



Cost-effectiveness of diagnostic tests during follow-up in lung cancer patients: an evidence-based study

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Background: Many patients with non-metastatic non-small cell lung cancer (NSCLC) are cured by surgery but part of them develop recurrence. Strategies are needed to identify these relapses. Currently, there is no consensus on the follow-up schedule after curative resection for patients with NSCLC. The objective of this study is to analyze the diagnostic capacity of the tests performed during follow-up after surgery.

Methods: We retrospectively reviewed 392 patients with stage I–IIIA NSCLC who underwent surgery. Data were collected from patients diagnosed between January 1st, 2010 and December 31st, 2020. Demographic and clinical data were analyzed, as well as the tests performed during their follow-up. We identified as relevant in the diagnosis of relapses those tests that prompted further investigation and change of treatment.

Results: The number of tests matches those included in clinical practice guidelines. A total of 2,049 clinical follow-up consultations were performed, of which 2,004 were scheduled (0.59% informative). A total of 1,796 blood tests were performed, of which 1,756 were scheduled (0.17% informative). A total of 1,940 chest computer tomography (CT) scans were performed, of which 1,905 were scheduled and 128 were informative (6.7%). A total of 144 positron emission tomography (PET)-CT scans were performed, 132 of which were scheduled, of which 64 (48%) were informative. In all cases, the tests performed by unscheduled request exceeded the informative result of the scheduled ones several fold.

Conclusions: Most of the scheduled follow-up consultations were not relevant for the patients' management, and only body CT scan exceeded the threshold of 5% profitability, without reaching 10% even in stage IIIA. The profitability of the tests increased when performed in unscheduled visits. New follow-up strategies based on scientific evidence must be defined and follow-up schemes should be tailored focused on agile attention of the unscheduled demand.

Keywords: Non-small cell lung cancer (NSCLC); cost-effectiveness; follow-up; computer tomography scan (CT scan)

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Introduction

Lung cancer is one of the main public health problems worldwide given its high incidence and mortality and one of the tumors with worst prognosis, due to its aggressiveness and the difficulty in making an early diagnosis. Despite advances in screening, detection, molecular classification, and treatment, lung cancer accounts for nearly a quarter of all cancer-related deaths in the United States (1).

The cost of treatment and follow-up of lung cancer patients in Spain is substantial. In an overburdened healthcare system such as the Spanish one, it is necessary to consider the cost-effectiveness of the range of management strategies at different points on lung cancer patients' care pathways to ensure that they provide adequate value for money (2).

Patients with early-stage disease may be cured by surgical treatment. And yet, disease recurrences are frequent in up to 30% of patients. To detect these cancer recurrences and to treat early and potentially curable relapses, cancer guidelines suggest follow-up of these patients using clinical and radiological examinations. However, no generally accepted follow-up regimens exist. Moreover, standards differ with respect to the timing of these examinations (3).

This work will focus on the management during follow-up of non-small cell lung cancer (NSCLC) patients, stages I to IIIA, where surgical resection with curative intent is the treatment of choice (4). In stages II–IIIA, a multidisciplinary work is necessary in order to establish the correct treatment, given the administration of chemotherapy platinum-based adjuvant is recommended in most cases.

Despite curative surgery, many patients may develop recurrent and/or metastatic disease. Therefore, a follow-up scheme needs to be established in these patients, which is usually controversial among the different specialists (5). There is a trend, but no clear evidence, that intensive follow-up reduces the time to detection of recurrence. However, follow-up programs may not be sensitive enough for identified recurrences to have an impact on overall survival (OS). In addition, false positives or early asymptomatic diagnosis of recurrence can affect quality of life (6). *Table 1* shows the follow-up protocol of the different guidelines after having performed surgery with curative intent. The probability of recurrence of NSCLC is greater during the first 2 years after surgery. From the 2nd year, the risk of developing a second tumor is notably higher (11).

The main hypothesis of this study is that the intense follow-up performed in patients with NSCLC after curative surgery in many cases does not imply any change in their disease, being necessary to establish an adequate protocol that increases efficiency of the health care systems. We present the following article in accordance with the STROBE reporting checklist (available at <https://tldr.amegroups.com/article/view/10.21037/tlcr-22-540/rc>).

