anatomic site of origin, use the appropriate code suggested in the alphabetic index for each ill-defined site in preference to the "NOS" category. Ill-defined sites, such as "upper limb," comprise various tissues and anatomic sub-sites. For example, a "squamous cell carcinoma of the upper limb" should be coded C44.6 (Skin of upper limb), rather than C76.4 (Upper limb, NOS). There are rare exceptions to this rule, as in the case of the chin and the forearm: for practical reasons these areas are considered to be predominantly made up of skin and therefore the NOS category is assigned to the skin.

Rule B: prefixes

If a topographic site is modified by a prefix such as "peri," "para-," or the like that is not specifically listed in the ICD-O, code to the appropriate ill-defined subcategory C76 (ill-defined site), unless the tumor's histological type indicates origin from a specific tissue. This general rule also applies to imprecise phrases such as "in the area of..." or "in the region of...."

Rule C: tumors involving more than one topographic category or subcategory.

Use subcategory ".8" (fourth digit) when a tumor overlaps the boundaries of two or more categories or subcategories and its point of origin cannot be determined.

Rule D: topography codes for lymphomas

If a lymphoma involves multiple lymph node regions, code to C77.8 (lymph nodes of multiple regions). If no site is indicated for a lymphoma, code to C77.9 (lymph node, NOS). Code extranodal lymphomas to the site of origin, which may not be the site of the biopsy.

Rule E: topography code for leukemias

Code all leukemias to C42.1 (bone marrow), with the exception of myeloid sarcoma (M-9930/3), which can arise from any site.

Rule F: behavior code in morphology

Use the appropriate fifth digit behavior code even if the exact morphological term is not listed in the ICD-O; for example, a diagnosis of "benign chordoma" should be coded M-9370/0. If according to the pathologist the behavior of the lesion differs from the usual behavior established by the ICD-O, coding must follow the pathologist's indications.

Rule G: grading or differentiation code

Assign the highest grade or differentiation code described in the diagnostic statement. If a diagnosis indicates two different grades or differentiations of the tumor, such as "well and scarcely differentiated" or "grade II-III", the higher grade must be coded.
The sixth digit of the morphology field can also be used to identify cell origin for lymphomas and leukemias (see Table 22, page 31 of ICD-O-3). In lymphatic and hematopoietic diseases the indication of cell type T (code 5), B (code 6), Null (code 7), and NK (code 8) takes priority over grade codes 1-4. Since with ICD-O-3 a morphologic diagnosis implies assignment of a cell line of origin, the sixth digit can also be used to emphasize that the diagnosis is supported by immunophenotypic characterization.

Rule H: site-associated morphology terms

Use the topography code provided in association with a specific morphology when a topographic site is not stated in the diagnosis. The appropriate site-specific codes are indicated in brackets after the morphological

term for neoplasms that usually arise within the same organ or tissue, e.g., retinoblastoma (C69.2).
Disregard the topography code if the tumor is known to arise at another site, since the code of the anatomic site declared in the diagnosis must be used. This, however, should be done after accurately revising the case to rule out that the presence of the neoplasm in the mentioned site is a metastasis.
Some neoplasms have names the interpretation of which may imply a specific anatomic site (pseudo-topographic morphology terms), but these lesions shouldn't necessarily be coded with a topography derived from their names. For example, a "biliary tract carcinoma" is a tumor frequently arising within the intrahepatic biliary tract (liver-C22.1).

Rule J: compound morphologic diagnoses

Change the order of word roots in a compound term if the term is not listed in the ICD-O, since not all compound terms are included in the ICD-O. For example, "myxofibrosarcoma" is not included, but "fibromyxosarcoma" is. Check the various possible orders of the prefixes if the first term is absent (see coding guidelines, page 33 of ICD-O-3).

Rule K: coding multiple morphology terms

When no single code includes all diagnostic terms, use the numerically higher code number if the diagnosis of a single tumor includes two modifying adjectives with different code numbers. If a term has two or more modifying adjectives with different numerical codes, use the code with the higher number, which is usually more specific.

IARC/IACR and ENCR rules

Following is a list of the main rules, divided by topic, which can be found on the websites of IARC, IACR, and ENCR (www.iarc.fr; www.iacr.com.fr; www.ENCR.com.fr/download.htm). Most rules are addressed in more detail in the individual chapters of this handbook.

Basis of diagnosis

- IARC/IACR recommendations for coding basis of diagnosis.
- ENCR recommendations for coding basis of diagnosis and the sources for which it is possible to assign a specific morphology in the absence of histology or cytology (1999).

Check and conversion programs

- IARC/IACR Guidelines (2005).

Confidentiality

- IARC/IACR guidelines for population-based cancer registration (2004).
- ENCR recommendations (2002).

Incidence date

- ENCR recommendations (1995, updated in 1997).

Condensed TNM for coding the extent of disease

- ENCR recommendations (1997).
- ENCR recommendations (2002).

Management of multiple primaries

- IARC/IACR guidelines for ICD-O-2.
- ENCR recommendations (1995, updated in 2000).
- IARC/IACR recommendations for ICD-O-3 (2004).

Morphology in the absence of histology and cytology

- ENCR recommendations for coding basis of diagnosis and the sources for which it is possible to assign a specific morphology in the absence of histology or cytology (1999).

Bladder tumors

- ENCR guidelines (1995) *undergoing revision*.

Cancer screening and registration

- ENCR recommendations (2001).

Standard dataset

- ENCR recommendations (2005).

Registry structure

- ENCR recommendations.

Non-melanoma skin cancers

- ENCR recommendations (2000).

Tumors of the brain and central nervous system

- ENCR recommendations (1998).

Multiple primaries

With the increase in survival as a result of the improvement in treatment and of earlier diagnoses, thanks in part to screening programs - as well as, more generally, due to the increase in life expectancy -, the likelihood that patients may develop more than one cancer in their lifetime has increased. At the same time, awareness of cases of hereditary-familial diseases and their association with an increased frequency of multiple neoplasms has also grown.
The discovery of multiple primaries in the same patient can be subdivided into the following cases:

- two or more separate neoplasms in different topographic sites;

- two or more morphologically different neoplasms arising from the same organ;
- two or more neoplasms with the same or similar morphology but with a different behavior code, arising from the same organ even at a different time;
- two or more neoplasms with the same or similar morphology, and the same code of behavior, arising from the same organ even at a different time;
- two neoplasms arising in paired organs;
- a single neoplasm involving multiple sites, the precise origin of which cannot be determined;
- systemic cancer (lymphomas, Kaposi's sarcoma) where often multiple lymph node stations and/or sites are already involved at first diagnosis.

In such cases, the registrar must therefore assess the following:

- the actual existence of a second tumor: it could be an extension, metastasis, or recurrence of the first tumor;
- the date of the actual incidence of the first tumor and of subsequent tumors;
- whether it should be registered and entered as an incidence case.

As regards the latter issue, the preferable approach is to consider the two aspects as independent. The duty of the registrar is to register and annotate, whereas evaluation of whether cases are truly incident should be part of a subsequent step of data evaluation and of a recording system that makes possible to distinguish "true" incident cases from other cases. This also makes information available for uses other than solely the computation of incident cases according to international rules; for instance, documentation of non-invasive cases or of lesions that can be useful for screening assessments.

