Cisplatin-Docetaxel Induction plus Concurrent 3-D Conformal Radiotherapy and Weekly Chemotherapy for Locally Advanced Non-Small Cell Lung Cancer Patients: A Phase II Trial

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Key Words

Concurrent 3-D chemoradiotherapy • Docetaxel • Cisplatin • Chemotherapy • Locally advanced non-small cell lung cancer

Abstract

Concurrent chemoradiotherapy (CHRT) is the standard of care for unresectable locally advanced stage III non-small cell lung cancer. However, the optimal combination remains unclear. The aim of this study was to evaluate the efficacy of 2 induction chemotherapy cycles (days 1 and 22) with docetaxel 75 mg/m² and cisplatin 75 mg/m² followed by concurrent chemotherapy (weekly docetaxel-cisplatin, 20 mg/m²) and 3-D conformal radiotherapy for 6 weeks (66 Gy/5 fractions per week/2 Gy per fraction). The primary end-point was the response rate. Secondary objectives were toxicity, time to progression, and overall survival. Forty-four patients were included and 40 were eligible. The mean age was 60.5 years (range 40.7–72.1), and 75% had stage IIIB disease. Six patients underwent complete R0 resection including 2 pathologic complete responses after a planned intermediate evaluation. Thirty-three patients completed CHRT. The

objective response rate was 65% (95% CI 50.2–79.8). Grade 3–4 hematologic and digestive toxicities were observed mainly during the induction phase. Grade 3 esophagitis (5%) was experienced during CHRT. With a median follow-up of 38.7 months, the median progression-free survival was 28.3 months (95% CI 11.0–35.0) and the median survival rate was 31.4 months. Cisplatin-docetaxel induction followed by concurrent 3-D conformal radiotherapy and weekly chemotherapy is a feasible protocol associated with a promising response rate and acceptable toxicity.

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Introduction

Lung cancer is the most common malignancy among men in most countries and constitutes the leading cause of cancer death worldwide [1]. Non-small cell histology represents roughly 80% of lung cancer cases [2] comprising one third of patients with stage III, locally-advanced disease at diagnosis. Some stage IIIA cancers are considered resectable but many stage IIIA (with bulky N2) and stage IIIB (T4 any N M0, any T N3M0) cancers are

considered unsuitable for surgery [3]. However, some authors have shown that surgery after chemoradiotherapy (CHRT) is beneficial for at least progression-free survival (PFS) [4, 5]. Since the 90s, CHRT has become the cornerstone of inoperable locally advanced non-small cell lung cancer (NSCLC). A meta-analysis of 52 randomized studies showed a survival improvement of 3% at 2 years and 2% at 5 years for patients treated with CHRT versus radiotherapy alone [6]. Concomitant chemoradiation was demonstrated to be better than sequential administration in terms of overall survival (OS) in 3 out of 4 randomized studies with esophagitis as the dose-limiting toxicity [7–10]. Nevertheless, the median survival was around 16 months and improvement is needed. To better control micrometastatic disease and reduce distant relapses, one possibility is to increase radiosensitization with higher doses of chemotherapy [7, 11, 12]. The cisplatin-docetaxel combination demonstrates a benefit in locally advanced and metastatic NSCLC [13–15]. At the initiation of this study, cisplatin-docetaxel combined with concurrent radiation in patients with stage IIIA/B NSCLC showed encouraging results with good response rates and grade 3 esophagitis as the main dose-limiting toxicity. The recommended weekly dose was 20–25 mg/m² docetaxel and cisplatin with concurrent standard radiation in most phase I trials [16–18]. Otherwise, it has been demonstrated that 4–6 cycles with full doses of chemotherapy are necessary for effectiveness in advanced NSCLC [19]. In the conditions of chemoradiation, two induction cycles present the double advantage of better controlling micrometastatic disease and reducing the tumoral volume [20].

The aim of this phase II study was to evaluate the antitumoral activity of a weekly docetaxel-cisplatin combination administered concurrently with radiotherapy after 2 induction cycles with the same drugs.

Methods

Study Design

This was a prospective, open-label, multicentric, phase II study. It was designed and conducted in accordance with Good Clinical Practice Guidelines and the latest revision of the Declaration of Helsinki. The ethics committee approved the study in March 2004. Before inclusion, all patients provided written informed consent.