Methods

We conducted a descriptive, observational, retrospective study. All the data have been retrieved from electronic health records (EHR) between January 1st, 2010 and December 31st, 2020 of patients diagnosed at Puerta de Hierro-Majadahonda University Hospital (HUPHM).

Study population

Patients diagnosed with NSCLC, stages I to IIIA, who underwent surgery, between January 1, 2010 and December 31, 2020 at the HUPHM, were selected. The EHR of 686 patients were reviewed, of which 294 were withdrawn due to loss of follow-up or deceased due to postsurgical complications. A total of 392 patients were included.

The following variables were collected: sex, age, stage, histology and the different tests performed until relapse or last follow-up. The different tests analyzed were the clinical history, physical examination, laboratory tests, chest radiography (Rx), chest computer tomography (CT), positron emission tomography (PET)-CT and brain CT/magnetic resonance imaging (MRI). Tests were divided in

Highlight box

Key findings

- Most of the scheduled follow-up consultations were not relevant for the patients' management. Nevertheless, the profitability of the tests increased when performed in unscheduled visits.

What is known and what is new?

- CT scan stands as the complementary test of choice to detect relapses, resulting in greater profitability during the first 2 years post-surgery and in stage IIIA.
- The results obtained in our study confirm the importance and need of unscheduled visits for oncology patients.

What is the implication, and what should change now?

- Based on our results, we consider a priority to establish new follow-up strategies and fast-track consultations focusing on unscheduled demands.

Table 1 Summary of guidelines for follow-up of NSCLC after curative resection (7-10)

Organization	Follow-up
American College of Chest Physicians	Year 1–2: chest CT scan every 6 months After year 3: low dose chest CT scan annually
American Society of Clinical Oncology	Year 1–2: chest CT scan every 6 months After year 3: low dose chest CT scan annually
European Society for Medical Oncology	Year 1–2: clinical history, physical examination and CT every 6 months After year 3: clinical history, physical examination and CT every 12 months
National Comprehensive Cancer Network	Year 1–5: periodic follow-up (undefined frequency) that includes clinical history, physical examination and low dose CT w/wo contrast After year 5: follow-up every 12 months with clinical history, physical examination and low dose CT
Spanish Society of Thoracic Surgery	Year 1–2: CT every 6 months After year 3: CT every 12 months up to 10 years for possible risk of secondary neoplasms
Spanish Society of Medical Oncology	Year 1–2: clinical history, physical examination and CT every 6–12 months After year 3: clinical history, physical examination and CT every 12 months

NSCLC, non-small cell lung cancer; CT, computer tomography.

scheduled or unscheduled (those patients who came to the Emergency Room). The tests performed on each patient after undergoing surgery were considered. Those exams that presented suspicious findings of a possible relapse were considered informative. In addition, it was determined which was the test that detected the relapse and led to a change in the follow-up and/or treatment of the patient.

Statistical analysis

A descriptive analysis of the collected data was performed. The summary of the quantitative variables was expressed through the median/mean and the qualitative variables as percentages. OS was defined as the time from the time of diagnosis to the time of death from any cause, progression-free survival as the time from the time of diagnosis to detection of progression or death from any cause, and the median follow-up from the date of surgery to the date of progression or death from any cause. For the statistical analysis of the data, the SPSS program, version 26, was used.

Ethical aspects

The study was conducted in accordance with the requirements expressed in the Declaration of Helsinki (as

revised in 2013), as well as with the current legislation in Spain on conducting observational studies (Ministerial Order SAS/3470/2009). The study was approved by the HUPHM Clinical Research Ethics Committee (No. PIE14/00064) and individual consent for this retrospective analysis was waived.