Evaluation for incidence

The following IARC recommendations should be followed:

1. recognition of the existence of two or more primary cancers does not depend on time;
2. a primary cancer is one that originates in a primary site or tissue and is not an extension, nor a flare-up, nor a metastasis;
3. only one tumor of the same histological type shall be recognized as primary, for incidence purposes, in an organ or pair of organs or tissue, based on the first 3 digits of the topography code (some groups of codes are considered to be a single organ for the purposes of defining multiple primaries, as shown in Tables 1a and 1b, pages 15 and 16);
4. multifocal tumors – that is, discrete masses apparently not in continuity with other primary tumors originating in the same primary site or tissue, for example bladder – are counted as a single tumor;
5. Rule 3 does not apply in two circumstances:
   - 5.1 systemic or multicentric cancers, potentially involving many different organs, which include four histological groups: lymphomas, leukemias, Kaposi's sarcoma, and mesothelioma; only one of the cancers of its group is considered for incidence purposes, but this does not exclude registration of the others;
   - 5.2 the histological types are divided into groups: within these groups the histological types are considered the same for the purpose of counting multiple primaries, therefore only two histological types belonging to different groups can be considered different for the purpose of identifying multiple primaries for incidence purposes; as a consequence, a tumor within the same organ with a different histological type is considered a new tumor. Groups 5 and 12 in Table 2a (page 17) and groups 5, 14, and 17 in Table 2b (page 18) include tumors that are not perfectly characterized from the histological point of view and consequently cannot be distinguished from the other groups. In the case of bladder cancers and intracranial and intraspinal neoplasms, behavior codes are also included that are different from the malignant ones: therefore, if the histological types are the same, the incident case could easily be the first in order of time, with an uncertain behavior code of /1 or /2(*in situ*).

Some sites with a different topography code are considered a single site, and this is an element which was maintained in the various editions of the ICD-O until 2004, as shown in Table 1a, shown here to provide a means of weighing earlier data.

In 2004, a new IARC guideline was issued which profoundly revised the situation and the reporting method, as shown in Table 1b.[1]

In practice, the bladder was added to the urinary tract, whereas the kidneys (which after all have a different morphology) were removed; the upper aerodigestive tract was integrated; grouping for nasal cavities, mediastinum, male and female genital areas, and endocrine glands were eliminated.

Moreover, when two tumors have been diagnosed at different times, the topography code of the first is used; if they are synchronous, the site code given in the last column should be used.

Over time, there have been significant changes with respect to morphology, including changes from the Second to the Third edition of the ICD-O (Table 2a, shown to provide a means of weighing historical data) and, especially, with the 2004 IARC guidelines (Table 2b). Apart from the increased precision of morphology codes, the most relevant changes can be seen in the case of

lympho-hematological diseases, with the new differentiation of myeloid leukemias and Hodgkin's lymphomas, as well as the disaggregation of lymphoid neoplasms.
IARC, in any case, acknowledges that individual registries may follow different rules: in the United States, for example, the SEER takes into consideration when the diagnoses were made and considers incident tumors in different parts of the colon as single tumors, whereas the IARC considers the colon as one site. The important thing is to code consistently and, when publishing data, to provide a description of the rules followed in considering tumors "multiple."
The present handbook takes an intermediate stance on this issue: IARC rules are used for the evaluation of incidence, whereas another approach is taken for registration.

Evaluation for registration

At the registration stage the following are considered:

- all solid metachronous tumors of the same site (diagnosed with an interval of over 6 months), malignant and *in situ* or uncertain whether benign or malignant, provided the tumor is not a recurrence, independent of the morphology allocation in Table 3 (page 19) with the exception of epithelial neoplasms of the skin;
- bladder and intracranial/intraspinal tumors irrespective of behavior and morphology, provided they are not a flare-up of the disease;
- synchronous tumors (diagnosed within an interval of no more than 6 months) are always subject to registration if arising from different sites (for instance, different parts of the colon or the contralateral site of paired organs), or if they belong to different histological groups when in the same site; in the latter case, if the histological group is the same it can be registered, and the more aggressive behavior form should be privileged (normally it is the one with the higher morphology code, except for bladder cancer in which the flat form, which is more aggressive than the papillary form 8130, can be coded only as 8120) and/or the one with the more aggressive grading.

In the case of a series of different biological behaviors of the same histological type or group of histological types (if they are contemporary the malignant code prevails) Table 3[2] can be used. In the case of cancer of the lymphatic system, can be used instead Table 4 (page 20), however always in cases belonging to the same group of histological types.[3] In all cases where the second registration does not fall within the IARC rules, a specific indication must be adopted that is useful for exclusion during the analytical phase of incidence (see Chapter 2). This rule is valid for both synchronous and metachronous cases. Moreover, when the second diagnosis turns out to be actually a reassessment of the original diagnosis, the original diagnosis is simply modified.

Management of relapses

A neoplastic site is considered a relapse when a clinician has ascertained one of the following conditions:

1. recurrence of the disease in the organ, with the same morphology, and in the absence of surgical treatment;
2. distant recurrence after an interval free of the original disease;
3. recurrence of the disease at the site of the surgical scar.

Cases 1-2-3 can be recorded, but are not reported as a new case when a clinician has made a diagnosis of recurrence, regardless of the fact that the disease may show a more aggressive behavior.
Further onsets of disease within the organ after surgical treatment are instead subject to registration, although they are not used to compute incidence according to international rules. Special cases may be as follows:

- when a solid benign tumor, either *in situ* or with uncertain behavior shows metastatisation, this points to a diagnostic problem with the first histology; registrars must change the morphology and behavior codes to malignant (as well as ICD-9 and ICD-10 codes), keeping the incidence date of the first histology;
- in the case of bladder tumors, it is frequent to find the presence of flare-ups with different grading and degrees of infiltration; however, morphology, grading and behavior code of the first case need to be kept, registering as separate cases, complete with date:
  - any /3 cases ascertained after /1 or /2 cases;
  - any /2 cases ascertained after /1;
  - any flat forms 8120/ ascertained after papillary forms 8130/.

Alternatively, the procedure outlined in the previous paragraph can be followed, as long as the method chosen is explicitly stated.

Multiple primaries and survival

It must be borne in mind that when measuring and estimating survival nowadays, the analysis is normally carried out only on the patient's first malignant tumor (if the first tumor is a bladder tumor then other behaviors are also considered), unless it is epithelial skin cancer. As a consequence:

- if the first eligible tumor arose before the beginning of the activity of registration, tumors that are subsequently incident are not considered in the analysis of incidence;
- neoplasms subsequent to the first reportable one are registered so as to prevent their inclusion in the

analysis, if necessary by using a specific data field (see also the section on database layout).

Tumors with no microscopic confirmation

Histological or cytological confirmation is one of the main elements of neoplasm validation and is therefore a fundamental indicator of the quality of the data, since it makes possible an exact classification of the disease in terms of tumor morphology. However, certain conditions may prevent a correct morphology classification from being reached or retraced:

- the patient underwent diagnostic assessment with a **positive pathology result** in an unknown center or one that cannot be contacted, and underwent no subsequent hospitalizations or histological assessments;
- the patient underwent diagnostic assessment with a **negative or inconclusive pathology result** and did not undergo further histological assessments;
- the patient **did not receive** a histo-cytological diagnosis.

Cases of uncertain interpretation

The first problem that the registrar has to face is whether the neoplasm really exists or is a result of an incorrect interpretation. Apart from cases which are a result of HDD coding errors, resulting in a search for information on an inexistent case, histology data can sometimes be actually missing, or cannot be found on the basis of the available data flow.

The elements needed to make a decision are essentially the following:

- the existence of one or more hospital admissions in which the tumor diagnosis was confirmed and not disputed;
- the treatment undertaken (radiotherapy, chemo-therapy, palliative care, etc.)
- death from cancer;
- considerations in relation to the site of the tumor (for skin, stomach, colon and rectum, uterus, and bladder a high level of histopathological diagnostic confirmations are expected; for lung, liver, pancreas, and other internal organs, on the contrary, a lack of histological confirmation is likely, whereas generally cytological confirmation is more frequently present in these cases)
- the age and co-morbidity of the patient, which can lead to an evaluation without an in-depth diagnostic assessment;
- health tax exemption of the patient due to cancer.

Cases in which documentation is inconclusive and a follow-up of the patient is needed after publication of the data will be discussed more extensively in the sections “Refutable diagnosis” and “NSE/DCI cases”.

Assignment of topography in neo-organs

When primary tumors have arisen (i.e., excluding flare-ups, infiltrations, or metastasis from other neoplasms) in organs reconstructed surgically via transplant of other organs or tissues (e.g., ileal neobladder), these have to be entered within the incidence calculation with topography site referring to the tissue of origin (e.g., in the case of an ileal neobladder, the ileum), taking note of the surgery undergone by the patient.

