



## 2. Stades I et II cliniques inopérables du fait d'une exploration fonctionnelle respiratoire médiocre ou médicalement inopérables

Si l'état général du patient le permet, une radiothérapie à visée curative est recommandée sous la forme d'une radiothérapie en conditions stéréotaxiques pour les stades T1N0 ou T2aN0, voire certains T2bN0 (tumeur jusque 5 cm). Le taux de contrôle local est lié à la taille du volume cible et est supérieurs à 85% à 3 ans dans la majorité des séries et le taux de toxicité tardive, y compris la toxicité pulmonaire, est acceptable, inférieur à 10 % (76).

En cas d'impossibilité d'obtenir un diagnostic histo-cytologique, une radiothérapie stéréotaxique doit être discutée en RCP devant une lésion suspecte au scanner, évolutive (>2mm sur deux TDM à 3 mois d'intervalle) et hyper métabolique au TEP-FDG, après élimination d'une cause infectieuse respiratoire (→ Référentiel nodules). Il n'y a aucune contre-indication formelle sur le plan de l'état respiratoire.

Une dose totale équivalente biologique d'au moins 100 Gy permet d'obtenir de meilleurs résultats en terme de contrôle local (77). Les schémas validés sont ceux en 3 à 5 fractions (45-54Gy/3F, 48Gy/4F à 50Gy/5F)<sup>9</sup> pour les tumeurs périphériques. Le schéma doit être plus fractionné pour les tumeurs centrales (< 2cm / trachée, carène, bronches souches, cœur, gros vaisseaux, canal médullaire, plexus et oesophage), en 5 à 8 fractions (50Gy/5F à 60Gy/8F)<sup>8</sup> voir 10 ou 15 fractions pour les tumeurs ultra-centrales. Il est préférable que les tumeurs ultra-centrales soient traitées en centre expert.

Pour les stades IIB, l'indication de chimiothérapie (après un diagnostic cyto- ou histologique) associée à la radiothérapie sera discutée en RCP.

La gestion des mouvements respiratoires est importante : scanner 4D, respiration contrôlée, *gating* respiratoire, *tracking*, CBCT, CBCT 4D si disponible.

### Recommandations

Dans les stades I et II inopérables, si l'état général du patient le permet, une radiothérapie à visée curative est recommandée sous la forme d'une radiothérapie en conditions stéréotaxiques pour les tumeurs N0.

Une radiothérapie stéréotaxique à visée curative est recommandée, dans les stades I voire certains IIA (T≤5cm) inopérable.

En l'absence de preuve cyto- ou histologique, une radiothérapie sans preuve, à visée curative, des stades cI à cIIA est envisageable en cas de contre indication au bilan diagnostic invasif sous réserve d'une évolution d'au moins 2mm entre deux scanners à 3 mois d'intervalle et d'une hyperfixation en TEP.

**OPTION : Ablation thermique ou autres techniques de radiologie-interventionnelle pour les tumeurs de moins de 3 cm**

## 3. Stades pIB à pIIIA réséqués avec mutation EGFR

L'essai ADAURA, publié en 2020, a testé un traitement par osimertinib pendant 3 ans (contre placebo), après chirurgie et chimiothérapie adjuvante (autorisée mais non obligatoire<sup>10</sup>, décision prise en RCP) dans les CBNPC non-épidermoïdes de stades IB, II et IIIA réséqués (selon la TNM7). Ceci correspond donc aux stades IB à IIIA (plus les actuels T4N2 soit certains IIIB) dans la classification TNM8. Le délai d'initiation de l'osimertinib était de 10 semaines après la chirurgie en l'absence de chimiothérapie adjuvante, 26 semaines alternativement. Les patients

<sup>9</sup> Fractionnements fréquemment utilisés, donnés à titre indicatifs.

