

 <p>ISSN NO. 2320-5407</p>	<p>Journal Homepage: -www.journalijar.com</p> <h2>INTERNATIONAL JOURNAL OF ADVANCED RESEARCH (IJAR)</h2> <p>Article DOI:10.21474/IJAR01/10284 DOI URL: http://dx.doi.org/10.21474/IJAR01/10284</p>	 <p>INTERNATIONAL JOURNAL OF ADVANCED RESEARCH (IJAR) ISSN 2320-5407 Journal Homepage: http://www.journalijar.com Journal DOI:10.21474/IJAR01</p>
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RESEARCH ARTICLE

HYPOFRACTIONATED RADIOTHERAPY IN BREAST CANCER: CAN IT BECOME A STANDARD?

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Manuscript Info

Manuscript History

Received: 23 November 2019

Final Accepted: 25 December 2019

Published: January 2020

Key words:-

Hypofractionated Radiotherapy, Breast Cancer, Survival

Abstract

Radiation therapy has long demonstrated its benefit of local control in breast cancer, but also of recurrence and overall survival. However, this treatment is not stripped of constraints, essentially socio-economic: Few centers for a large number of patients, long duration of treatment occupying the majority of the activity of a radiotherapy service, high cost for patients living in remote regions. Which made think of more practical schemes in hypofractionation for a shorter duration of treatment. Indeed, hypofractionated radiotherapy is currently said to be equivalent to conventional irradiation in breast cancer in terms of local control for patients regardless of age or stage after conservative surgery, but not yet validated in the event of invasion lymph node or after mastectomy. Our study gathered 60 patients with breast cancer, at different stages, of which 75% had lymph node invasion and 72% operated by patey, with or without the presence of factors of poor prognosis (vascular embolism, SBR III, negative RH, Her2 positive), noting that only one patient had not received chemotherapy. The results in terms of overall survival and recurrence at 5 years after hypofractionated protocols have been very encouraging, which may suggest the adoption of these regimens more commonly.

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Introduction:-

Around the world, breast cancer is the subject of most of the activity in radiotherapy centers. It is therefore important to optimally treat this cancer, while ensuring good socio-economic management. Thus, more and more, it is a question of shortening the duration of radiotherapy to save time, cost and better adherence to treatment, while retaining the benefit of radiotherapy.

The objective through our work is to study the impact of the hypofractionated protocol on the survival of patients treated for breast cancer, including in situations where this protocol is not usually prescribed: after radical surgery and chemotherapy, in case of lymph node invasion as well as other poor histo-prognostic factors.

Material and Method:-

Analysis of 60 patients treated at the oncology and radiotherapy center of Marrakech for breast cancer with hypofractionated radiotherapy schemes, regardless of age, type of surgery, treatment or not with chemotherapy, stage, lymph node status and other histo-prognostic factors. With a 5-year follow-up, studying recurrence-free survival and overall survival.

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Results:-

The age group with the highest number is [41-50] years. With an average age of 50 (Figure 1). The majority of surgical treatment was radical with Patey (Figure 2). Locally advanced stages represented by far the largest number of patients with 77% of cases. 75% of which had lymph node invasion.

The hypofractionated protocols did not exclude patients with high histo-prognostic grade, with lymphovascular involvement, hormone receptor negative and Her2 positive, although they were not predominant (Table 1). Only one case did not receive adjuvant chemotherapy. The majority of patients (75%) received lymph node radiotherapy, including 11% at the axillary level.

The most often used scheme is 40.05 Gy in 15 fractions of 2.67 Gy in 77% of the cases (Table 2). In case of conservative treatment, a boost was carried out on the tumor bed with the following schemes: 12.5 Gy in 5 fractions of 2.5 Gy (the most used: 60%), 10 Gy in 4 fractions of 2.5 Gy or 13 Gy in 5 fractions of 2.6 Gy. Sometimes with a posterior axillary complement of 5.34 Gy in 2 fractions of 2.67 Gy (during axillary irradiation following massive lymph node involvement).

15 patients were lost to follow-up. 1 death was noted after 2 years, following cerebral and pulmonary metastases and 45 patients remained under continuous surveillance, and therefore 98% of overall survival (OS) at 5 years. As for survival without recurrence, it is 91%. 4 patients had recurrences (contralateral, bone, pulmonary and cerebral). But without any loco-regional recurrence.