Assignment of a specific morphology in the absence of microscopic confirmation

The general rule in ICD-O-3 is that in the absence of microscopic confirmation (basis of diagnosis from 1 to 4) code 8000/3 must be used; this indication replaces code 9990/3 of the First edition. Undoubtedly it is quite unlikely, when not outright impossible, to make a specific morphologic diagnosis with no microscopic assessment. There are however cases in which it is possible to assign a specific morphology on the basis of other assessments, when information regarding the histology of the tumor is absent or poor.

It is, after all, not the function of the ICD-O morphology code to specify the basis of diagnosis. A series of plausibility checks are therefore necessary in the data assessment stage, between ICD-O morphology and basis of diagnosis (in particular for codes 0-4 and 9 of the latter).

As an exception to the general rule, some morphological definitions can be accepted according to the IARC/ENCR indications (see Table 5, page 22).[4]

If the patient received a histological-cytological diagnosis (e.g., at another center) and does not have the original documentation, but the diagnosis is explicitly reported in subsequent clinical documentation (medical records, case files, discharge letters), the diagnosis must be considered valid. All diagnoses which can only be made by histological assessment (e.g., *in situ* carcinomas) cannot be accepted with other diagnostic methods.

Markers

Markers have different uses in oncology:

- some are used to diagnose disease;
- others support a diagnosis of disease (e.g., in paraneoplastic syndromes or in pituitary tumors);
- all make an evaluation of the effectiveness of therapy over time possible (monitoring during follow-up).

Even according to ENCR guidelines, registries may record a diagnosis with a specific morphology code in the absence of microscopic confirmation when a tumor marker consistent with a morphology is found, according to the criteria listed in the inset in this page. In the reported cases the morphologic diagnosis can be supported by a “4” code of basis of diagnosis (unless the documents available point to different evidence). The possibility of using PSA testing

(as described by the guidelines) has been ruled out, as in current clinical practice this marker alone does not make a prostate cancer diagnosis possible, since correlation with other markers such as free PSA and, ultimately, microscopic assessment are needed (see also the chapter on prostate cancer). In the latter case then, as for other hormone-producing tumors, morphology classification is only possible if it is explicitly confirmed after clinical assessment and can, in the absence of histology, be supported by a "2" code of basis of diagnosis.

Diagnostic imaging

The quality of diagnostic imaging in some cases makes detailed differential diagnosis possible with a clinical impact equal to that of microscopic examination, allowing registries to assign morphology at this diagnostic level according to the previously listed indications.

Endoscopic diagnostics

Endoscopic or laparoscopic diagnosis in the absence of a histopathological examination does not make specific morphologic diagnosis possible.

The possibility that samples may have been altered or lost can make microscopic morphological specification impossible, thus further surgical, clinical, and laboratory exams are needed, along with diagnosis of metastasis or other revealing clinical behavior, if present.

Biological markers	Diagnosis and conditions
Human Chorionic Gonadotropin (HCG)	choriocarcinoma (>100,000 IU urine)
alpha-fetoprotein (AFP)	hepatocellular carcinoma (>200 ng/ml serum)
catecholamine metabolites (HVA, VMA)	neuroblastoma
serum immunoglobulins	❖ myeloma (IgG >35g/l or IgA >20g/l) ❖ Waldenström's macroglobulinemia (IgM >10g/l)
urinary immunoglobulin	myeloma (light chain immunoglobulin >1g/24h)
pituitary hormones	pituitary tumors
gastrin and other polypeptide hormones of the gastrointestinal system	islet cell tumors, gastrinoma, etc.

Exploratory surgery/autopsy

Exploratory surgery and autopsy, unless accompanied by a histological examination, are not sufficient for a morphologic diagnosis, except in the cases considered in the previously mentioned IARC/ENCR guidelines. However, they do provide adequate information regarding the extension of the disease.

Clinical diagnostics and treatment

Clinical diagnosis of cancer is defined as diagnosis of disease in the absence of further laboratory and histological examinations: this corresponds to basis of diagnosis code "1".

A clinical diagnosis of a malignant tumor may not be refuted by registrars, unless particular conditions are met which are dealt with in the chapter relevant to the specific tumor.

The reason for this is that there are sometimes previous diagnostic procedures, unbeknownst to the registrar, as they are not reported in the medical record or are not available, and which in any case have no effect on therapeutic possibilities. In such cases, information regarding the disease is garnered from the causes of death or from later care approaches:

- palliative surgery;
- palliative radiation;
- assistance from palliative care units.

In other cases, there may be interference by therapies undertaken to stabilize a patient that suffers from other diseases, before oncological treatment is begun.

Based on clinical diagnosis alone, even according to ENCR guidelines, it is possible to register the case with a specific morphology code in the following situations:

Code	Morphology	Conditions
9590	lymphoma NOS	
9800	leukemia NOS	
8720	melanoma	
9140	Kaposi's sarcoma	in HIV positives (excluding Africa)

It must be emphasized that it is not possible to differentiate between Hodgkin's and non-Hodgkin's lymphoma via clinical observation only, nor between myeloid and lymphocytic leukemias; therefore, ascertainment of leukemia based simply on complete blood count is not to be considered a clinical diagnosis (base " 1"), but rather a diagnosis made on the basis of clinical investigations (base "2") and is sufficient for the assignment of specific morphology.

Post-mortem diagnoses

With regards to the date of incidence, subjects with cancer who undergo diagnosis can be divided into four main groups, as follows:

A: subjects with a cancer already diagnosed during life;

B: subjects in whom the cancer was not diagnosed with certainty during lifetime (for example in cases where the subject passed away before exams were complete), but with confirmation of death due to cancer after post-mortem examination;

C: a symptomatic tumor that was neither recognized nor suspected during lifetime is verified during autopsy in a subject whose death was apparently due to another cause, but the autopsy shows that it was instead due to cancer (in this case the pathologist modifies the ISTAT record);

D: incidental verification of a clinically asymptomatic neoplasm in a subject who died from another cause (in this case the pathologist makes not changes to the ISTAT record).

The inclusion in registration of cases belonging to the latter group is consistent with the principle that no cancer incidentally found during lifetime as a consequence of resection due to other causes is excluded from registration or from the calculation of incidence. Information that the subject belongs to this group can be in any way gleaned from the association between basis of diagnosis (3 or 8), date of incidence (corresponding to the date of death), and cause to which death is attributed.

The registrar must apply the following criteria:

Group	Basis of diagnosis	Incidence date	Cause of death
A	different from 3 or 8	histology date or other (see Chapter 2)	with tumor
B	3 or 8	date of hospital admission	with tumor
C	3 or 8	date of death	with tumor
D	3 or 8	date of death	without tumor

Cytogenetic and molecular diagnosis

Cytogenetic and molecular diagnosis should be considered at a par with histology on a primary tumor, and therefore requires use of basis of diagnosis code "7" ("8" for autopsy). Moreover, for the purpose of assigning a morphology code in leukemia and lymphoma, cytogenetic and molecular diagnosis ranks higher than simple histology, even if carried out on peripheral blood or blood from the bone marrow.[5]

Refutable or ineffective diagnosis

In current practice, registrars may not make or change a diagnosis, their task is limited to registering and coding. However, since source acquisition systems must give priority to the sensitivity of the method, they also include problematic cases which should be managed according to the criteria described in the chapter devoted to "non sufficient evidence" diagnoses (NSE, see below).

Registrars, following the internal procedures of each registry and having first run the necessary checks, may eliminate from the data set the following cases:

- NSE the evaluation of which has had a negative outcome;
- a histological benignity diagnosis (preferably on a surgical specimen) in contrast with the diagnosis on discharge (excluding intracranial and intraspinal neoplasms);
- erroneous double registration due merely to recording errors (coinciding dates and site/morphology combinations);
- subjects erroneously labeled as residents by sources, but who actually though temporarily living in a place have never been officially resident.

Managing special cases

Not sure eligibility (NSE) cases

Definition and treatment

Cases with insufficient clinical documentation (NSE) are cases in which there is a diagnosis of cancer or suspected cancer in the absence of definite diagnostic elements. This situation occurs when:

- the patient is old and compromised, therefore clinical suspicion is not followed up by clinical investigations, especially if they are invasive;
- clinical investigations, if carried out, are such that they cannot confirm the diagnosis with certainty, in particular with regards to the malignant behavior of the neoplasm.