<sup>10</sup> Dans cet essai 32% des patients de chaque bras étaient de stade IB, 31% dans le bras osimertinib étaient de stade N2 (30% dans le bras placebo) ; et 40% dans chaque bras n'ont pas reçus de chimiothérapie adjuvante.



inclus dans l'étude étaient PS 0-1 lors de la randomisation (après chirurgie et chimiothérapie), et atteint d'un CBNPC avec une mutation *EGFR* L858R ou Del19 (seules ou associées à une autre mutation *EGFR*). L'objectif principal était la survie sans maladie (*disease free survival*) chez les patients de stades II et IIIA. Au total 682 patients ont été inclus dont 470 de stades II et IIIA (TNM7)<sup>11</sup>. Lors de la publication des résultats, les données étaient matures à 33%. A 2 ans, 90% [IC95% 84%-93%] des patients du bras osimertinib et 44% [37%-51%] du bras placebo étaient en vie et sans maladie. Ainsi, la médiane de survie sans maladie n'était pas atteinte dans le groupe osimertinib (38,8-NC) et de 19,6 mois (16,6-24,5) dans le bras placebo (HR 0,17 [IC 99.06% 0,11-0,26]). Le bénéfice dans les stades IB (IIA dans la TNM 8) (objectif secondaire) semble moins important numériquement mais reste significatif (HR=0.39 [IC95% 0.18-0.76]). Il existe en outre un bénéfice sur les progression au niveau du système nerveux central (médiane de survie-sans maladie au SNC HR 0.18 [0.10-0.33]) (78). Des données actualisées à 4 ans, allant dans le même sens, ont été présentés à l'ESMO 2022<sup>12</sup>. Concernant la survie globale, un communiqué de presse de la société Astra Zeneca vient d'annoncer qu'elle était positive et « cliniquement significative ». Les données complètes n'ont toutefois ni été présentées, ni publiées.

## Recommandations

L'osimertinib est recommandé pendant 3 ans, en cas de mutation *EGFR* L858R ou Del19, chez les patients de stades IB, II et IIIA (plus les T4N2 dans la classification TNM8), réséqués, après chimiothérapie adjuvante lorsqu'elle est indiquée ou réalisable, et restant PS 0-1.

### 4. Formes localement avancées (stades IIIA non opérables, IIIB, IIIC)

Les stades IIIB et IIIC sont jugés inopérables sauf quelques cas particuliers (*cf. infra*). Les limites de la résectabilité concernent les stades IIIA, en fonction de l'envahissement ganglionnaire homolatéral (N2).

**Tous les dossiers doivent être discutés en RCP pour déterminer la stratégie optimale (séquence traitement systémique et traitement local).**

#### 4.1 Stades IIIA non résectable, IIIB et IIIC ou patients non médicalement opérables

**Il y a lieu de réaliser une association de chimiothérapie et de radiothérapie suivie d'une immunothérapie si l'état du patient le permet.** La chimiothérapie doit comporter 2 à 4 cures à base de sels de platine, associées à une radiothérapie à une dose comprise entre 60 et 66Gy en fractions de 2 Gy par fraction, 5 fractions par semaine (79). En cas de chimiothérapie d'induction, le volume cible macroscopique tumoral (GTVT) doit être fondé sur l'imagerie post chimiothérapie mais l'imagerie pré-chimiothérapie doit tout de même être prise en compte. Le volume cible macroscopique ganglionnaire doit inclure les ganglions envahis avant la chimiothérapie. Seuls les structures ou volumes anatomiques considérés comme tumoraux sont irradiés (80). Le volume cible anatomoclinique CTV inclut le volume tumoral macroscopique augmenté de la maladie infraclinique (CTVT = GTVT + 5 à 8mm et CTVN = GTVN + 3 à 8 mm selon la taille du ganglion (<2 cm ou > 2 cm)). Le volume cible prévisionnel PTV doit être déterminé par chaque centre selon ses techniques de traitement et de repositionnement ; le plus souvent PTV = CTV + 5 mm. Les mouvement internes de la tumeurs peuvent être pris en compte soit avec un

<sup>11</sup> Les différences sont minimes toutefois pour la sélection des patients. Tous les stades IB de la TNM7 étaient éligibles (soit les tumeurs de 3 à 5cm correspondant désormais aux stades IB (T de 3 à 4cm) et IIA (T de 4 à 5cm). De plus, les patients atteints de tumeur ex-T3 (de moins de 7cm mais envahissant la paroi, ou le diaphragme, ou le nerf phrénique, ou la plèvre, ou la bronche souche (<2cm de la carène), ou associé à une atélectasie ou une pneumopathie obstructive de tout le poumon ou avec des nodules tumoraux dans le même lobe) et N2 étaient classés IIIA dans la précédente classification TNM et sont désormais catégorisés IIIB. De même, les

<sup>12</sup> Tsuboi M, Osimertinib as adjuvant therapy in patients with resected EGFRm stage IB-IIIa NSCLC : updated results from ADAURA. ESMO 2022, Paris, #LBA47.



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