Discussion:-

Since 1985, and after noticing the lack of use of radiotherapy in elderly women with breast cancer due to the difficulties of movement, the distance from the centers, the general condition. Some countries, such as Canada or the United Kingdom, have developed accelerated radiation treatments in order to shorten treatment times. This so-called hypofractionated radiotherapy consists in delivering high doses per fraction (> 2 Gy, as opposed to standard fractionation), a limited number of fractions, and therefore a reduced total dose to limit the incidence of late radio-induced toxicity. This was done through randomized non-inferiority trials which evaluated the efficacy of these schemes compared to the standard 50 Gy irradiation scheme in 25 fractions, including more than 7000 patients in total, suffering from invasive breast cancer. non-metastatic (a Canadian trial, an English pilot trial Royal Marsden Hospital / Gloucestershire Oncology Center (RMH / COG) and the START A and B trials) [1-2]. Note that the majority of patients treated were menopausal and suffering from breast cancer at low risk of local recurrence (infiltrating ductal carcinoma, pT1N0 stage, histopronostic grade I / II, expressing hormone receptors and not overexpressing the Her2 oncoprotein) [3-4].

The Canadian trial showed in the different subgroups (Figure 3) that the efficacy of the hypofractionated treatment (42.5 Gy in 16 fractions) is not statistically different from that of the control arm (Figure 4) or the age of the patients, the size of the tumor, the status of hormone receptors and the administration or not of an adjuvant systemic treatment. On the other hand, the hypofractionated protocol seems less effective in the subgroup of patients with a grade III tumor (cumulative incidence of local recurrences at ten years of 15.6% in the experimental arm versus 4.7% in the control arm; $p = 0.01$) [1].

The English RMH / COG trial included 1,410 patients between 1986 and 1998, with a median age of 55 years, suffering from stage T1 or T2 breast cancer, of which 37% with axillary lymph node invasion among the 60% who had axillary dissection. After conservative surgery, the patients were randomized between conventional irradiation of 50 Gy in 25 fractions and two modalities of hypofractionated irradiation, either 42.9 Gy in 13 fractions or 39 Gy in 13 fractions. The ten-year local recidivism rates were 12%, respectively; 9.6% and 14.8% ($p = 0.0027$) [5]. The latter scheme therefore seemed less effective.

In the English multicentre Standardization of Breast Radiotherapy (START) A trial, 2236 patients were included between 1998 and 2002. Three irradiation methods were compared (50 Gy; 41.6 Gy and 39 Gy, respectively) [6]. It should be noted that 15% of the patients had had a mastectomy. With a median decline of ten years, the locoregional recurrence rates were 7.4% respectively; 6.3% and 8.8% (Figure 5). No difference in mortality was found between the three groups.

The START B trial, conducted from 1999 to 2001, included 2215 patients treated for stage pT1-3a pN0-1 cancer by conservative surgery (92%) or mastectomy (8%) [7]. In the majority of cases, the patients were ≥ 50 years old (84%) and even over 70 years old in 11.5%. The tumors were predominantly pT1 stages (64%), and there was axillary lymph node involvement in 23% of the cases. The patients were randomized between conventional irradiation of 50 Gy, 25 fractions and 35 days and concentrated irradiation of 40 Gy in 15 fractions of 2.67 Gy and 21 days. With a median follow-up of 10 years, the loco-regional recurrence rates were 5.5% in the conventional radiotherapy arm versus 4.3% in the hypofractionated arm (Figure 6). On the other hand, there were statistically fewer recurrences at a distance in the 40 Gy group (12.3% versus 16%, $p = 0.014$), which translates into an improvement in survival without recurrence (18.3% of recurrence versus 22.2% in the standard arm, $p = 0.022$) and overall survival at 10 years (15.9% mortality versus 19.2% in the standard arm, $p = 0.042$).

And so these trials seem to indicate well that a moderate hypofractionation with a reduction in the adapted total dose makes it possible to obtain results comparable to conventional fractionation in terms of effectiveness. However, it is not possible to conclude on the efficacy of a hypofractionated regimen in the subgroups of patients having had lymph node irradiation, adjuvant chemotherapy, mastectomy or even in the high grade III according to the Canadian trial. Also, when there is an indication for the boost, the data does not allow to specify the benefit of hypofractionation, or even the modalities of realization of the boost (In the 3 English tests the boost was carried out in 43% to 74% cases at 10 Gy / 5f or 14Gy / 7f).

Therefore the INCA and the SFSPM recommend hypofractionation in women over 50 years of age, in cases of T1, T2, pN0, RH + tumors, which are not of high histo-prognostic grade, and in the absence of lymphovascular invasion. And this with the following 3 schemes: 42.5Gy / 16 fractions over 22 days; 41.6 Gy / 13 fractions over five weeks and 40 Gy / 15 fractions over three weeks [8]. As for ASTRO, these protocols can be used regardless of age, stage and whether or not they are preceded by chemotherapy (Table 3).