Results

Patients characteristics

A total of 392 patients were included in the study. Patients' characteristics are detailed in *Table 2*. Regarding gender, 263 were men (67.1%) and 129 were women (32.9%). The mean age at diagnosis was 66 years. Regarding stage, 193 patients presented stage I, of which 114 patients were stage IA (29.0%) and 79 patients were stage IB (20.2%); 87 patients presented stage II, of which 43 patients were stage IIA (11.0%) and 44 patients were stage IIB (11.2%); and 112 patients presented stage IIIA (28.6%). Regarding histology, 237 patients were diagnosed with adenocarcinoma (60.4%), 111 patients with squamous cell carcinoma (28.3%), 4 patients with adenosquamous cell carcinoma (1.0%), 19 patients with large cell carcinoma (4.8%), 12 patients with large cell neuroendocrine carcinoma (3.1%), 1 patient with sarcomatoid (0.3%), 1 patient with undifferentiated (0.3%),

Table 2 Patient's characteristics

Clinical characteristics	N	%
Age (years), median (IQR)	65.5 (64.6–66.3)	
Sex		
Male	263	67.1
Female	129	32.9
Stage		
IA	114	29.0
IB	79	20.2
IIA	43	11.0
IIB	44	11.2
IIIA	112	28.6
Histology		
Adenocarcinoma	237	60.4
Squamous cell carcinoma	111	28.3
Large cell carcinoma	19	4.8
Neuroendocrine large cell carcinoma	12	3.1
Adenosquamous	4	1.0
Sarcomatoid	1	0.3
Undifferentiated	1	0.3
Carcinoid tumor	1	0.3
Others	6	1.5
Chemotherapy		
Adjuvant	132	33.7
Neoadjuvant	50	12.8
Radiotherapy	49	12.5
Surgery	392	100.0

IQR, interquartile range.

1 patient with carcinoid tumor (0.3%), and 6 patients presented other histological diagnosis (1.5%).

Relapse, follow-up, survival time, progression-free survival and vital status

A total of 175 patients relapsed (44.6%) in our cohort. At the end of the study, 141 patients have died (36%), 198 patients are alive without disease (50.5%) and 53 patients are alive with disease (13.5%). Of the 217 patients who did

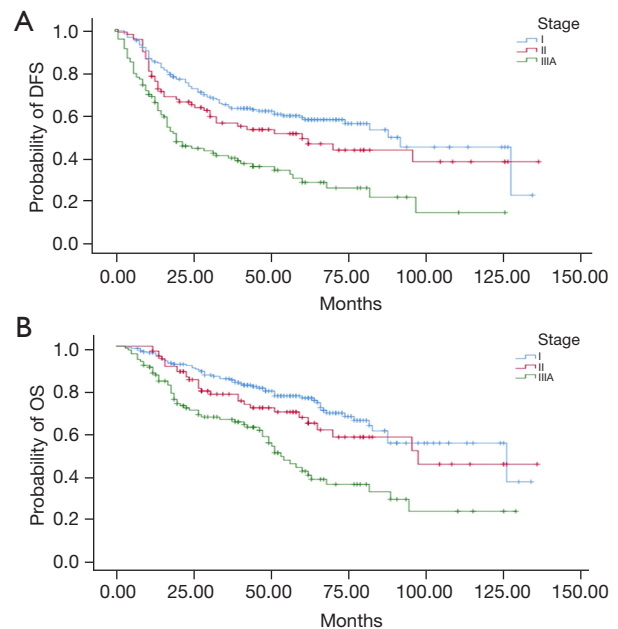


Figure 1 Survival curves showing probability of DFS (A) and probability of OS (B) for stages I, II, IIIA. DFS, disease-free survival; OS, overall survival.

not relapse, 198 are currently alive and 19 died for other causes. As for the 175 patients who did relapse, 122 have died and 53 are alive with disease. Median OS was 89.0 [interquartile range (IQR), 75.7–102.3] months and median disease-free survival (DFS) was 58.0 (IQR, 38.9–77.1) months. As shown in *Figure 1*, in stage I the mean was 46.2 (IQR, 41.9–50.5) months, in stage II 41.0 (IQR, 33.8–48.1) months and in stage IIIA 28.5 (IQR, 23.2–33.3) months.

As for patients alive without disease, the mean follow-up was 59.9 (IQR, 55.6–64.2) months. With regard to patients alive with disease, the mean follow-up until relapse has been 32.1 (IQR, 25.8–38.4) months.

Scheduled and unscheduled tests performed

Table 3 shows the total number of scheduled and unscheduled tests classified by stage, the mean per patient, the number of tests that were informative, and their total percentage.

Clinical consultations

A total of 2,049 clinical consultations were performed, of which 2,004 were scheduled and 45 unscheduled. As for the scheduled ones, only 12 (0.59%) were informative and of the unscheduled ones, 45 (100%) were informative.