Patient Selection Criteria

To enter the study, the patients had to have histologically or cytologically confirmed NSCLC, stage IIIB (excluding malignant pleural or pericardial effusions, tumoral volume exceeding one

radiation field, N3 supraclavicular, and contralateral hilar nodal involvement) or inoperable stage IIIA defined by the new International Staging System [21], 18 ≤ age ≤ 75 years, Eastern Cooperative Oncology Group Performance Status (ECOG PS) ≤ 2, weight loss <10%, at least one measurable lesion according to RECIST 1.0 criteria, adequate hematopoietic function (absolute neutrophil count ≥ 2 × 10⁹/l, platelets ≥ 100 × 10⁹/l, and hemoglobin level ≥ 10g/dl), adequate hepatic function [total serum bilirubin less than or equal to the institutional upper limit of normal (ULN), aspartate aminotransferase ≤ 1.5 × ULN, and alkaline phosphatase ≤ 5 × ULN], and adequate renal function (serum creatinine ≤ 1.5 × ULN). Exclusion criteria included: patients previously treated with radiotherapy or chemotherapy for NSCLC, previous cancer except basocellular carcinoma and in situ carcinoma of the cervix curatively treated and other cancers curatively treated for at least 5 years, peripheral neuropathy NCI-CTC grade ≥ 2, noncontrolled severe disease, pregnant or breast-feeding women.

Treatment and Drug Administration

Chemotherapy Administration

Two cycles of induction chemotherapy were administered before CHRT consisting of docetaxel 75 mg/m² as a 1-hour infusion followed by cisplatin 75 mg/m² as a 30-min infusion on days 1 and 22. Chemoradiation was started on day 43 consisting of weekly administration of docetaxel 20 mg/m² as a 1-hour infusion and cisplatin 20 mg/m² as a 30-min infusion, both for 6 weeks.

Radiation Therapy

All patients underwent CT simulation for three-dimensional conformal radiotherapy planning, after the induction phase. Radiation was delivered with a 15-MV linear accelerator. The target dose to the original volume was 66 Gy in 33 fractions of 2 Gy/fraction, 5 fractions per week. Radiotherapy was delivered with a 3-D technique and involved field irradiation (IFI). The gross target volume included the persistent tumoral volume after chemotherapy induction and involved nodes with one or more of the following characteristics: a shortest diameter >1 cm, and/or a positive biopsy and/or a positive PET scan at the initial evaluation (if performed – not mandatory). The clinical target volume (CTV) was defined as the gross target volume plus a 3-D expansion of 0.8–1.1 cm including the ipsilateral hilum. The planning target volume was defined as the clinical target volume plus a 1- to 1.5-cm expansion in the inferior directions and 0.5–1 cm in the superior directions. There was no prophylactic node irradiation except for apical tumor. In this case, ipsilateral supraclavicular irradiation was done at a dose of 46 Gy. The total dose of the spinal cord had not to exceed 45 Gy. The maximal dose for the esophagus was 58 Gy and 30 Gy for the circumference.

Surgery

Four weeks after radiotherapy initiation (between 40 and 46 Gy), patients were evaluated via imaging for surgery. If the disease was subsequently downstaged, patients were operated with intent to achieve R0 surgery. The decision for surgery was confirmed by a multidisciplinary meeting. Operated patients were analyzed separately.

Clinical Evaluation and Follow-Up

At inclusion, complete physical examination and standard initial laboratory tests were required. Radiological exams included a

computed tomography (CT) scan of the chest and upper abdomen, including adrenals and the liver, as well as a bone scan and cerebral CT scan or magnetic resonance imaging performed within 28 days. Before each chemotherapy cycle, physical, hematological, and biochemical exams were repeated.

Radiological imaging procedures were performed 4 weeks after radiotherapy initiation (between 40 and 46 Gy) and without interruption, in order to define patients eligible for surgery [22, 23]. In case of R0 surgery, radiotherapy was stopped. For R1 or R2 surgery, radiotherapy was continued until 60 and 66 Gy, respectively. Data quality was ensured via careful review of the data by a local Data Monitoring Committee and by the study chairperson following sponsor standard policies.