Our study has the particularity of analyzing patients with predominantly young age, mastectomies, locally advanced stages with lymph node invasion and whatever the other histo-prognostic factors (grade SBR, lymphovascular invasion, hormonal status and Her2). The results were favorable, most often using the 40.05 Gy scheme in 15 fractions of 2.67 Gy (77%) after a 5-year follow-up in terms of survival: 98% overall survival and 91% survival without recurrence, in the absence of any loco-regional recurrence. The experience of our center could therefore encourage offering this hypofractionation for all patients with the indication of adjuvant radiotherapy for breast cancer, regardless of age, type of surgery, lymph node status or other factors.

Figures and tables :-

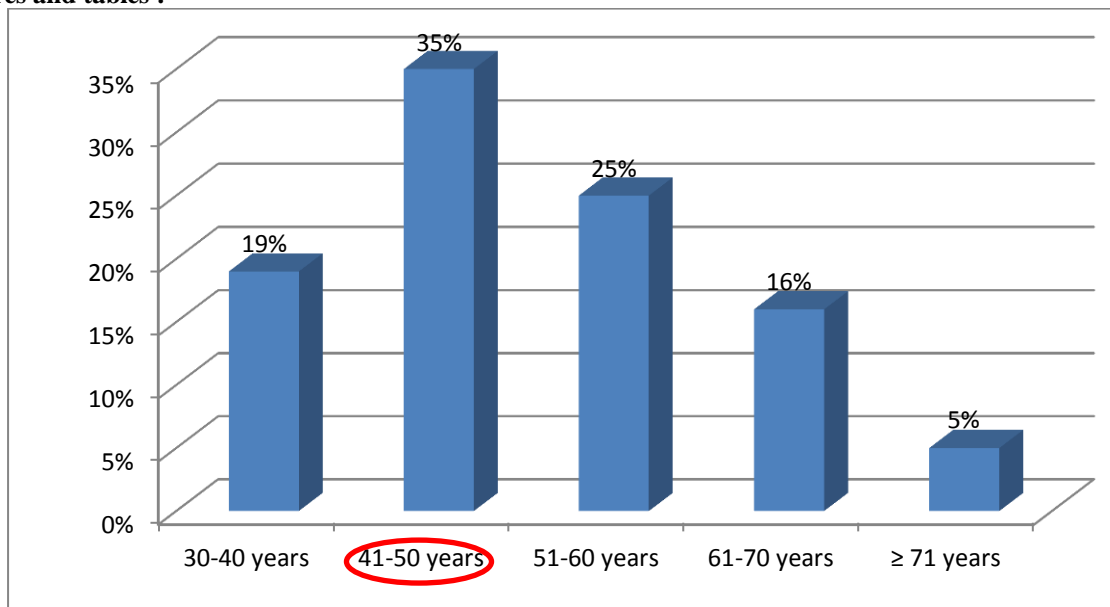


Figure 1:- Age of patients.

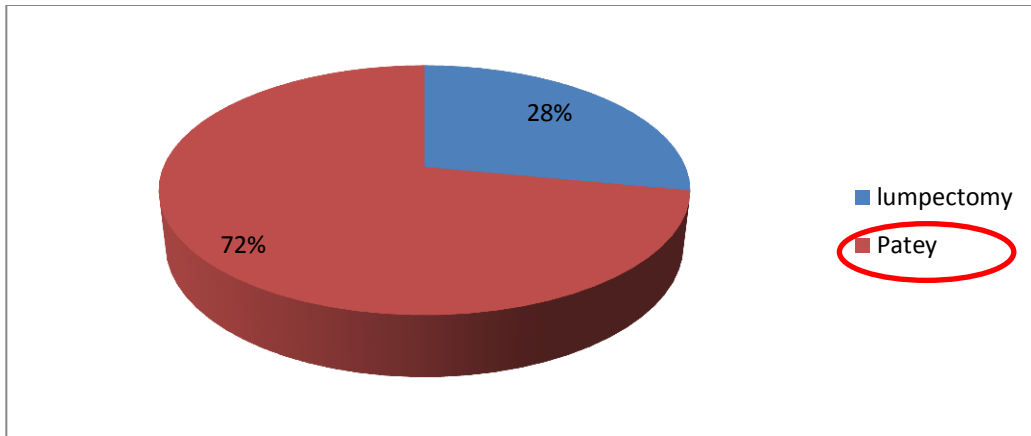


Figure 2:- Type of surgery.