Table 3 Total number of scheduled and unscheduled tests according to stage

Tests	Total	Mean	Informative	% informative
Scheduled				
Stage I				
Clinical consultation	1,029	5.33	2	0.19
Physical exam	1,023	5.30	0	0.00
Laboratory tests	828	4.29	0	0.00
Chest X-ray	62	0.32	0	0.00
CT scan	966	5.01	48	4.96
PET-CT	54	0.28	29	53.70
Brain CT/MRI	5	0.03	2	40.00
Stage II				
Clinical consultation	473	5.44	3	0.63
Physical exam	478	5.49	2	0.41
Laboratory tests	450	5.17	1	0.22
Chest X-ray	14	0.16	0	0.00
CT scan	457	5.25	32	7.00
PET-CT	37	0.43	13	35.13
Brain CT/MRI	4	0.05	2	50.00
Stage III				
Clinical consultation	502	4.48	7	1.39
Physical exam	507	4.53	4	0.78
Laboratory tests	478	4.27	2	0.41
Chest X-ray	4	0.04	1	25.00
CT scan	482	4.30	48	9.95
PET-CT	41	0.37	22	53.65
Brain CT/MRI	0	0.00	–	–
Unscheduled				
Stage I				
Clinical consultation	15	0.08	15	100.00
Physical exam	15	0.08	13	86.00
Laboratory tests	13	0.01	1	7.69
Chest X-ray	2	0.01	1	50.00
CT scan	10	0.05	7	70.00
PET-CT	7	0.04	7	100.00
Brain CT/MRI	7	0.04	7	100.00

Table 3 (continued)

Table 3 (continued)

Tests	Total	Mean	Informative	% informative
Stage II				
Clinical consultation	7	0.08	7	100.00
Physical exam	7	0.08	5	71.40
Laboratory tests	7	0.08	0	0.00
Chest X-ray	0	0.00	–	–
CT scan	3	0.03	2	66.60
PET-CT	1	0.01	1	100.00
Brain CT/MRI	6	0.07	5	83.30
Stage III				
Clinical consultation	23	0.21	23	100.00
Physical exam	23	0.21	19	82.60
Laboratory tests	20	0.18	3	15.00
Chest X-ray	2	0.02	2	100.00
CT scan	13	0.05	9	69.20
PET-CT	4	0.04	3	75.00
Brain CT/MRI	13	0.07	12	92.30

CT, computer tomography; PET, positron emission tomography; MRI, magnetic resonance imaging.

Most of the latter correspond to patients who went to the Emergency Room, generally with symptoms such as headache and who ended up being diagnosed with brain metastases.

Physical exams

A total of 2,053 physical examinations were performed, of which 2,008 were scheduled and 45 unscheduled. Regarding the programmed ones, 6 (0.29%) were informative and regarding the unscheduled ones, 37 (82.2%) were informative.

Laboratory tests

A total of 1,796 laboratory tests were performed, of which 1,756 were scheduled and 40 unscheduled. The low degree of information they present is observed, with only 3 scheduled tests (0.17%) and 4 unscheduled tests (10%) being informative. Despite the high percentage of information on the unscheduled tests (10%), it should be noted that none of them determined the change in patient follow-up, since these patients already presented symptoms that were the determining factors for tumor relapse

suspicion.

Chest X-ray

A total of 84 chest X-rays were performed, of which 80 were scheduled and 4 unscheduled. As for the scheduled ones, 1 (1.25%) was informative and of the unscheduled ones, 3 (75%) were informative.

Chest CT scan

A total of 1,940 chest CT scans were performed, of which 1,905 were scheduled. Of note, the highest percentage of informative chest CT-scans were those performed in stage III (9.95%). Additionally, regarding the timeline distribution of chest CT scans after surgery, during the first 2 years, 909 CT scans were performed, 81 (8.9%) being informative. During the 3rd to 5th years, 792 CT scans were performed, 37 (4.67%) being informative. As of the 5th year, 204 CT scans were performed, 10 (4.9%) being informative. Thus, of the informative CT scans, 63% were performed during the first 2 years, 29% during the 3rd to 5th years, and 8% beyond the 5th year. As for the unscheduled CT scans, a total of 25 were performed, 15 (60%) being informative,

and of those only 4 (26.6%) determined the change in patient's follow-up. Results of the total number of chest CT scans performed are shown in *Table 3*.