These situations occur most frequently in cases of neoplasms of the internal organs (lungs, pancreas, kidneys, etc.)

These cases represent a problem for registration because their uncritical inclusion can, when registration does not reflect reality, result in:

- an overestimation of overall incidence;
- an overestimation of localization.
  - more frequent;
  - more frequent in the elderly;
  - more frequently lethal;
  - less susceptible to treatment;
  - of more difficult differential diagnosis.

It is therefore necessary to try and control these occurrences by defining rules to limit and quantify them.

Since registrars are not entitled to refute a diagnosis without further proof, they must wait for one of the following to occur:

- the clinical suspicion is disproved (refutable and deletable case);

- the clinical suspicion becomes a certainty, for example due to clinical evidence of progression/metastatisation;
- the clinical suspicion becomes a certainty because of positive clinical investigations carried out subsequently;
- the clinical suspicion remains a suspicion until death.

In current practice the last three events tend to coincide, since any examinations or the worsening of the disease can take place outside a hospitalization situation and not be picked up by the registration system. This is why in these cases other sources such as diagnostic imaging or palliative care centers become important.

The death certificate that officializes the pathological status of the patient therefore becomes decisive. Although there is an imprecision in the death certificates, seeing as after the demise there is no possibility of changing the diagnosis, the death certificates certify the presence or absence of cancer. One can therefore proceed applying the following rules.

Rule "0"

NSE cases are kept pending, i.e., they don't enter the incidence calculation until:

a: the evidence becomes sufficient;

b: death occurs.

In situation "b" a situation must be made in the presence of the following:

- death diagnosis corresponds to NSE tumor;
- death diagnosis caused by a tumor different from the NSE tumor;
- non-cancer death diagnosis.

The evidence is sufficient when:

- there are positive clinical investigations;
- a specific therapeutic plan for cancer was defined, including palliative treatments (even if therapy was not actually started).

Rule 1

For deceased NSE cases with no autopsy or other positive diagnostic examinations, the statements on the death certificate influence the decision of whether to report the case or not in the following ways:

Rule 2 (rule of credit):

Case b2 should be accepted anyway if:

a: the insufficiently documented diagnosis comes from a source where diagnoses are considered highly credible and the lack of documentation can be considered incidental;

b: the diagnosis is nosographically specified, precise, and plausible and the registry cannot take the responsibility of refuting it.

Event	Certainty of case	Data incidence	Basis of diagnosis
b1. death diagnosis corresponding to NSE tumor	yes	first diagnosis	1
b2. death diagnosis with generic indication of tumor		see rule 2	
b3. non-cancer death diagnosis	no		
b4. diagnosis of death from a tumor different from NSE tumor			
◆ due to concrete errors in the death certificate	yes		1
◆ compatibility with the NSE tumor	yes*		1
◆ non compatibility with the NSE tumor	DCI**		

** the certain case is the one recorded in the ISTAT record*
*** the DCI procedure refers to the tumor mentioned in the ISTAT record. Final decisions are made based on the trace-back*

Management schema for NSE cases

Registries cannot make or change diagnoses, but only transcribe them. However, in the current practice it is possible to come across vague or ambiguous terminology that raises the suspicion of cancer, both in clinical records and in anatomical pathology or diagnostic imaging reports. As recommended by the NIH and SEER, we therefore propose a non-exhaustive and unbinding list of terms based on which registrars can decide whether to record the case; if the case is recorded, the standard rules then apply (see Table 6, page 23). The types of NSE cases are shown in Table 7 (page 24).

Reporting NSE cases

Decisions must be kept track of through a field in the data set for first recording of NSE cases, and another field showing whether the problem was solved only at death and not beforehand. The following indicators must therefore be computed:

- initial NSE/incidental cases x 100
- NSEs resolved only after death/incidental cases x 100 for all sites and preferably for: 151,153-154, 155, 157, 162, 174, 183, 185, 188, 191, 200-208.

DCI and DCO cases

Definition and treatment

DCO (death certificate only) are defined as cases documented only by a death certificate.

Once a clinical and pathological survey for a given period has been completed (based on hospital admissions, diagnoses, medical records, etc.) registries must compare these data with the mortality from cancer of the people resident in the area they cover. Cases where the cancer cause appears only as an associated disease are also included in mortality from cancer. Two types of situations can arise:

- the deceased is a case known to the registry: documents are completed with date, place, and cause of death.
- the deceased is a case unknown to the registry: the case is DCI (death certificate initiated)

DCI cases are subject to trace-back; registries must try to trace back the clinical and pathological documentation of every DCI case; to do this, registries can use the information found in ISTAT records (hospital or nursing home where the death occurred), the files of patients discharged from regional hospitals and all sources registries normally use for their routine activity. If time and staff resources allow for it, registries may also carry out specific actions such as contacting the physician of the deceased person or taking family history.

Once the trace-back has been performed, DCI cases are divided into two groups:

a. those for which no further information has been traced and which therefore are entered in incidence as "true" DCO cases, which in any case must not be considered when computing survival;
b. those which, on the basis of the information collected, are found to be incident cases that were overlooked by the first assessment and which therefore qualify as ex DCO cases.

The following are not "true" DCO cases:

- cases which are not clearly defined as malignant tumors by the death certificate (e.g., "mediastinal mass," "cerebral expanding lesion") are not reportable;
- cases for which a suspicion is expressed (e.g., "suspected lung cancer", "probable ovarian cancer") are not to be registered;
- cases where it has been verified that the patient became resident within the area covered by the registry after the date of onset of the disease.

In no case can the date of incidence be deduced only by the "time interval" data field of the ISTAT record.

Ex DCO cases have four possible outcomes:

- registration as "non resident at the moment of diagnosis" (see Chapter 2) if the disease is found to have arisen before the subject became resident in the area covered by the registry;
- registration as prevalent cases, if they fell into a period prior to the initiation of the activity of the registry;
- registration as missing cases, if they fall within a period subsequent to the beginning of the registry's activity, but have already been submitted to the IARC for publication in *Cancer Incidence in Five Continents*;
- registration as definite cases.

The final share of DCI and DCO cases (at the end of the trace-back) are measures of registry quality (obviously, the higher the percentage of DCI and DCO cases, the lower the quality).

The proportion of cases considered as DCI which at the end of retrospective verification turn out to be incident cases at first overlooked is an indication of the sensitivity of registries' flow of information and measures the capacity of retrieving information during the clinical history of the patient (through hospital admissions, diagnoses, etc.) that is useful in defining the case. If the proportion of cases that the registry was able to recover this way is high, the effectiveness of the information flow of the registry is low.

The proportion of final DCO cases is a more general indicator of quality and availability of primary information sources (availability of information, need for long-distance research due to travel for medical care, etc.) which in any case contributes in defining the efficiency of the system of registration and the final quality of the data produced.

To interpret these indicators correctly, DCI/DCO cases need to be followed back only when registrars feel they have exhausted all clinical-pathological sources; this prevents classification as DCI cases of cases in which clinical-pathological confirmations would come independently.

Finally, it must be kept in mind, as specified further on, that the collection of data from death certificates only partially re-balances data lost during the clinical history of the patient. A disease with 80% mortality, for instance, means only 8 out of 10 lost cases at first registration may be found this way. The analysis of these indices disaggregated by anatomic site may enable registries to evaluate in more detail any underestimates and to study possible corrections.

It must be emphasized that, with the introduction of ICD-10 in mortality registration, the ISTAT rules in case of concurrent neoplasms state: [7]

- a lung cancer defined as "bronchial or bronchogenic carcinoma" must always be considered primary;
- a lung cancer should be considered primary if the lung is mentioned differently (even as metastasis) and the following sites are specified:
  - heart
  - diaphragm
  - brain
  - liver

- lymph nodes
- mediastinum
- meninges
- spinal cord
- bones
- peritoneum
- pleura
- lung
- retroperitoneum
- ill-defined sites classifiable as C76;

- a lung cancer should be considered secondary if the lung is mentioned differently and sites not mentioned in the above list are specified (e.g., breast, prostate, colon, etc.);
- similar procedures should be followed for other sites with frequent metastatic localization (liver, brain).