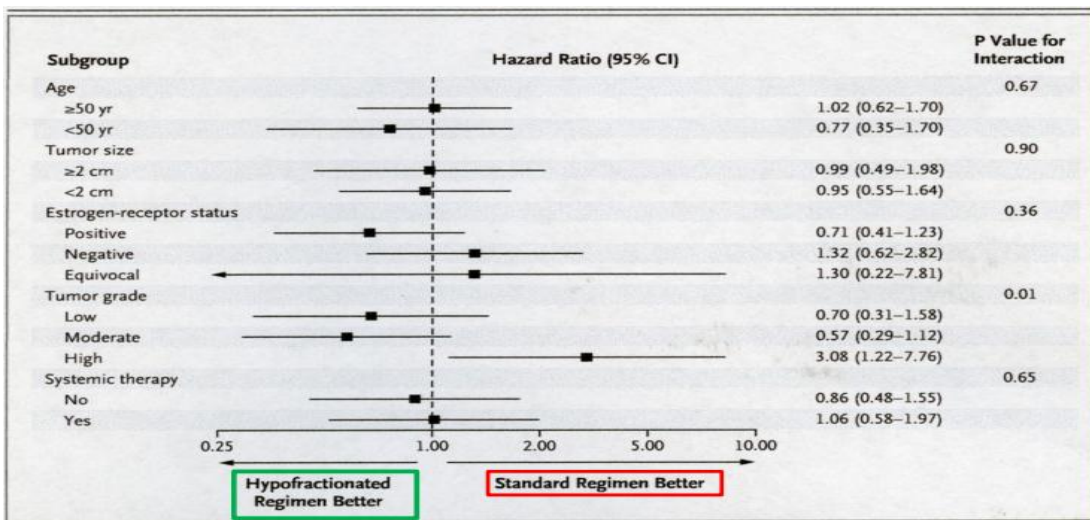


Figure 3:- Hazard ratios for ipsilateral recurrence of breast cancer in subgroups of patients.

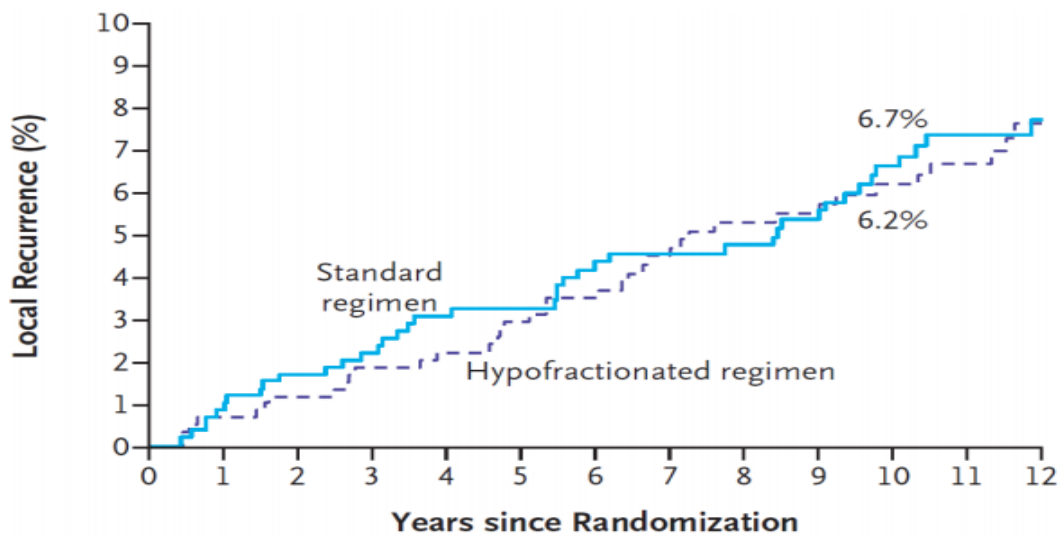


Figure 4:- Local recurrence at 10 years in the canadian study.