Toxicity and Dose Modifications

Toxicity was recorded before each cycle and graded based on NCI-CTC v3.0. Treatment modifications were planned as follows: in case of grade 4 neutropenia lasting ≥ 7 days and/or febrile neutropenia and/or grade 4 thrombocytopenia, a 20% decrease in both drugs doses was planned. Chemotherapy was interrupted until toxicity had resolved to grade 1 or less and then resumed at 80% of the intended dose. In the CHRT phase, if hematological toxicity persisted after 2 weeks, radiotherapy was continued alone. Granocyte colony-stimulating factors were authorized and left at the investigator's discretion. For nonhematological toxicities grade 2 or less, the full dose was administered and corrective treatments established, except for grade 2 peripheral neuropathy and creatinine clearance between 40 and 59 ml/min leading to a 20% dose decrease of both drugs. A 20% docetaxel dose reduction was proposed for grade 3 bilirubin toxicity. Definitive cessation of chemotherapy was planned in case of peripheral neuropathy grade 3 or greater, grade 4 total bilirubin, creatinine clearance < 40 ml/min, and esophagitis/mucositis grade 3 or greater persisting after 2 weeks.

Response Criteria

Responses were assessed using the standard RECIST 1.0 criteria [24]. Imaging assessment of tumoral target lesions was repeated between days 71 and 73 (corresponding to a delivery of 40–46 Gy of radiation) and between days 130 and 144. Patients who were adequately downstaged were evaluated for surgery. Then, every 6 months, patients were assessed for progression. OS and PFS were calculated from study inclusion to death from any cause and to progressive disease or death, respectively. Disease-specific survival (DSS) was calculated from inclusion to death from cancer or toxicity.

Statistics

The primary objective was to determine the objective response rate (ORR), defined as complete response (CR) and partial response (PR), after induction chemotherapy and CHRT. The secondary objectives were to evaluate OS, DSS, PFS, and tolerance of the treatment. All statistical analyses were done using R.2.12.2 software for Windows. Statistical tests used were the χ^2 test, Fisher test, Student t test, log-rank test, non-parametric tests according to variables, and their distribution. Survival rates were calculated using the Kaplan-Meier method. The number of patients required was calculated according to Simon's 'minimax' model with $\alpha = 0.05$ and $\beta = 0.20$. Treatment was considered ineffective if the ORR was $\leq 40\%$ and effective if it was $> 60\%$. A sample size of 39 evaluable patients was required.

Table 1. Patient characteristics (40 patients in total)

Characteristics	Mean	SD
Age, years	60.5	8.1
Characteristics	Patients, n	Patients, %
Sex		
Male	30	75.0
Female	10	25.0
Performance status		
ECOG 0	19	47.5
ECOG 1	18	45.0
ECOG 2	3	7.5
Histology		
Adenocarcinoma	18	45.0
Squamous cell carcinoma	13	32.5
Large cell carcinoma	1	2.5
NSCLC cytology	8	20.0
Stage		
IIIA	10	25.0
T2N2	4	10.0
T3N2	6	15.0
IIIB	30	75.0
T2N3	2	5.0
T3N3	2	5.0
T4N0-N2	15	37.5
T4N3/Nx	9	22.5
TxN3	2	5.0

Results

Patient Characteristics

Between May 2004 and November 2007, forty-four patients were included at 7 centers. Four patients were ineligible and were not treated (1 withdrew his consent, 1 had stage IV NSCLC, 1 had hemoglobin < 10 g/dl, and 1 had inadequate renal function) leading to 40 evaluable patients. Patient characteristics are listed in table 1. The patient population had a mean age of 60.5 years (SD = 8.1). The majority was male (75%) with a stage IIIB NSCLC (75%). Adenocarcinoma was the most frequent type of histology (45%). Three patients had ECOG PS 2.

Treatment Delivery

All forty patients received 2 cycles of induction treatment. Administration of the second cycle was delayed in two patients (lymphocytic meningitis, patient inconvenience). The median induction doses of cisplatin and docetaxel were 74.8 and 74.9 mg/m² (range 1.0–78.3), respectively. Six out of 40 patients required dose reductions

Table 2. Response to induction and CHRT in the population without surgery and with surgery

Response rate	Population without surgery (n = 34)		Population with surgery (n = 6)	
	n	%	n	%
CR	0	0.0	2	33.3
PR	21	61.7	3	50.0
Stable disease	9	26.5	1	16.7
Progression	4	11.8	0	0.0
ORR	21	61.7	5	83.3

Table 3. Site of relapse

Site	n	%
Relapses	15	100
Local	2	13.3
Distant	13	86.7
Brain	4	26.6
Suprarenal gland	2	13.3
Liver	2	13.3
Bone	1	6.7
Other	4	26.6

Some patients had more than 1 relapse site.