Moreover, if various multiple primary sites are recorded which are not included in the previous list and for which no .8 or .9 subcategory is available, they must be coded to C97., i.e., "multiple independent sites" (e.g., prostate and bladder). This implies the need of directly referring to the death certificate to manage NSE cases and find DCI cases. See Figure 1 and Figure 2 (pages 25-26).

Reporting DCI and DCO cases

For correct reporting of DCI cases, a field in the mortality data set must be used to write down the situation of the case classified as DCI with an indication of whether the follow-up has been completed or not, whereas the reporting of DCO cases requires use of the data field "basis of diagnosis" (only in these cases = 0) in the registry database, at the end of the trace-back.

The calculation of DCI and DCO cases remaining after trace-back results produces three indicators, that may be evaluated for each site and overall, even dividing the analysis by age (e.g., 0-34, 35-64, 65-74, 75+):

- proportion of DCI cases out of the total number of registered cases;
- proportion of DCO cases out of the total number of registered cases;
- proportion of unresolved DCI cases (DCI/DCO x 100).

Analysis of these indicators can reveal the presence of underregistration (very low proportions of DCI and DCO cases) or incomplete active casefinding (very high DCI/DCO numbers). These considerations can be further disaggregated by critical age groups or anatomic site, in relation to the expected diagnostic quality.

Traditionally, a maximum value of 5% for DCO cases has been the reference value for the IARC.

It must however be stressed that there are no coded threshold reference values for these indices; they are very useful instruments for evaluation, which in any case must be based on the context of each specific situation, in relation to expected results and problems.

Use of behavior codes /6 and /9

As indicated in the introduction to the Third edition of the ICD-O, codes /6 and /9 must not be used by cancer registries to avoid confusion about the primary site of the lesion.

Behavior /6

When a tumor case becomes known on the basis of a diagnosis of a metastasis, with unknown primary site, topography code C80.9 (IDC-O-3) must be used, corresponding to topography code 199.9 in ICD-O-1 and codes 196-199 in the ICD-9. The morphology behavior code must always be /3. Registries have the option to provide indication of the metastatic sites by registering them in the appropriate additional fields. If a discharge diagnosis is made with a generic site, the site is coded as primary, unless further information is in contrast with this.

In the case of a cytological or histological examination performed on a metastasis, the use of behavior /6 is not allowed, but a primary site (explicit or assumed, if given) must be referred to or else the neoplasm must be defined as having an "unknown primary site"; the information on the site of the histological examination is safeguarded by use of the appropriate "basis of diagnosis" code which makes it possible to distinguish when the histology is carried out on a primary tumor or on a metastasis.

Behavior /9

If the primary site is indicated as probable, this is preferred over a "primary site unknown" code. In these cases, a level of confirmation (basis of diagnosis) can be assigned, to indicate the uncertainty of the site.

When uncertainty about the primary site of a tumor persists, the reliability of the data needs to be assessed before making a decision between the mentioned primary and registration as metastasis from an unknown primary site. In any case the behavior code must be /3.

Correct coding in a few specific instances

Tumors with no microscopic confirmation

As discussed in greater detail earlier, the appropriate ICD-O-3 morphology code is 8000/3 with basis of diagnosis from 1 to 4; this indication replaces ICD-O-1 code 9990/3. When registries have discharge reports available, clinical records (or other records) that report non-specific or generic morphologic diagnoses (e.g., "ADK", "carcinoma", "epithelioma") without any reference to the document on which the diagnosis was based, a problem of reliability of the data arises; if the source is not reliable, in these cases it is suggested to use code 8000/3.

NOS malignant tumors with cytological or histological confirmation

When a neoplasm has been histologically or cytologically ascertained to be malignant without the possibility of ascertaining a specific morphology, the appropriate code is again 8000/3, with a basis of diagnosis from 5 to 8.

Use of the 8001/3 code ("malignant cancer cells")

This coding generally assumes a cytology examination.

The following codes:

8002/3 = malignant tumor, small cell type
8003/3 = malignant tumor, giant cell type
8004/3 = malignant tumor, spindle cell type

are used when the examination report contains some cell features, but is not able to provide further information on the histological type, nor therefore to confirm whether it is a carcinoma, sarcoma, or lymphoma. In the absence of further specifications the use of these codes shows that the basis of diagnosis is only cytological and therefore must be reported in the corresponding field.

Code 8050/3 ("papillary carcinoma")

The term "papillary carcinoma" not followed by other specifications is used quite frequently in histopathological diagnosis. The objective is to describe a polypoid tumor growth, i.e., having papillae of variable thickness with a connective-vascular axis covered by epithelial tissue with a cylindrical, transitional, or pavement-like appearance. Quite seldom, and incorrectly, the term is used to describe a papillary pattern within a glandular differentiation; in these cases the term "papillary adenocarcinoma" is more correct.

More frequently, specific mention of the type of epithelium that covers the papillary structures can be omitted, because it might be implicit in the structure of the organ from which the specimen is taken (thyroid, breast, ovary, urinary tract).

In the ICD-O classification, use of the code 8050/ automatically places the case within the group of squamous epithelium tumors (805-808); correct specifications that should follow the term "papillary," such as "transitional" or "serous epithelium," imply instead aggregation into completely different morphological groupings. Other tumors that are commonly defined as "papillary" without other specifications are papillary carcinomas of the thyroid and of the breast, for which the most appropriate code is 8260/3 (papillary adenocarcinoma). Finally, for papillary tumors of the urinary tract, the correct code is 8130/.

Consequently, code 8050/ can be used only in the NOS papillary forms with squamous histological type.

The section of this handbook devoted to specific tumor sites includes for each a list of the most appropriate morphologies according to WHO indications.

Special cases

Variation of behavior from /1 to /3

The problem no longer occurs as in the past for lympho-hematological neoplasms, but concerns, for instance, tumors of the connective tissue (fibromatosis, hemangiopericytoma, etc.) the /1 or /3 behavior of which is not deducible from the histological diagnosis, but is revealed during the clinical evolution of the disease. These tumors must be considered incident at the moment at which the malignant behavior is manifested.

The date of incidence, on the other hand, must refer to the first diagnosis in cases classified as 8000/1 or 8000/3 because of the lack of histopathological confirmation, when histopathological confirmation is obtained at a later time (over 3 months)[8], as well as in cases of malignant bladder tumors with undetermined degree of infiltration. Cases lacking certain diagnosis and with imprecise wording that implies a suspicion of cancer (neoformation, opacity, mass, etc.) must be collected and coded 8000/1 and considered as NSE cases; in case information gained subsequently confirms malignancy, their behavior must be updated to /3, whereas the incidence date remains that of onset of suspicion (according to the criteria for the management of NSE cases).

Likewise, a case that was discharged with a diagnosis of "lesions of a nature to be determined" or similar terminology and therefore without sufficient diagnostic evidence of a tumor does not necessarily have to be registered, but may be archived separately, and later readmitted (with the same incidence date) if its nature is subsequently clarified. To be defined "of uncertain behavior," a case always requires an explicit diagnosis of this type and must be registered but not counted in incidence, except for specific site exceptions (see Chapter 4).

Variation of behavior from /2 to /3

In situ tumors (behavior code /2) are gathered and coded by the registries to gain a more complete picture of the diseases in which these forms take on particular importance (breast, cervix, bladder, etc.), but their incidence must be kept apart from that of malignant neoplasms. Even in these cases the date of incidence should be the moment when a passage from behavior /2 (*in situ*) to behavior /3 (invasive) should occur; actually, it is recommended to carry out a double registration (according to the rules of registration for multiple primaries). If, instead, a surgical resection documents invasion by a tumor considered *in situ* from the relevant previous biopsy, the registration must

obviously concern only a single case with behavior of /3 and with a date corresponding to the biopsy.
The only exception to these rules concerns urothelial carcinomas of the bladder (see Chapter 4)).