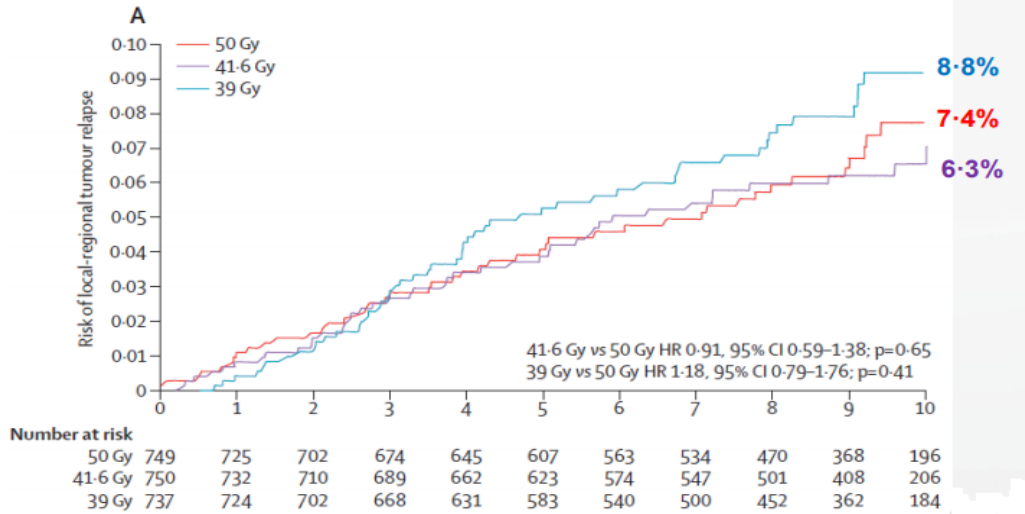


Figure 5:- START A TRIAL : Taux de rechute locale cumulée à 10 ans.

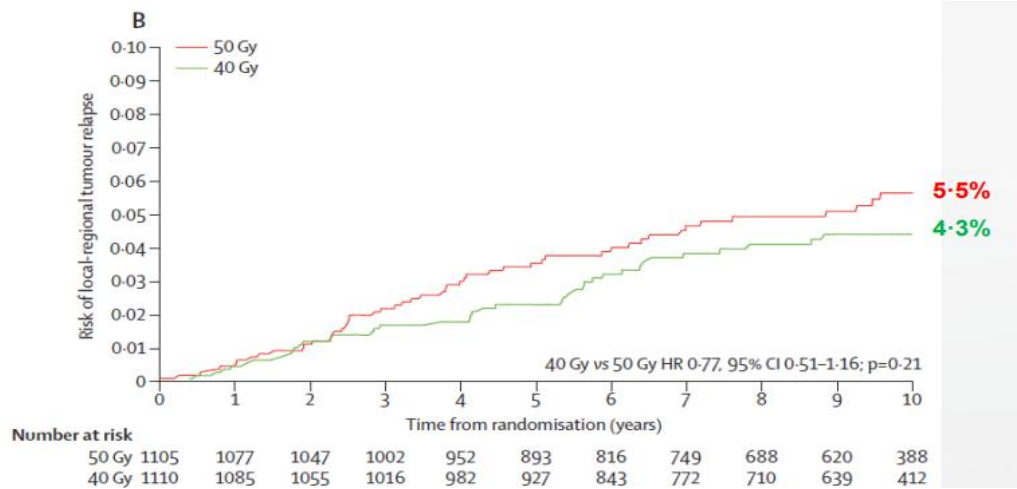


Figure 6:- START B TRIAL : Taux de rechute locale cumulée à 10 ans.

Histo-prognostic factors	Low risk	High risk
Tumor grade SBR	I, II : 64%	III : 36%
Lymphovascular invasion (LVI)	negative: 59%	positive: 41%
Estrogen receptor status	positive : 72%	negative : 28%
HER2 status	negative: 73%	positive : 27%

Table 1:- Histo-prognostic factors.

wall / breast / lymph node radiotherapy	
42 Gy in 15 fractions of 2.8 Gy	15%
40.05 Gy in 15 fractions of 2.67 Gy	77%
40.02 Gy in 15 fractions of 2,668 Gy	6%
39.9 Gy in 15 fractions of 2.66 Gy	2%

Table 2:- Protocols for hypofractionated radiotherapy.

Factor	2011 Guideline	2018 Guideline
Age	≥ 50 ans	Any
Stage	T1-T2 N0	Any stage provided intent is to treat the whole breast without an additional field to cover the regional lymph nodes
Chemotherapy	None	Any chemotherapy

ASTRO*: American Society for Radiation Oncology

Tableau 3:- Patients for whom consensus supports use of HF-WBI: A comparison of the 2011 and 2018 ASTRO* Guidelines.

Conclusion:-

In general, hypofractionated radiotherapy in the curative situation of breast cancer has demonstrated efficacy equal to that of conventional fractionation irradiation. But it is still necessary to question the indications which at present are validated especially for the breasts in place and without lymph node involvement. The satisfactory results of our center mark a positive point for this hypofractionation outside of these indications, and could provide for the standardization of these schemes.

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