Fig. 1. OS (proportion) in patients (n = 40) with locally advanced NSCLC (95% CI).

during the induction phase. Three patients received lower doses of both drugs during the 2 cycles, 1 patient only during the first treatment cycle, and 2 patients only during the second cycle. Forty patients entered the chemoradiation phase. Twenty-five patients received 6 weekly cycles of chemotherapy with radiotherapy, including 1 patient who received 1 extra cycle. Five cycles were not administered because of hyperleucocytosis (1 patient), esophagitis (2 patients), and other reasons (2 patients). Thirteen cycles were delayed due to toxicity (3 patients), logistical problems (4 patients), patient inconvenience (3 patients), and other reasons (3 patients). One patient never received cisplatin due to irreversible hearing toxicity occurring during the induction phase. The mean cisplatin and docetaxel doses received during the concomitant phase were 18.9 mg/m² (SD = 4.1) for both drugs. Eleven out of the 40 patients received less than 66 Gy due to clinical progression (2 patients), esophagitis (1 patient), dysphagia (1 patient), logistical problems (3 patients), and interruption for surgery (4 patients). The mean radiotherapy dose received by all evaluable patients (n = 40) was 60.9 Gy (SD = 13.1). For patients receiving full chemoradiation treatment (n = 19), the mean radiotherapy dose was 63.7 Gy (SD = 5.2).

Surgery

Six patients with clinical PR at the first evaluation underwent surgery and received lower radiotherapy doses (mean 53 Gy; SD = 11.1) concomitantly with 5 cycles (n = 5) and 6 cycles (n = 1) of chemotherapy. According to International Association for the Study of Lung Cancer (IASLC) criteria, surgery was complete (R0) in all patients: 3 patients had lobectomy and 3 had pneumonectomy, all with complete lymph node dissection [23]. Pathologic complete (no viable cancer cell), major ($\leq 35\%$ viable cancer cells), and minor responses ($>35\%$ viable cancer cells) were observed in 2 patients, 3 patients, and 1 patient, respectively.

Response to Treatment

Forty patients were evaluable for response after induction and CHRT (between days 130 and 144). The ORR was 65% (95% CI 50.2–79.8). In the 34 nonoperated patients, the ORR was 61.7% (95% CI 45.4–78.0); 21 of 34 patients had PR (61.7%), 9 patients (26.5%) had stable disease, and 4 had progressive disease (11.8%). For patients undergoing surgery, the ORR was 83.3%; 2 patients had CR (33.3%), 3 had PR (50%), and 1 patient had stable disease (16.7%) at assessment between days 130 and 144 (table 2).

Table 4. Adverse events by patient per grade per treatment phase

	Induction phase			Chemoradiation phase		
	grade 1–2	grade 3	grade 4	grade 1–2	grade 3	grade 4
Hematological events						
Leucopenia	5	1 (16.7%)	–	9		
Neutropenia	6	8 (20%)	4 (10%)	7	–	–
Febrile neutropenia	–	1 (2.5%)	1 (2.5%)	–	–	–
Anemia	26	–	–	23	–	–
Thrombocytopenia	3	–	–	5	–	–
Nonhematological events						
Nausea	23	2 (5%)	–	14	–	–
Vomiting	8	2 (5%)	–	3	–	–
Asthenia	13	–	–	15	–	–
Esophagitis	3	–	–	12	2 (5%)	–
Pneumonitis	–	–	–	4	–	–
Neuropathy	3	–	–	1	–	–
Diarrhea	6	1 (14.3%)	–	2	–	–
Renal	3	–	–	–	–	–

PFS and OS

With a median follow-up of 38.7 months, the median PFS in the eligible population ($n = 40$) was 28.3 months (95% CI 11.0–35.0). The median OS was 31.4 months (95% CI 15.2–not reached) (fig. 1a). The median DSS was 44.2 months (95% CI 19.5–not reached). The 1-, 2-, and 3-year OS were 75.0% (95% CI 62.7–89.7), 52.5% (95% CI 39.1–70.5), and 45.0% (95% CI 31.9–63.4), respectively. After a 3-year follow-up, 17 patients were still alive, 6 of whom have had progression.