Prevalent cases

At the beginning of the activity of a registry, many of the cases are identifiable as "prevalent," i.e., referring to a period preceding the registry's first year of official data collection. To avoid erroneous inclusion of prevalent cases as incident cases, newly activated registries must have a historical database that covers an adequate period before starting publication (in general at least two years). Since the criteria for the evaluation of multiple primaries refer to the history of the patient and not that of the registry, it is recommended to register prevalent cases accurately and to re-include them when carrying out multiple tumor checks. This aspect is important for the evaluation of registry completeness, as it provides the best guarantee as to data collection completeness.
In any case, indicators of prevalence should be built and their background methods given due importance, so as to offer increasingly more reliable and comparable data.

Non resident cases at diagnosis

As already discussed previously, between the "resident population at risk" and the "resident incident cases" there should be a close time correspondence, but inevitably the residence data is measured with higher precision in the latter, the migration of which is followed with more care.
The correspondence between the two populations ("cases" and "residents") is consequently more of a quality goal than a stable condition of work.
The already cited criteria of identification for "residence" for the cases are:

- restrictive criteria: being officially resident on the day of the diagnosis.
- broad criteria: being officially resident in the year of the diagnosis (at least: emigrated on the 1st of January or immigrated on the 31st of December).

For reasons already mentioned in the previous section the "restrictive" criterion appears to be preferable.

Cases identified after incidence has been "closed"

Given official statistic relevance (regional, national, and international) of the incidence and survival data published by cancer registries, there needs to be a standardization of the procedures of closing and publishing data for a certain period, while still considering the need for ongoing updates of the registry databases with data that emerge after publication (subsequent topography and/or morphology indications, correction of the actual incidence date, etc.)
Official statistics must be definitive: the data published, which capture trends over time, must therefore be considered unalterable, even when updates become available or when (marginal, it is to be hoped) errors emerge at a later date. We therefore propose the following rules.

1. Files based on which data were published must be "frozen" and preserved with no further changes, to make it possible for future studies to use the same data, and to allow for necessary verifications. Data can be "closed" every year or on a multiple year basis, according to each registry's needs. Obviously, longer periods offer more opportunity to correct and update data before closing. After that, no further variations may be made.
2. Bearing in mind that the original files of each publication must remain unchanged, each registry should however keep a central and original archive of all cases. This archive should be constantly updated and regularly corrected, and used to compare subsequent periods, to provide cross-references with other databases, and to update survival data and calculation of estimates. Obviously, this master file can yield data from longer or different periods than those already published by the registries (e.g., particular periods of time, combined publications), which can then be kept separately, following the methods proposed above in rule 1. The data submitted to the central AIRTUM Database or to other international databases must come from the master file in its most recently updated form.

Variations (duly documented) that follow closing of incidence mainly concern:

- inclusion of newly retrieved cases with registration of incidence subsequent to the period published (e.g., during systematic searches in non-computerized archives);
- changes occurring when cases are moved to other years of incidence or eliminated when errors in case files or identification could be ascertained (different or previous diagnoses, errors in vital statistics, etc.);
- revision of dubious or suspect cases (with consequent chance in the method of diagnosis and level of certainty) when new diagnostic information is found.

Any methodological variations in registration within each registry – as, for example, the revision of specific modes of coding – must be decided in the incidence data collection phase and must always be specified at the time of publication. More widespread and structured use of

automatic control programs on registry databases should increasingly reduce the need for substantial corrections after incidence has been closed.

Autopsy in tumor carriers

Post-mortem diagnosis of tumors can be made

- as a confirmation of previous clinical data, therefore with a previously determined incidence date;
- ”incidentally” with respect to the request of diagnostic verification: the incidence date in this case is that of the death of the subject.

All “incidental” tumors are entered in registration and incidence. The information provided by autopsy sources comes from mode “3” or “8” of the diagnosis data field. Especially during the feasibility study of new registries, local relevance of autopsy activities should be carefully assessed, even with regards to data validation.

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Tables

Table 1a. Groups of topography codes of the Second and Third edition of the ICD-O considered a single site in the definition of multiple primaries

BACK

Second/Third edition	Site	First edition
C01 C02	base of tongue other and unspecified parts of tongue	141
C05 C06	palate other and unspecified parts of mouth	145
C07 C08	parotid gland other and unspecified major salivary glands	142
C09 C10	tonsil oropharynx	146
C12 C13	pyriform sinus hypopharynx	148
C19 C20	rectosigmoid junction rectum	154
C23 C24	gallbladder other and unspecified parts of biliary tract	156
C30 C31	nasal cavity and middle ear accessory sinuses	160
C33 C34	trachea bronchus and lung	162
C37	thymus	164
C38.0-3	heart and mediastinum	164
C38.8	overlapping lesion of heart, mediastinum and pleura	165.8
C40 C41	bones, joints and articular cartilage of limbs bones, joints and articular cartilage of other and unspecified sites	170
C51	vulva	184.4
C52	vagina	184.0
C57.7	other specified parts of female genital organs	184.9
C57.8-9	overlapping lesion of female genital organs	184.8, 184.9
C56	ovary	183.0
C57.0	Fallopian tube	183.2
C57.1	broad ligament	183.3
C57.2	round ligament	183.5
C57.3	parametrium	183.4
C57.4	uterine adnexa	183.9
C60 C63	penis other and unspecified male genital organs	187
C64 C65 C66 C68	kidney renal pelvis ureter other and unspecified urinary organs	189
C74 C75	adrenal gland other endocrine glands and related structures	194

Table 1b. Groups of topography codes of ICD-O-3 considered a single site in the definition of multiple primaries (IARC 2004) BACK

Third edition	Site	Modified code
C01	base of tongue	C02.9
C02	other and unspecified parts of tongue	
C00	lip	C06.9
C03	gum	
C04	floor of mouth	
C05	palate	
C06	other and unspecified parts of tongue	
C09	tonsil	C14.0
C10	oropharynx	
C12	pyriform sinus	
C13	Hypopharynx	
C14	other and ill-defined sites in lip, oral cavity and pharynx	
C19	rectosigmoid junction	C20.9
C20	rectum	
C23	gallbladder	C24.9
C24	other and unspecified parts of biliary tract	
C33	trachea	C34.9
C34	bronchus and lung	
C40	bones, joints and articular cartilage of limbs	C41.9
C41	bones, joints and articular cartilage of other and unspecified sites	
C65	renal pelvis	C68.9
C66	ureter	
C67	bladder	
C68	other and unspecified urinary organs	

Table 2a. Groups of malignant neoplasms considered histologically "different" in the definition of multiple primaries (ICD-O-3) BACK

Groups		Morphology codes
	carcinomas	
1.	squamous cell carcinoma	805-808, 812, 813
2.	basal cell carcinoma	809-811
3.	adenocarcinomas	814, 816, 819-822, 826-833, 835-855, 857, 894
4.	other specific carcinomas	803, 804, 815, 817,818, 823-825, 834, 856, 858-867
(5.)	unspecified carcinomas (NOS)	801, 802
6.	**sarcomas** and soft tissue tumors	868-871, 880-892, 899, 904, 912, 913, 915-925, 937, 954-958
7.	**lymphomas**	959-971*
8.	**leukemias**	980-994, 995,996,998
9.	**Kaposi's sarcoma**	914
10.	**mesothelioma**	905
11.	**other specified types of cancer**	872-879, 893, 895-898, 900-903, 906-911, 926-936, 938-953, 973-975, 976
(12.)	**unspecified types of cancer**	800**, 997

** M-975 only in ICD-O-1*
*** in ICD-O-1, M-9990 was the current M-800*

Table 2b. Groups of malignant neoplasms considered histologically "different" in the definition of multiple primaries (ICD-O-3) (IARC 2004) BACK