PET-CT scan

A total of 144 PET-CT scans were performed, of which 132 were scheduled, being those performed in stages I and III the most informative (53.7% and 53.6%, respectively). As for the unscheduled, a total of 12 PET-CT scans were performed, of which 91.66% were informative. However, only 27.2% resulted in a change in the patient's follow-up. Results of the total number of PET-CT scans performed are shown in *Table 3*.

Brain CT/MRI

A total of 35 brain CT scans were performed, 9 of them scheduled, of which 4 were informative (44.4%). They were performed in patients with NSCLC stages I and II and none in patients with stage III. As for the unscheduled, 26 were performed, of which 24 (92.3%) were informative. Of important note, 13 were performed in stage III, and of these, 12 were informative (92.3%).

Discussion

Currently, there is no adequate standard follow-up protocol after NSCLC surgery. There is a lack of consensus and each guide offers a different follow-up. It is therefore necessary to develop studies to standardize surveillance care in these patients. NSCLC patients treated with radical intent should be followed for treatment-related complications, detection of treatable relapse or occurrence of second primary lung cancer. European Society for Medical Oncology Clinical Practice Guidelines for diagnosis, treatment and follow-up of early and locally advanced NSCLC recommend on surveillance every 6 months for 2 years with a visit including history, physical examination and—preferably contrast enhanced—volume chest CT scan at least at 12 and 24 months, and thereafter an annual visit including history, physical examination and chest CT scan in order to detect second primary tumors. For patients who are suitable for salvage treatment (e.g., surgery, local ablative therapy), follow-up with 6-monthly CT scans for 3 years is recommended, but there is no recommendations other than a personalized tailoring of the follow-up for those not suitable for salvage treatment, based on the oncologist's criteria (10). If the follow-up is based on Spanish and European oncology and thoracic surgery guidelines (7,9,10),

a total of 1,847 clinical consultations and chest CT scans should have been performed, corresponding to an average of 4.7 per patient. In addition, 1,221 (66%) would correspond to patients alive free of disease, 186 (10%) to patients alive with disease, and 440 (24%) to deceased patients. At the HUPHM, a total of 2,004 scheduled clinical consultations and 1,905 scheduled chest CT scans have been performed, corresponding to a mean of 4.8 and a median of 4 CT scans/patient. Of those, 1,252 (66%) have been performed in patients alive free of disease, 234 (12%) in patients alive with disease and 419 (22%) in deceased patients. Therefore, the follow-up conducted at HUPHM is adjusted to that proposed by the Spanish medical oncology guidelines.

Regarding the data obtained with the clinical consultations and the physical exams, it is of note the few cases of relapse detected in the scheduled ones. In addition, on many occasions, patients report symptoms (mostly dyspnea) that are normally attributable to a reduced lung function after surgery and are not related to a possible relapse. Therefore, these scheduled clinical consultations provide a very low level of information useful for relapse detection (0.59% and 0.29%, respectively, in the present study), and it is therefore of interest to consider reducing their number. On the other hand, in unscheduled clinical consultations and physical exams, totally opposite results have been obtained. Occasionally, oncology patients visit the Emergency Room or require an unscheduled visit, reporting specific signs or symptoms of a possible relapse. It should also be noted that 51% of these visits were stage III patients, despite only representing 28% of the whole cohort. Therefore, this study shows the great importance of unscheduled visits for oncology patients, resulting in the possibility of implementing, in Oncology Departments, specific consultations for this purpose.

In the present study, it is observed that, despite the large number of laboratory tests performed, only 7 were informative and, furthermore, none of them determined the change in follow-up. They stand as a complementary test that is performed routinely in cancer patients during each follow-up visit, accounting for 1–2 tests per year per patient. However, they have a limited role in contributing to relapse detection (4).