Survival data on the 34 patients not undergoing surgery were relatively lower, with a median PFS of 13.0 months (95% CI 10.6–32.4). The median OS was 20.7 months (95% CI 14.6–not reached). The 1-, 2-, and 3-year OS were 74.0% (95% CI 60.0–90.0), 47.0% (95% CI 33.0–67.0), and 38.0% (95% CI 25.0–59.0), respectively. In an exploratory analysis, we demonstrated a statistically significant difference in DSS rates between the group of patients who received at least 8 cycles of chemotherapy and the group of patients treated with less than 8 cycles ($p = 0.03$, log-rank test). In contrast, there was no significant difference regarding OS and PFS ($p = 0.09$ and $p = 0.12$, respectively). A difference in OS, PFS, and DSS was shown for nonoperated patients treated with 66–68 Gy and patients treated with less than 66 Gy ($p = 0.02$, $p = 0.008$, and $p = 0.005$, respectively).

Sites of Progression

We observed disease progression in 11 out of 40 patients. Local and distant relapses represented 13.3 and

86.7% of relapses, respectively. First failure was observed in the brain (26.6%), the suprarenal gland and liver (13.3% each), and other sites (26.6%) (table 3).

Safety and Toxicity Data

During the induction phase, the main toxicity was grade 3–4 neutropenia (30%) and febrile neutropenia (5%). Grade 3 diarrhea was noted in 1 patient. Interestingly, 3 patients had grade 2 esophagitis. During CHRT, grade 3 esophagitis was observed in only 2 patients (5%). Of note, radiation therapy was stopped in 4 patients between 44 and 50 Gy to pursue surgical resection. Other toxicities did not exceed grade 2. One resected patient also had documented infection after surgery, leading to death (table 4).

Discussion

The main objective of this phase II study was to evaluate chemotherapy induction with docetaxel-cisplatin followed by CHRT with the same drugs, in terms of ORR, in patients with locally advanced stage III NSCLC. Radiotherapy used 66 Gy delivered with a 3-D technique and IFI. The results further supported the benefits of this regimen, with an ORR of 65% (95% CI 50.2–79.8), and confirmed our initial hypothesis expecting an ORR >60%. The subgroup analysis demonstrated an ORR of 61.7% (95% CI 45.4–78.0) in nonoperated patients and 83.3% (5 out of 6

patients) in operated patients. Survival data were also promising, with a median OS, DSS, and PFS of 31.4 months (95% CI 15.2–not reached), 44.2 months (95% CI 19.5–not reached), and 28.3 months (95% CI 11.0–35.0), respectively. In terms of toxicity, the regimen seems to be well tolerated. Grade 3–4 white blood cells were the main toxicity observed with 30% neutropenia, 5% febrile neutropenia, and 16.7% leucopenia. Surprisingly, grade 3–4 esophagitis was relatively uncommon (5%) and was observed only in the CHRT phase. No grade 3–4 radiation pneumonitis occurred, but 10% grade 1–2 events were noted during CHRT. Our results show a trend toward a better DSS ($p = 0.03$, log-rank test) for nonoperated patients receiving full treatment in terms of chemotherapy (2 induction cycles and at least 6 treatment cycles in the CHRT phase). The OS, PFS, and DSS were also favorable in the group of patients receiving at least 66 Gy ($p = 0.02$, $p = 0.008$, and $p = 0.005$, log-rank tests, respectively). Some authors have treated stage III NSCLC patients with chemoradiation including a higher weekly dose of docetaxel (45 mg/m²) and cisplatin (40 mg/m²) and conventional radiotherapy. With an equivalent response rate and survival, they noted higher rates of grade ≥ 3 adverse events such as radiation esophagitis (19%) and radiation pneumonitis (5%) [25].