Groups		Morphology codes
	carcinomas	
1.	squamous and transitional cell carcinoma	8051-8084, 8120-8131
2.	basal cell carcinoma	8090-8110
3.	adenocarcinomas	8140-8149, 8160-8162, 8190-8221, 8260-8337, 8350-8551, 8570-8576, 8940-8941
4.	other specific carcinomas	8030-8046, 8150-8157, 8170-8180, 8230-8255, 8340-8347, 8560-8562, 8580-8671
(5.)	unspecified carcinomas (NOS)	8010-8015, 8020-8022, 8050
6.	**sarcomas** and soft tissue tumors	8680-8713, 8800-8921, 8990-8991, 9040-9044, 9120-9125, 9130-9136, 9141-9252, 9370-9373, 9540-9582
7.	**mesothelioma**	9050-9055
	tumors of hematopoietic and lymphoid tissues	
8.	myeloid	9840, 9861-9931, 9945-9946, 9950, 9961-9964, 9980-9987
9.	B-cell neoplasms	9670-9699, 9728, 9731-9734, 9761-9767, 9769, 9823-9826, 9833. 9836, 9940
10.	T-cell and NK-cell neoplasms	9700-9719, 9729, 9768, 9827-9831, 9834, 9837, 9948
11.	Hodgkin's lymphoma	9650-9677
12.	mast cell tumors	9740-9742
13.	histiocytes and accessory lymphoid cells	9750-9758
(14.)	unspecified types	9590-9591, 9696, 9727, 9760, 9800-9801, 9805, 9820, 9832, 9835, 9860, 9960, 9970, 9975, 9989
15.	**Kaposi's sarcoma**	9140
16.	**other specified types of cancer**	8720-8790, 8930-8936, 8950-8983, 9000-9030, 9060-9110, 9260-9365, 9380-9539
(17.)	**unspecified types of cancer**	8000-8005

Table 3. Multiple registrations based on behavior BACK

1. Case		**2. Case of the same histotype group**			
Behavior code		**benign (/0*), uncertain (/1)**	**in situ (/2)**	**malignant (/3)**	**metastatic**
benign /0* uncertain whether benign/malignant	/0*	1 registration	**2 registrations**	**2 registrations**	**2 registrations**
	/1				
in situ	/2	1 registration	1 registration	**2 registrations**	**2 registrations**
malignant	/3	1 registration	1 registration	**2 registrations** if metachronous and there is no recurrence of the disease	1 registration
metastatic		1 registration	1 registration	1 registration	1 registration

** only if intracranial-intraspinal*

Table 4. Multiple registrations in cancers of the lymphohematopoietic system BACK

First diagnosis	Second diagnosis	Guidelines for registration	Guidelines for incidence as multiple primary
nodal lymphoma	extra-nodal lymphoma	2 registrations, except in the case of bone marrow of nodal lymphoma,	multiple primaries only if the cell lineages are different (B vs. T vs. NK vs. Null)
low grade NHL	high grade NHL	2 registrations	multiple primaries only if the cell lineages are different (B vs. T vs. NK vs. Null)
high grade NHL	acute lymphoblastic leukemic phase	1 registration; evolution	not multiple tumor
chronic lymphocytic leukemia	high grade NHL (Richter's syndrome)	2 registrations	multiple primaries only if the cell lineages are different (B vs. T vs. NK vs. Null)
chronic lymphocytic leukemia	Hodgkin's lymphoma	2 registrations (IARC rule)	multiple primaries
NHL	Hodgkin's lymphoma	2 registrations (IARC rule)	multiple primaries
Hodgkin's lymphoma	NHL	2 registrations (IARC rule)	multiple primaries
Hodgkin's lymphoma	acute myeloid leukemia	2 registrations (IARC rule)	multiple primaries
Hodgkin's lymphoma	myelodysplastic syndrome	2 registrations (IARC rule)	multiple primaries
chronic myeloid leukemia	acute myeloid leukemia	2 registrations if it is not a blast crisis (for instance, presence of specific biomolecular markers)	not multiple tumor
chronic myeloid leukemia	acute lymphoblastic leukemia	2 registrations (IARC rule)	multiple primaries
myeloid leukemia	myelodysplastic syndrome	2 registrations if the myelodysplastic syndrome is considered secondary to therapy	not multiple tumor
lymphocytic leukemia lymphomas	myelodysplastic syndrome	secondary to the underlying disease	multiple primaries
myeloid leukemia or chronic myelomonocytic leukemia	acute myeloid leukemia	2 registrations if it is not a blast crisis (for instance, presence of specific biomolecular markers)	not multiple tumor
myelodysplastic syndrome	acute myeloid leukemia	2 registrations, myeloid leukemia is coded to 9895/3 (not to be used for single leukemia) to make it possible to check leukemia trends	not multiple tumor
polycythemia vera	acute myeloid leukemia	2 registrations, myeloid leukemia is coded to 9895/3 (not to be used for single leukemia) to make it possible to check leukemia trends	not multiple tumor
essential thrombocythemia	acute myeloid leukemia	2 registrations, myeloid leukemia is coded to 9895/3 (not to be used for single leukemia) to make it possible to check leukemia trends	not multiple tumor
multiple myeloma	acute myeloid leukemia	2 registrations (IARC rule)	multiple primaries
MGUS	❖ myeloma ❖ Waldenström's macroglobulinemia	2 registrations, except for synchronous tumors (maximum interval 6 months) in which only the second /3 disease is registered	only the second /3 disease is entered in incidence
MGUS	low grade NHL	if so, only NHL is registered	only NHL /3 is considered for incidence
myeloma Waldenström's macroglobulinemia	low grade NHL	2 registrations, unless the NHL is IgM-secreting (lymphoplasmacytic lymphoma)	multiple primaries, unless the NHL is IgM-secreting (lymphoplasmacytic lymphoma): if so, the NHL code is used

polycythemia vera	❖ primary myelofibrosis ❖ refractory anemias	2 registrations	not multiple tumor
essential thrombocythemia	❖ primary myelofibrosis ❖ refractory anemias	2 registrations	not multiple tumor
chronic myelomonocytic leukemia	myelodysplastic syndrome	1 registration	not multiple tumor
chronic lymphocytic leukemia	acute lymphoblastic leukemia	1 registration, acute leukemia is in this case a dedifferentiation of CLL	not multiple tumor

Table 5. Acceptable combinations of morphology and non microscopic basis of diagnosis BACK

Code	Morphology	Conditions
8800	Sarcoma, NOS	
9590	Lymphoma, NOS	
8720	Melanoma (ocular)	
9140	Kaposi's sarcoma (visceral)	HIV positive (except Africa)
8960	Nephroblastoma, NOS	0-8 years of age
9500	Neuroblastoma	0-9 years of age
9510	Retinoblastoma	0-5 years of age
9380	Glioma and glial cell tumors	topography C71.7 (brain stem)
9384/1	Subependymal giant cell astrocytoma	patients with tuberous sclerosis
9530-9539	Meningioma	topography C70.X
9350	Craniopharyngioma	
8270-8281	Pituitary tumors	topography C75.1 (associated to an increase in pituitary hormones)

Table 6. Terminology considered diagnostic or not considered diagnostic of cancer BACK

Case is reportable		Case is not reportable
appears	undoubtedly	to be followed up
comparable	potentially malignant	questionable
compatible with	presumed	equivocal
appearing	probable	excluding
with evidence of	probably	uncertain
with signs of malignancy	recalls	cannot be ruled out
consistent with	seems	possible
evident	suspect (for)	
suggests	typical (of)	undefined lesion
favors	most likely	lesion type to be determined

Table 7. NSE cases BACK

Cases	Conditions	Database inclusion	Inclusion in incidence
❖ diagnosis (with poor documentation) ❖ suspected diagnosis (vague, but explicit), no death within the same hospitalization, subsequently confirmed		yes yes	yes yes
❖ diagnosis (with documentation that seems to disprove it) ❖ suspected diagnosis (vague, but explicit), no death within the same hospitalization, subsequently disproved		no yes, then deleted	no no
suspected diagnosis (vague, but explicit), no death within the same hospitalization, without subsequent confirmation or disproof	subsequent death certificate certain or suspect	yes	yes
suspected diagnosis (vague, but explicit) without further confirmation, nor disproof	negative death certificate	yes, then deleted	no
suspected diagnosis (vague, but explicit) without further confirmation, nor disproof	patient is alive	yes, under follow-up	no
suspicion implicit in inexplicit wording	explicit death certificate	yes	yes
suspicion implicit in inexplicit wording	without further confirmation	yes, then deleted	no