Regarding chest X-ray, it is the less frequent test performed during follow-up, since it is not indicated in the evaluation after surgery. In our patients, only 84 chest X-rays were performed, the majority stage I and II during the 2nd or 3rd year of follow-up, in whom the chest X-ray and a chest CT were combined. It could be useful to consider its

Table 4 Survival outcomes of the study cohort by stage

Outcomes and scheduled CT scans	Stage I	Stage II	Stage III
Total	193	87	112
Median follow-up (months), median (IQR)	46.2 (41.9–50.5)	41.0 (33.8–48.1)	28.5 (23.2–33.3)
Number of CT scans per year	1.30	1.53	1.70
Median OS (months), median (IQR)	128.0 (72.4–183.6)	99 (57.3–140.7)	52.0 (44.4–59.6)
Median DFS (months), median (IQR)	89.0 (71.1–106.9)	61.0 (25.9–96.1)	20.0 (14.2–25.8)

IQR, interquartile range; CT, computer tomography; OS, overall survival; DFS, disease-free survival.

use in patients with low risk of relapse, thus exposing these patients to less radiation.

As for chest CT scans during follow-up, it is the complementary test of choice after surgery for patients with lung cancer, both to detect new relapses and to detect new primary tumors (12). In addition, after the first 2 years of surveillance, follow-up with low-dose CT is convenient given the higher risk of secondary tumors in this period (4). In our study, it should be noted the great importance of scheduled chest CT scans during follow-up after surgery, given the high percentage of informative ones that lead to a change in patient's management. Moreover, stage III entails the highest percentage of informative chest CT scans, despite having the lowest average of tests per patient. This highlights the need to conduct a closer surveillance scheme in this stage, compared to stages I and II (*Table 4*). Furthermore, we observed that most of the informative CT scans were performed during the first 2 years (63.2%) of follow-up, showing the importance of a closer follow-up during the 1st year post-surgery. Finally, these results prove the need to perform a different follow-up of the disease according to the stage, with a closer follow-up in more advanced stages.

PET-CT scans are not considered a routine test, but it is usually requested when a recurrence is suspected based on symptomatology or results from other imaging tests (13). It has been shown that it is capable of identifying recurrence in postoperative follow-up in 94% of patients who present recurrence. However, it has also been associated with false-positive results due to the uptake of inflammatory lesions (14). In this study, most of the PET-CT scans were scheduled and performed after suspicious CT scan findings. As a matter of fact, 64 (48%) of the PET-CT scans performed were informative. We may therefore conclude that almost 50% of the suspicious CT scans that resulted in disease relapse were confirmed with a PET-CT scan.

According to different studies, this test is more useful in stage III patients and during the first 3 years of follow-up (10).

Finally, brain CT/MRI imaging tests are not a routine test in the follow-up of NSCLC after surgery. The incidence of brain metastases in these patients ranges from approximately 5–40%. To date, no trials have been conducted evaluating the use of MRI in follow-up. However, several trials performing prophylactic cranial irradiation have not shown an increase in survival (15). In this study, scheduled brain CT/MRI were performed only in stage I and II patients and only 4 were informative (44.4%), while unscheduled ones were mostly performed in stage III patients, and 12 were informative (92.3%). Of note, most of these patients had neurological symptoms, and only 8.3% of the unscheduled brain CT/MRI determined a change in the patient's follow-up.

The main limitation of this study is its retrospective, descriptive nature, based on the activity conducted in a single center, HUPHM.

Conclusions

The results obtained confirm the importance and need of unscheduled visits for oncology patients, which may lead to a change not only in follow-up strategies, but also in the oncology department's structure, establishing "fast-track" consultations for symptomatic patients. Our results also show that laboratory tests are not profitable in the early postoperative follow-up of NSCLC patients after surgery. Moreover, chest X-ray could be useful after the 3rd year of follow-up in stage I–II patients with low risk of relapse, thus reducing radiation received and reducing the risk of developing new primary tumors. CT scan stands as the complementary test of choice to detect relapses, resulting in greater profitability during the first 2-year post-surgery and in stage IIIA. PET-CT is very useful in patients with

doubtful chest CT or symptomatic patients with suspected recurrence. New monitoring strategies based on scientific evidence must be defined to improve profitability.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was

conducted in accordance with the requirements expressed in the Declaration of Helsinki (as revised in 2013), as well as with the current legislation in Spain on conducting observational studies (Ministerial Order SAS/3470/2009). The study was approved by the HUPHM Clinical Research Ethics Committee (No. PIE14/00064) and individual consent for this retrospective analysis was waived.

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