Similarly, high levels of grade 3 esophagitis and pneumonitis were noted in chemotherapy protocols without 3-D conformal and IFI [26, 27]. However, it has also been shown that dosimetric factors such esophageal volume treated above 45–50 Gy are risk factors for developing esophagitis [28, 29]. In a randomized phase III study with stage III NSCLC patients, Yuan et al. [30] found no advantage for elective node irradiation (ENI) compared to IFI on response rate (79 vs. 90%, $p = 0.032$). Moreover, the 2-year survival rate favored the IFI group (38.7 vs. 25.6%, $p = 0.048$) and radiation pneumonitis was lower (29 vs. 17%, $p = 0.048$) [30]. Applying the IFI technique and EORTC recommendations instead of ENI [31], we observed low rates of grade 3 esophagitis and grade 1–2 pneumonitis and an improved response rate. Indeed, the grade 3 esophageal toxicity observed in our study was inferior to the data reported in the meta-analysis of Auperin et al. [19] comparing concomitant chemoradiation to sequential CHRT (18%). However, the reported rates vary widely (from 4% in the trial conducted by Furuse et al. [9] to 25% in the RTOG9410 trial [7]). In addition, the majority of these trials used a technique of 2D radiotherapy and an ENI approach. Fernandes et al. [32] reported a significant reduction in the risk of esophageal toxicity with the use of an IFI technique compared to an ENI type approach (significantly lower risk of high grade esophagitis, OR 0.31, $p = 0.036$).

Moreover, the passage of esophagitis grade 2 to grade 3 according to NCI-CTC AE v3.0 is only conditioned by the placement of a percutaneous feeding tube or total parenteral nutrition for more than 24 h. These criteria can be assessed differently from one center to another. Thus, it is interesting to note that in the Senan et al. [33] trial using the same regimen as ours, esophageal toxicity grade 3 was increased by the systematic implementation, by some centers, of a feeding tube in patients considered at high risk for esophagitis. Recently, Aydiner et al. [34] demonstrated a grade 3 esophagitis rate of 2.85% (1 out of 35 patients).

Distant recurrence occurs in approximately 40% at 5 years in locally advanced NSCLC treated by CHRT [19]. The IFI technique could allow the delivery of chemotherapy at the full dose and thereby limit the dose delays or dose reductions.

Encouraging results have been obtained from concurrent CHRT trials with full-dose chemotherapy during radiation [8, 9, 35, 36]. In the past decade in phase II or III trials, some authors have tested the benefit of induction or consolidation chemotherapy. No significant benefit or higher toxicity was observed for docetaxel in consolidation after a CHRT regimen [37], leading to its decreased use [38]. CALGB 39801 has failed to show a benefit of induction chemotherapy prior to CHRT [39]. It should be noted nonetheless that Fournel et al. [40] found no difference in toxicities and response rates between induction and consolidation associated with CHRT. However, chemotherapy drugs and doses were different and it is hazardous to make inter-trial comparisons of median survivals or toxicity rates.

Moreover, the EORTC 08984 study showed that induction with cisplatin 40 mg/m² and docetaxel 85 mg/m² every 3 weeks for 3 cycles in stage IIIA N2 NSCLC, was effective (response rate 45%) but led to high toxicity (65% grade 3–4 neutropenia, 17.4% febrile neutropenia, 1 chemotherapy-related death) [41]. The use, in our study, of only 2 induction cycles at a slightly lower dose followed by chemoradiation resulted in greater efficacy with less hematologic toxicity and no toxic deaths. The recently published study by Aydiner et al. [34] offered similar promising results with 3 induction cycles. Currently, there are no data privileging the administration of chemotherapy in induction or consolidation, the most important factor being the administration of the entire treatment [42]. Our results show a better DSS for nonoperated patients receiving full treatment in terms of chemotherapy. It has also been shown on OS and DSS when the total dose of radiotherapy (at least 66 Gy) was administered. The 3-year survival of 5 of the 6 operated patients (3 lobectomies, 2 pneu-

monectomies) supports the findings of Albain et al. [4, 5] finding that lobectomy after CHRT provides an additional advantage at least in terms of PFS. Surgery may provide a significant additional benefit for patients whose disease adequately downstaged after chemotherapy.

Conclusion

Chemoradiation with cisplatin-docetaxel preceded by induction with the same drugs is effective and safe in advanced stage III NSCLC. IFI and 3-D conformal irradiation contribute to good tolerance of the treatment. Patients undergoing surgery have an improved prognosis compared to nonoperated patients.

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