Figures

Figure 1. NSE case management flow chart BACK

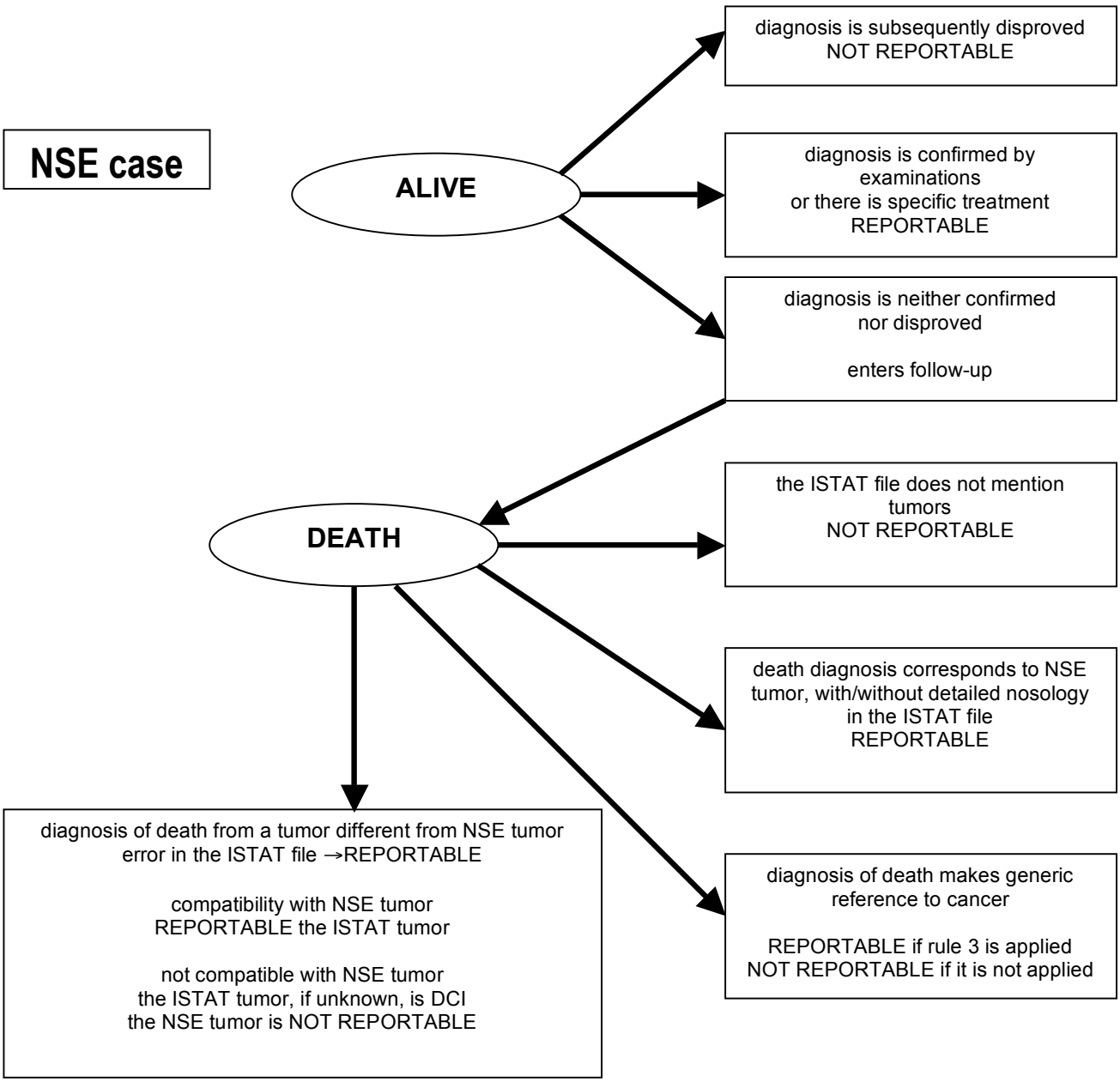
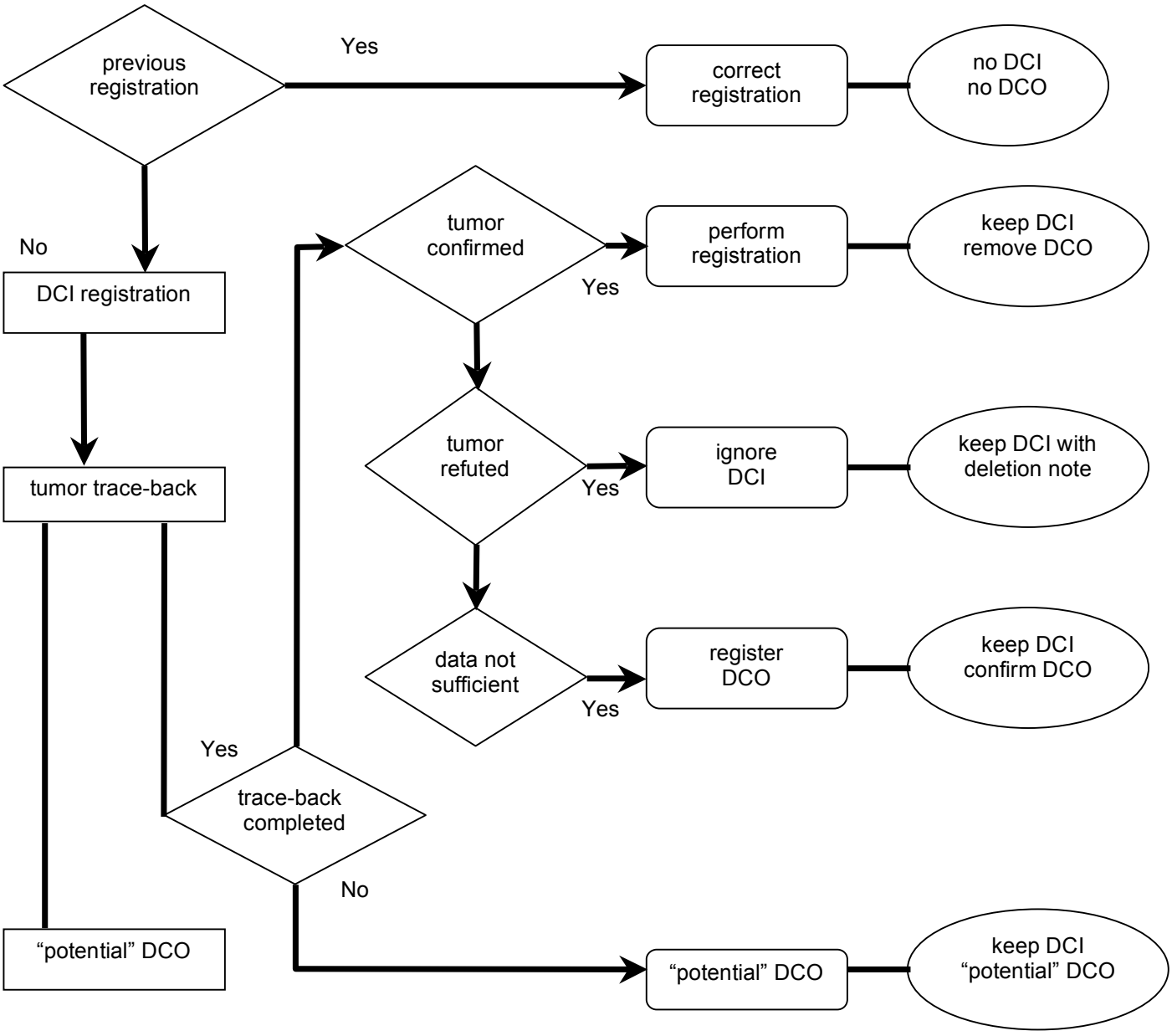


Figure 2. DCI case management flow chart BACK



Modified by: UKACR [6]